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EVALUATION OF BLOOD PARAMETERS AND CLINICAL FINDINGS AS POTENTIAL PREDICTORS OF THE DEVELOPMENT OF AZOTEMIA IN CATS WITH HYPERTHYROIDISM

KAČIŲ, KURIOMS DIAGNOZUOTA HIPERTIROZĖ, KRAUJO PARAMETRŲ IR KLINIKINIŲ POŽYMIŲ, KAIP GALIMŲ AZOTEMIJOS ŽENKLŲ, ĮVERTINIMAS

MASTER THESIS

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Caroline Annelie Mikaela Petersson

Master Thesis

SUMMARY

Feline hyperthyroidism is one of the most common diseases in the elderly cat. Chronic kidney disease and feline hyperthyroidism can occur concurrently but the presence of azotemia often goes unnoticed until after the treatment of hyperthyroidism.

The objective of this study was to evaluate significant blood parameters, clinical signs, physical examination findings and their relationship to the development of azotemia after the initiation of treatment in cats diagnosed with hyperthyroidism.

A retrospective study with 30 cats diagnosed with feline hyperthyroidism was performed from clinical records between September 2015 and January 2020. Pre-treatment biochemical, hematological blood tests, clinical signs and physical examination findings were compared for azotemic and non-azotemic cats to evaluate if any of these parameters could be a predictor for the development of azotemia.

The most common clinical sign or physical examination finding in cats diagnosed with feline hyperthyroidism was weight loss (96.7%) followed by tachycardia (56.7%) and a palpable thyroid gland (50%). High activities of alkaline phosphatase, alanine aminotransferase and lymphopenia were the most common blood test abnormalities. A mean difference of 16.7% for weight loss (chi-square = 4.138, df = 1, $p<0.05$) and of 58.3% for polyphagia (chi-square = 6.563, df = 1, $p<0.01$) was measured between azotemic (n=6) and non-azotemic (n=24) cats. No significant mean differences for pre-treatment hematological and biochemical blood results between azotemic and non-azotemic cats were detected. Despite significant mean differences for polyphagia and weight loss, clinical signs overlapped.

This study suggest that the results of pre-treatment blood parameters and clinical findings cannot be used to reliably predict the development of azotemia following treatment.

Keywords: feline hyperthyroidism; thyroid gland; azotemia; creatinine

KAČIŲ, KURIOMS DIAGNOZUOTA HIPERTIROZĖ, KRAUJO PARAMETRŲ IR KLINIKINIŲ POŽYMIŲ, KAIP GALIMŲ AZOTEMIJOS ŽENKLŲ, ĮVERTINIMAS

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Magistro baigiamasis darbas

SANTRAUKA

Kačių hipertirozė yra viena iš labiausiai paplitusių vyresnių kačių ligų. Lėtinė inkstų liga ir kačių hipertirozė gali pasireikšti tuo pačiu metu, tačiau azotemija dažnai nepastebima po hipertirozės gydymo.

Šio tyrimo tikslas buvo įvertinti reikšmingus kraujo rodiklius, klinikinius požymius, kitus ženklus ir jų ryšį su azotemijos išsivystymu pradėjus gydymą katėms, kurioms diagnozuota hipertirozė.

Buvo atlikta retrospektyvi 30 kačių, kurioms diagnozuota kačių hipertirozė, klinikinių įrašų nuo 2015 m. rugsėjo mėn. iki 2020 m. sausio mėn. analizė. Buvo analizuojami biocheminiai ir hematologiniai kraujo tyrimai, bei klinikiniai ir kiti požymiai šioms katėms. Šie duomenys palyginti, norint įvertinti, kurie iš šių rodiklių galėtų būti azotemijos vystymosi ženklai.

Dažniausia pasiteikę klinikiniai požymiai katėms, kurioms diagnozuota hipertirozė, buvo svorio kritimas (96,7%), tachikardija (56,7%) ir apčiuopiama skydliaukė (50%). Didelis šarminės fosfatazės, alanino aminotransferazės aktyvumas ir limfopenija buvo dažniausios kraujo tyrimo anomalijos. Buvo nustatytas vidutinis 16,7% svorio netekimo (chi kvadratas = 4,138, df = 1, $p < 0,05$) ir 58,3% polifagijos (chi kvadratas = 6,563, df = 1, $p < 0,01$) skirtumas tarp azoteminių (n = 6) ir neazoteminių (n = 24) kačių. Reikšmingų hematologinio ir biocheminio kraujo tyrimo rezultatų vidutinių skirtumų tarp azoteminių ir neazoteminių kačių nenustatyta.

Šis tyrimas parodė, kad prieš gydymą gautų kraujo parametrų rezultatai ir klinikiniai požymiai negali patikimai prognozuoti azotemijos vystymąsi po gydymo.

Raktažodžiai: kačių hipertirozė; skydliaukė; azotemija; kreatininas

LIST OF ABBREVIATIONS

CKD Chronic kidney disease

GFR Glomerular filtration rate

T_3 Triiodothyronine

T_4 Thyroxine

TSH Thyroid-stimulating hormone

ALT Alanine aminotransferase

ALP Alkaline phosphatase

MCV Mean corpuscular volume

RAAS Renin-angiotensin-aldosterone system

MCH Mean corpuscular hemoglobin

INTRODUCTION

Ever since feline hyperthyroidism was uncovered in 1979, the disease has increased in prevalence and more than 10% of all older cats will eventually suffer from this disease (1,2). The etiology remains undiscovered but some of the suggested risk factors are middle-aged to elder cats, domestic short- and long-haired breeds, canned food, polybrominated diphenyl ethers (PBDEs), insufficient or excessive amounts of iodine and isoflavones in the diet (2-8).

A common presentation of feline hyperthyroidism is weight loss despite a good appetite and during the clinical examination the presence of a palpable thyroid gland or auscultation of tachycardia is frequently noted (1,9,10).

Different diagnostic methods must sometimes be used in order to make an accurate diagnosis of feline hyperthyroidism since the perfect thyroid function test does not exist (11).

Oral antithyroid drugs or dietary management can be used as a life-long therapy or to temporarily stabilize the cat prior to a thyroidectomy or radioiodine therapy (1,12).

Chronic kidney disease (CKD) and feline hyperthyroidism often occur concurrently in the geriatric cat but the hormonal effects of hyperthyroidism complicates the diagnosis of CKD. Feline hyperthyroidism may cause the function of the kidneys to appear normal since it increases the glomerular filtration rate (GFR) and decreases creatinine concentrations. Therefore, the presence of azotemia often goes unnoticed until after the treatment of hyperthyroidism, once the cat is euthyroid. Post-treatment azotemia has been reported to occur in approximately 15-49% of hyperthyroid cats. The ability to predict if the hyperthyroid cat will develop azotemia after the initiation of treatment would allow for earlier implemented management strategies (13,14)

Objective of the work: To evaluate significant blood parameters, clinical signs, physical examination findings and their relationship to the development of azotemia after initiation of treatment in cats diagnosed with hyperthyroidism.

Tasks of the work:

1. To determine the most common clinical signs and physical examination findings for feline hyperthyroidism.
2. To determine biochemical and hematological blood parameters significant for feline hyperthyroidism.
3. To evaluate the relationship between investigated parameters and the development of azotemia after initiation of treatment in cats with hyperthyroidism.

1. REVIEW OF LITERATURE

1.1. Anatomy and physiology of the thyroid gland

The thyroid gland (*glandula thyroidea*) consists of two lobes, one on each side of the trachea, ventral to the larynx. The two lobes are connected caudally by a connective tissue strand *(isthmu*s) (15,16). In the cat, the lobes are flat and spindle-shaped. The lobes extend over the first seven to ten tracheal rings. The bilaterally paired parathyroid glands are embedded within the thyroid gland (*glandula parathyroidea interna*) and on the surface of the capsule (*glandula parathyroidea externa*). The arterial blood supply of the thyroid gland protrudes from the cranial thyroid artery, a branch of the common carotid artery. The venous blood leaves the thyroid gland by cranial and caudal thyroid veins that subsequently flow into the internal jugular vein. Lymph is drained to the deep cervical lymph node or directly to the tracheal trunk. The sympathetic innervation of the thyroid gland originates in the cranial cervical ganglion. The parasympathetic nervous system supplies organs from branches of the caudal and cranial laryngeal nerves (15).

Microscopically, the thyroid gland consists of spherical thyroid follicles which are lined with follicular cells that encloses a lumen filled with a fluid called colloid. Thyroid hormones are formed within the colloid of the follicles from iodinated molecules of the amino acid tyrosine. Iodine in food is absorbed in the small intestine and transported into the colloid. There are two forms of thyroid hormones: triiodothyronine (T_3) and thyroxine (T_4). T_4 is the primary product of the thyroid gland and has a concentration 50-60 times higher than the concentration of T_3. However, T_3 is several times more potent than thyroxine and the primary mediator of biological effects. Some of the biological effects include metabolic rate and oxygen consumption, promotion of normal growth and development, heat generation and stimulation of an increase in adrenergic receptors. T_4 functions as a prohormone and can be converted into T_3 in tissues by deiodination in order to mediate biological effects. In the blood, most of the T_4 and T_3 is transported bound to thyroxine-binding globulin (TBG), albumin and transthyretin. A very small fraction of T_4 circulates unbound (16).

Thyroid hormones are produced and secreted in response to the thyroid-stimulating hormone (TSH). TSH is produced in the pituitary gland. In order for TSH to be released, it must be stimulated by the thyrotropin-releasing hormone (TRH) which is produced in the hypothalamus. A negative feedback mechanism from the thyroid hormones inhibit the secretion of TRH and TSH. Follicular cells are inactive in the absence of TSH while a prolonged period of increased concentration will stimulate an increase in size of the gland through hypertrophy and hyperplasia (16).

1.2. Etiology and risk factors in feline hyperthyroidism

Feline hyperthyroidism was uncovered for the first time in 1979 and has since then steadily increased in prevalence (1,2). Although with some geographical variation, it is calculated that more than 10% of all older cats will eventually suffer from this disease (2).

Many risk factors have been described as possible contributors to the development of feline hyperthyroidism though the etiology remains undiscovered. Above all, feline hyperthyroidism is most commonly seen among middle-aged to elder cats (3,4,17). In fact, only 3% of cats younger than 9 years old are diagnosed with this condition. The average age of diagnosis is 13 years old (3). According to one study (3), female cats are more susceptible to hyperthyroidism than male cats while other studies show that a gender difference cannot be proven (4,17). The risk of developing the disease is greatest for domestic short- and long-haired cats, while purebred cats such as Siamese, Burmese and Persian suffer less frequently (3,4).

Risk factors are not only related to the individual, but also to the feeding regiment and the environment. Cats regularly exposed to flea sprays, fertilizers, pesticides or insecticides in its environment are more frequently diagnosed with hyperthyroidism (3). PBDEs congeners can be discovered in cats with hyperthyroidism in higher concentrations than in euthyroid cats. For example, PBDE is used in flame retardants. This substance is a persistent organic pollutant known to disrupt thyroid function, due the similarity in chemical structure between total thyroxine and PBDE (2,5-7).

Regarding a cat's diet regiment, a greater incidence of feline hyperthyroidism is found in cats who are fed mostly canned food (3,4,17). The lining of the interior in metal cans may contain bisphenol A (BPA) and this is a chemical known to disrupt thyroid function (2).

Iodine is required for the production of thyroid hormones, hence why many attempts have been made to identify iodine as a causal factor, both in relation to an insufficient or excessive amount in diets. The majority of these attempts are based on data extrapolated from humans (2). Fluctuant iodine intake is also suggested as one of the causal factors (8).

Isoflavones can be found in soybeans which are often used in cat diets. Soy isoflavones can interfere with the conversion of T_4 to the biologically active T_3. Feeding healthy cats with a soy-containing diet has shown a slight increase in total T_4 and free T_4 concentrations compared with cats receiving a soy-free diet (2).

Despite the unclear etiologies, the thyroid pathological morphology in cats with hyperthyroidism has been well described. Benign adenomatous hyperplasia or adenoma are the most common findings in hyperthyroidism. Thyroid carcinoma also occurs but stands for less than 4% of the cases. Hyperplastic thyroid tissue can be found in one or both thyroid glands, multifocally, or as ectopic thyroid tissue but the most commonly, bilaterally (18,19). Ectopic thyroid tissue can be

located anywhere between the tongue and the mediastinum (19). Thyroid cysts appear to develop in cats with long-standing hyperthyroidism but no clear association has been found between the T_4 concentrations in the cyst fluid compared to the serum T_4 concentration (20).

1.3. Diagnostic methods applicable for feline hyperthyroidism

1.3.1. Clinical signs and physical examination

The most commonly noticed clinical sign is weight loss despite a normal appetite and sometimes even an increased appetite (1,9,10). The increased level of thyroid hormones has a catabolic effect which results in higher energy and protein requirement and increased breakdown of fat (21). Other classical signs include hyperactivity, polyuria/polydipsia, vomiting, diarrhea, increased vocalization, tachypnea or dyspnea and an unkempt haircoat (1,9,10). A state called "apathetic hyperthyroidism" affects around 10-20% of the diseased cats and is characterized by decreased appetite and apathy (1,9).

Thyroid gland palpation is an important part of the physical examination. A palpable thyroid gland can be found in 80-90% of the hyperthyroid cats, which is suggestive, but not necessarily indicative of clinical hyperthyroidism (1,11,22).

Excessive circulating thyroid hormones can cause hemodynamic changes. These changes can lead to the development of hypertrophic cardiomyopathy but also to changes noticed during the physical examination in form of tachycardia, heart murmurs or gallop sounds, increased intensity of the heart and arrhythmias (23). Cardiac abnormalities are diagnosed in approximately 50% of hyperthyroid cats while congestive heart failure (CHF) occurs infrequently as it constitutes only 1.4% of the diagnoses. The prevalence of cardiac abnormalities is significantly higher in cats with severe hyperthyroidism in comparison to those with mild or moderate hyperthyroidism (24).

Hypertension occurs in approximately 10% (14,25) and can be related with a reduced lifespan in hyperthyroid cats (14).

1.3.2. Biochemical and hematological parameters

The most common biochemical abnormalities are mild; however, they mark increases in the activity of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and lactate dehydrogenase (LDH). Approximately 95% of affected cats prove elevation in at least one of these enzymes. Another biochemical abnormality detected in approximately 25% of the hyperthyroid cats is a mild to moderate increase of blood urea nitrogen (BUN) and creatinine (CREA), also called azotemia. Mild hyperglycemia and hyperphosphatemia can be detected in 15% and 20% of the cats, respectively (9,10).

Occasionally encountered hematological abnormalities are mild to moderate erythrocytosis (increased packed cell volume (PCV), red blood cell (RBC) count and hemoglobin concentration)

and a higher mean corpuscular volume (MCV) (9,10). These changes presumably reflect thyroid hormone-mediated stimulation of erythropoietin secretion (23). Other hematologic findings that can be detected include neutrophilia, lymphopenia, eosinopenia, or monocytopenia (9,10).

1.3.3. Thyroid function tests

A perfect thyroid test does not exist and we have still yet to discover a thyroid test in which can confirm the diagnosis of thyroid disease in all hyperthyroid cats and decipher from cats that are not hyperthyroid (11). The commonly available thyroid function tests to diagnose feline hyperthyroidism are serum total T_4, free T_4, T_3 and TSH. T_3 suppression and TRH stimulation tests were previously a part of the work-up to confirm the diagnosis of hyperthyroidism but are not recommended today (1,11).

In most cases it is sufficient to measure total T_4 alone in order to confirm a diagnosis of feline hyperthyroidism (1,11). Serum total T_4 consists of a protein-bound fraction and a free (unbound) fraction (1). An increased serum total T_4 is found in 92% of the hyperthyroid cats (11,26).

Although T_4 is the primary hormone secreted from the thyroid gland and found in a high concentration in the circulation, the serum free T_4 fraction constitutes less than 1% of this circulating pool (1,16). Interestingly, free T_4 is a more sensitive test than the serum total T_4 and 98% of the cats have free T_4 above the reference interval (1,11,26). Because free T_4 is the only fraction which is able to diffuse across cell membranes, it is also the fraction affected by nonthyroidal factors (1). For this reason, the free T_4 is nonspecific and it is unclear how much additional useful information this test gives compared to the use of total T_4 tests alone (1,11).

Serum total T_3 is also not useful as a sole diagnostic test since approximately 30-40% of cats with hyperthyroidism have values that remain within the reference interval (22,26).

There are occasions when a hyperthyroid cat has normal T_4 and T_3 values. This may be due to an early or a subclinical hyperthyroidism, severe nonthyroidal disease or just due to the fact that total T_4 normally fluctuates during the day. It is recommended to repeat total T_4 after a few weeks and to treat concurrent diseases when T_4 and T_3 are within the reference values but a suspicion of feline hyperthyroidism remains (11).

In human medicine, the measurement of serum thyroid-stimulating hormone (TSH) concentration is generally used as the primary test to evaluate thyroid function. Physiologically, even insubstantial increases in circulating T_4 and T_3 will suppress pituitary TSH secretion through the negative feedback mechanism. By measuring canine TSH, concentrations are suppressed in 96-98% of hyperthyroid cats. Measurement of canine TSH is highly sensitive but poorly specific since euthyroid cats also can have suppressed levels of TSH and the test cannot accurately differentiate a low-normal TSH concentration from an undetectable level. Therefore, TSH cannot be used alone to diagnose feline hyperthyroidism (11,27).

Since the perfect thyroid function test is yet to exist, in order to make an accurate diagnosis of feline hyperthyroidism, the veterinarian is required to interpret thyroid function tests in the context of the anamnesis, clinical signs, physical examination findings and other laboratory findings (11).

1.3.4. Scintigraphy

Thyroid scintigraphy produces an image of the thyroid tissue based on the degree of thyroid gland radionuclide uptake (1,11,19,28,29). These images can aid in the differentiation of quantitative factors such as bilateral versus unilateral diseases, assessment of thyroid size and identification of ectopic or metastatic thyroid tissue (1,19,29,29). The uptake of the radionuclide can be measured by quantifiable factors such as the thyroid to salivary gland (T/S) ratio, the thyroid to background (T/B) ratio and the percentage of radionuclide uptake by the thyroid glands (%TcU) (11,19,28,29). Both T/S and T/B ratio have a higher sensitivity and specificity than the total T_4, indicating that scintigraphy can diagnose feline hyperthyroidism prior to typical thyroid function tests (19,28). Unfortunately, the equipment is expensive and requires special licensing, which explains why very few clinics have access to it (11).

1.4. Treatment options for feline hyperthyroidism

1.4.1. Reversible treatments (oral antithyroid drugs and dietary management)

Two main pharmaceutical active substances, methimazole and carbimazole, are used as oral antithyroid drugs. These substances can be used as a life-long therapy to control the thyroid hormones or to temporarily stabilize the cat prior to a thyroidectomy or radioiodine therapy. Methimazole inhibits the thyroid peroxidase that is required for the synthesis of thyroid hormones. Carbimazole is a pro-drug that is transformed into methimazole after oral absorption. Methimazole and carbimazole are given orally as tablets, however as an alternative, methimazole can be applied transdermally (1,12). The transdermal application is usually more convenient for the owner but it appears to be more difficult to maintain a constant T_4 within the reference range (1,12,30). The recommended starting dose for the oral methimazole is 2.5 mg twice a day and for carbimazole it is 10 mg once a day. After the initiation with antithyroid drugs, a revisit should be booked after 2-3 weeks to monitor TT_4 and adjust the dose if necessary. Follow-up visits should be scheduled every 2-3 weeks after dosage changes, 3 months after return to euthyroidism and thereafter every 6 months. Over-treating should be avoided since this can cause iatrogenic hypothyroidism (1,12). The most frequently noted side-effects are gastrointestinal signs, mild hematological abnormalities and dermatological reactions (1,12,30).

Iodine is required for thyroid hormone synthesis which explains why an iodine deficient diet would decrease the synthesis of T_4 and T_3 (2). This effect can be taken advantage of by feeding an

iodine-restricted diet in the management of feline hyperthyroidism. Information on when an improvement of clinical signs can be expected and the ability of an iodine-restricted diet to normalize high levels of TT_4 varies between studies (31,32). Van der Kooji M et al. (31), reported that TT_4 normalized in 55/88 cats (62.5%) and an improvement in clinical signs was noticed within 4 weeks. Hui, T.Y. et al. (32), reported that only 20/40 cats (42%) had normalized TT_4 at 21-60 days but 39/47 (83%) at 61-180 days. Cats with an initially high TT_4 might require a longer period of time to normalize TT_4 (32). If the dietary management option is chosen, the cat has to exclusively eat this type of food, hence why owner compliance is vital (31,32). Iodine-restricted food has some benefits, including prevention of the stress associated with medical therapy and the fact that it is a reversible alternative, and because of that, another treatment option may still be used (31). Side effects of a long-term usage with an iodine-restricted diet has not been evaluated nor have any short-term side effects been identified (31,32).

1.4.2. Irreversible treatments (thyroidectomy and radioiodine therapy)

Surgical removal of the thyroid gland is a curative treatment. Since a bilateral thyroid disease is the most common finding, both lobes must be removed in most cats (1). Different surgical approaches for removal of the thyroid gland have been described, some involve resection of the capsule (extracapsular technique) and others preserve the capsule (intracapsular technique) (33).

Complications associated with thyroidectomy are surgery-related mortality, postoperative hypoparathyroidism and recurrence. Thyroid hormones increase the sensitivity to adrenergic receptors and this poses a risk for cardiac complications. The best way to prevent this is to achieve euthyroidism before surgery. Euthyroidism would also allow for the assessment of renal function prior to surgery. Recurrence may be observed from an incomplete thyroidectomy, or the development of hyperplastic changes in an unnoticed ectopic thyroid tissue. It can also occur if the unilateral thyroidectomy is performed and later hyperplastic changes develop in the normal thyroid lobe. If possible, thyroid scintigraphy should be performed prior to surgery. Permanent hypocalcemia occurs in approximately 6% of the cats due to accidental removal or damage of the parathyroid gland or its blood supply. In order to identify the cats with hypoparathyroidism, the calcium concentration must be measured postoperatively. Cats with hypoparathyroidism require calcium supplementation to maintain a normal calcium level. However, definitive conclusions about hypoparathyroidism should not be made too quickly since transient hypocalcemia can occur after surgery due to local edema of the thyroid gland (18).

Radioactive iodine (^{131}I) is one of the options that can be used to cure feline hyperthyroidism. Iodine transporters in the body do not distinguish between radioactive iodine and naturally present iodine. Thus, any injected or ingested radioactive iodine concentrates within the thyroid gland. The

concentrated radioisotopes emit β-particles, which exerts local effects in the form of cell death in hyperactive thyroid tissue (1)

Different methods for calculation of ^{131}I do exist. Variable (adapted to the individual) dosing protocols of radioactive iodine have not been demonstrated to have an advantage over standard fixed dose protocols in the achievement of euthyroidism (34). The achievement of euthyroidism is successful in approximately 60-70% of the cats (34,35).

Disadvantages of ^{131}I include the potential for iatrogenic hypothyroidism and persistent hyperthyroidism (34,35). Another disadvantage is the requirement of hospitalization since the waste products (urine, feces and saliva) from the cat are radioactive for a period of time after treatment. It has been concluded that two weeks after treatment, the level of radioactivity is low enough to allow the cat to be released from the hospital. This, however, is under the conditions that waste precautions are followed and direct contact with pregnant women and young children is avoided for at least two additional weeks (36).

Long term survival can be achieved after treatment with radioiodine and a median survival time of 3 years has been reported. However, cats with a low body weight or the male sex is associated with a shorter survival time (37).

1.5. Development of azotemia in hyperthyroid cats

1.5.1 Effects of hyperthyroidism on kidney function

The physiologic effects of an overactive thyroid gland results in hemodynamic changes in the body. Many of these changes will directly or indirectly affect the kidney. The biologically active T_3 mediates a vasodilatory effect on vascular smooth muscles which will lead to a decreased peripheral vascular resistance. The renin-angiotensin-aldosterone system (RAAS) is upregulated and the renal sodium reabsorption is stimulated in response to a decreased peripheral vascular resistance in an attempt to increase the plasma volume. The increased plasma volume combined with the decreased peripheral vascular resistance increases cardiac output (13,23).

Likewise, another biological effect of thyroid hormones is the stimulation of an increase in β-adrenergic receptors, both within cardiac tissue and renal cortex, that can cause further increased activity of the sympathetic nervous system and RAAS (13,23).

The combination of the following events - decreased peripheral vascular resistance, increased plasma volume, increased cardiac output and upregulation of β-adrenergic receptors results in increases of renal blood flow, glomerular capillary hydrostatic pressure and glomerular filtration rate (13,23).

Increased levels of thyroid hormones may cause the function of the kidney appear normal due to the increase in glomerular filtration rate and renal blood flow as well as decreased creatinine

concentrations. Creatinine production is also reduced with the loss of muscle mass. Regardless of chosen treatment option, GFR decreases and creatinine concentration increases post-treatment. This means that a diagnosis of CKD might not be made until after the achievement of euthyroidism. Post-treatment azotemia is found in nearly 15-49% of the cats with hyperthyroidism and might not be detectable until 6 months after the initiation of treatment (13,14).

1.5.2 Prediction of post-treatment azotemia

The pretreatment plasma concentration of urea and creatinine have been found to be positively correlated with the development of post-treatment azotemia (14). This identical positive correlation has not been confirmed in all studies (13,38).

Symmetric dimethylarginine (SDMA) is a biomarker which is correlated with GFR and increases as GFR decreases. SDMA is not as influenced by the loss of muscle mass and expected to be a more effective renal marker when compared with creatinine. The test has shown to have a low number of false positive results but unfortunately fails to predict azotemia in most hyperthyroid cats (39).

Regarding urine parameters, mild proteinuria is commonly present in hyperthyroid cats with a subsequent resolution upon treatment of hyperthyroidism. The mechanism is not fully understood but thought be due to the hypertension and hyperfiltration in the glomerulus of the untreated hyperthyroid cat. Proteinuria can be measured as urine protein to creatinine ratio (UP/C) but the use of pre-treatment UP/C as an indicator of post-treatment azotemia is not supported (13,14).

There seems to be no difference in frequency of azotemia between cats with mild, moderate, or severe hyperthyroidism (24).

2. RESEARCH METHODS AND MATERIAL

2.1. Sample collection and study design

Clinical records from a Swedish small animal hospital "X" between September 2015 and January 2020 were reviewed retrospectively and cats diagnosed with hyperthyroidism were identified. The cats were identified as hyperthyroid based on a serum total thyroxine (TT_4) concentration greater than the laboratory reference range (>45 nmol/L) together with clinical signs and physical examination findings. A total number of 95 records were received and a total number of 30 cats were used in this study.

Inclusion criteria involved cats with hematological and biochemical blood samples collected at the time of diagnosis, detailed patient history, a complete physical examination. The record also had to involve serum creatinine concentration and serum total thyroxine concentration (TT4) measured for a period of 6-12 months after the date of diagnosis in order to identify if hyperthyroid cats developed azotemia after the initiation of treatment.

Reasons for exclusion from the study were: insufficient documentation on medical history, clinical examination and/or laboratory tests; referred from another clinic and/or only admitted for radioiodine therapy, euthanized, owner declined treatment, records could not be found in a 6-12-month period after the diagnosis.

The average age at diagnosis was 13 years and ranged from 9 to 17 years. For sex distribution, 10 (33%) of the cats were female and 20 (67%) were male: all except one male were castrated. Out of the 30 cats, 24 (80%) were of mixed breed (domestic short-haired and long-haired); other breeds included the Norwegian Forest Cat (3 cats; 10%), Burmese (1 cat; 3.3%), Maine coon (1 cat; 3.3%), Oriental Shorthair (1 cat; 3.3%).

Of all the cats, 15 (50%) were treated with Felimazole (Methimazole, tablet) and 5 (16.7%) with Apelka (Methimazole, oral solution) as their sole treatment. Hill's Prescription Diet™ y/d™ Feline was used as the sole treatment for 3 cats (10%). The remainder of the cats underwent combined treatments, in which 5 cats (16.7%) were treated with Felimazole (Methimazole, tablet) prior to radioactive iodine therapy and 2 cats (6.7%) were fed Hill's Prescription Diet™ y/d™ prior radioactive iodine therapy. Methimazole and Hill's Prescription Diet™ y/d™ were discontinued at least 1 week prior to radioactive iodine therapy. None of the cats were treated with a thyroidectomy.

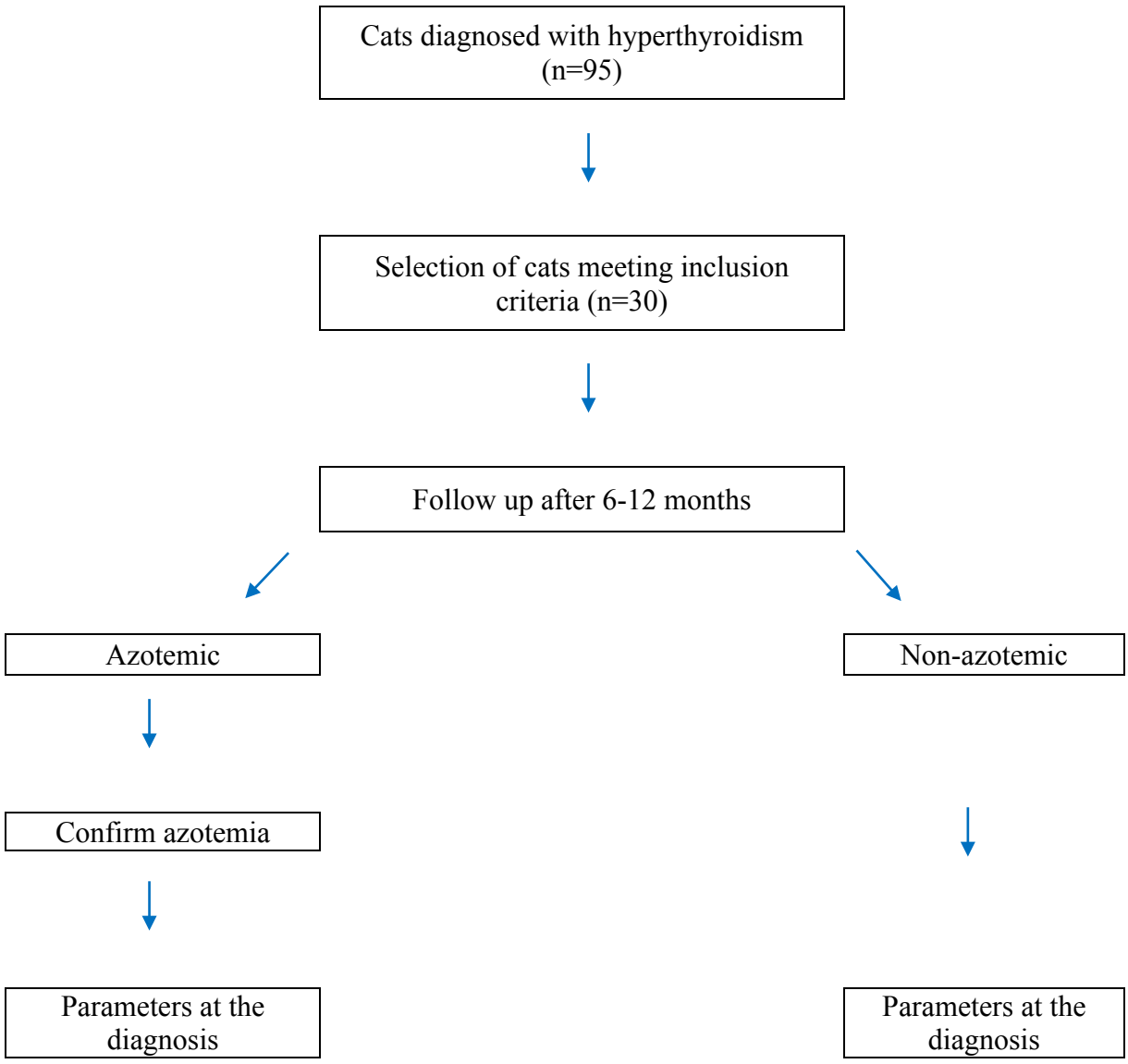

Figure 1. *Study design*

2.2. Investigated clinical parameters

Data was collected from the patient history concerning weight loss, polyphagia, vomiting, vocalizing, hyperactivity, polydipsia and polyuria, diarrhea, decreased activity, decreased appetite, dyspnea and haircoat changes. During the physical examination, the heart was auscultated for evidence of heart murmur and/or tachycardia (≥ 220 bpm). It was also documented whether the thyroid gland was palpable or not.

2.3. Determination of laboratory blood parameters

Blood was collected from *vena cephalica* and *vena saphena* to be analyzed in the laboratory of the hospital. For determination of hematological parameters, blood was collected into EDTA tubes and analyzed in the IDEXX procyte Dx. Blood was also collected into serum tubes in order to determine biochemical parameters. These serum tubes were left to stand for 20-30 minutes before they were to be centrifuged at 3500 rpm for 10 minutes. The serum tubes were then ready to be used in the Thermo Scientific Konelab Prime 30 analyzer. A fluorescence enzyme immunoassay (Tosoh AIA-360) was used to measure serum TT_4 in all cats' blood.

2.4. Development of azotemia

All of the hyperthyroid cats in this study had serum creatinine and urea measured at the time of diagnosis. These cats were followed-up after a minimum of 6 months and maximum of 12 months in order to identify if azotemia had been unmasked. Urea was not consistently followed-up on so it was determined that azotemia was defined as a serum creatinine concentration > 170.00 μmol/L on two consecutive occasions. Cats were categorized into azotemic and non-azotemic. Cats found azotemic on the first occasion but not on the second were not considered to be azotemic. Clinical signs, physical examination findings and blood parameters at diagnosis were compared between these two categories to evaluate if any of these parameters could be a predictor for the development of azotemia.

2.5. Statistical analysis

The statistical analysis was performed using the IBM SPSS Version 22. Tables were created in Microsoft Office Excel 2016. The data was analysed using descriptive statistics (frequency distributions, mean, standard error of mean, minimum and maximum values). The strength of the association between serum total thyroxine and blood parameters was measured by a Karl Pearson correlation coefficient. Paired samples t-tests were used to determine the statistical significance of creatinine, at diagnosis and after treatment. Independent sample t-tests and chi-square tests were used to determine variables associated with the development of azotemia following treatment. Results were considered to be statistically significant at * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

3. RESEARCH RESULTS

3.1 Clinical signs and physical examination findings

Clinical signs reported by owners and physical examination findings in cats with hyperthyroidism (n=30) are presented in Table 2. The most common clinical sign was weight loss (96.7%). Some of the clinical signs or physical examination findings were reported in approximately half of the cats. These included tachycardia (56.7%), a palpable thyroid gland (50%), polyphagia (46.7%), vomiting (43.3%), hair changes (43.3%) and an auscultated heart murmur (43.3%). Dyspnea (6.7%) and decreased activity (3.3%) were clinical signs reported the most infrequently.

Table 2. *Clinical signs and physical examination findings at the time of diagnosis in cats diagnosed with hyperthyroidism (n=30)*

Variable	n	Percentage (%)
Weight loss	29	96.7
Polyphagia	14	46.7
Vomiting	13	43.3
Hair changes	13	43.3
Polyuria/Polydipsia	11	36.7
Vocalizing	7	23.3
Diarrhea	6	20.0
Decreased appetite	4	13.3
Hyperactivity	3	10.0
Dyspnea	2	6.7
Decreased activity	1	3.3
Tachycardia (>220 bpm)	17	56.7
Palpable thyroid gland	15	50.0
Heart murmur	13	43.3

3.2 Biochemical and hematological blood parameters

Results of biochemical blood parameters in cats with hyperthyroidism (n=30) are presented in Table 3. The most common biochemical abnormality included high levels of liver enzymes. Alanine aminotransferase and Alkaline phosphatase were increased above the reference range by 90% and 46.7% of the cats, respectively. Hypoproteinemia and hypernatremia were present in 30% of the cats. No cats presented azotemia in regards to creatinine while blood urea nitrogen was increased above the reference range in 10 % of the cats. Creatinine was decreased below the reference range in 26.7% of the cats with the remaining 73% within the reference range. Hyperkalemia was present in 16.7% of cats. Neither calcium nor albumin was peculiarly affected nor did it have an increase or decrease of more than 6.7% in relation to the reference range.

Table 3. *Biochemical parameters at the time of diagnosis in cats diagnosed with hyperthyroidism (n=30)*

Parameter	Mean [minimum-maximum]	Std.Error of Mean	No./% above RR	No./% below RR	Unit	Reference range
Urea	9.20 [5.60-19.00]	0.58	3/10	0/0	nmol/L	4.50-13.00
Creatinine	83.93 [35.00-158.00]	5.60	0/0	8/26.7	µmol/L	60.00-170.00
TP	69.10 [50.00-88.00]	1.70	1/3.3	9/30	g/L	65.00-85.00
ALB	30.53 [23.00-41.00]	0.62	1/3.3	2/6.7	g/L	28.00-37.00
Na	155.13 [151.00-162.00]	0.51	9/30	0/0	mmol/L	147.00-156.00
K	4.33 [3.30-5.40]	0.10	5/16.7	1/3.3	mmol/L	3.50-4.70
Ca	2.49 [1.80-3.12]	0.05	2/6.7	1/3.3	mmol/L	2.00-3.00
ALT	4.61 ↑ [0.58-16.27]	0.68	27/90	-	µKAT/L	0.00-1.20
ALP	2.74 ↑ [0.40-10.30]	0.44	14/46.7	-	µKAT/L	0.00-2.10

TP= total protein, ALB= Albumin, Na= Sodium, K= Potassium, Ca= Calcium, ALT = Alanine aminotransferase, ALP= Alkaline phosphatase, RR= reference range

Results of hematological blood parameters in cats with hyperthyroidism (n=30) are presented in Table 4. The most common hematological abnormality included lymphopenia which was present in 53.3% of the cats. Leukopenia was found in 16.7 % of the cats. The other hematological parameters did not have an increase or decrease higher than 13.3% in relation to the reference range.

Table 4. *Hematological parameters at the time of diagnosis in cats diagnosed with hyperthyroidism (n=30)*

Parameter	Mean [minimum-maximum]	Std.Error of Mean	No./% above RR	No./% below RR	Unit	Reference range
Hb	12.84 [7.70-16.60]	0.37	1/3.3	3/10	g/dL)	9.80-16.20
HCT	40.82 [27.10-61.40]	1.43	2/6.7	3/10	%	30.30-52.30
MCV	43.26 [33.30-54.90]	0.96	1/3.3	2/6.7	fL	35.90-53.10
MCH	13.79 [11.00-16.80]	0.25	0/0	1/3.3	pg	11.80-17.30
MCHC	31.95 [26.40-35.30]	0.46	0/0	3/10	g/dL	28.10-35.80
WBC	10.45 [3.92-28.20]	1.03	3/10	5/16.7	x 10^9/L	5.50-19.50
NEU	7.43 [3.06-22.30]	0.90	4/13.3	0/0	x 10^9/L	2.50-12.50
SEG NEU	0.10 [0.00-2.80]	0.09	1/3.3	-	x 10^9/L	0.00-0.30
LYMPH	1.94 [0.20-7.02]	0.29	1/3.3	16/53.3	x 10^9/L	1.50-7.00
MONO	0.38 [0.00-1.37]	0.06	2/6.7	-	x 10^9/L	0.00-0.85
EOS	0.59 [0.00-1.50]	0.09	0/0	-	x 10^9/L	0.00-1.50
BASO	0.00 [0.00-0.10]	0.00	1/3.3	-	x 10^9/L	0.00-0.00
BAND NEU	0.00 [0.00-0.10]	0.00	1/3.3	-	x 10^9/L	0.00-0.00

Hb= Hemoglobin, HCT= Hematocrit, MCV= Mean corpuscular volume, MCH= Mean corpuscular hemoglobin, MCHC= Mean corpuscular hemoglobin concentration, WBC= white blood cell, NEU=Neutrophil, SEG NEU= Segmented neutrophil, LYMPH= Lymphocyte, MONO= Monocyte, EOS=Eosinophil, BASO= Basophil, BAND NEU= Band neutrophil, RR= reference range

The correlation coefficient was determined with a significance level of P = 0.05 to measure the strength of relationship between total thyroxine and blood parameters. The mean value of TT_4 was 146.79 ± 13.33 nmol/L and the mean value of blood parameters are presented in Table 3 and 4. Fig. 5-8 demonstrate the relationships measured with significant correlations. As shown by the Fig. 5, a strong negative relationship was found - the more total thyroxine increased, the more the creatinine value decreased ($p<0.01$; correlation -0.516). Fig. 6 illustrates a strong positive correlation between alkaline phosphatase and total thyroxine values. From this we can conclude that the higher the total thyroxine value, the greater the alkaline phosphatase value ($p<0.01$; correlation 0.572). As shown by Fig. 7 and 8, total thyroxine concentrations have a strong negative correlation with both mean corpuscular volume ($p<0.05$; correlation -0.40) and mean corpuscular hemoglobin ($p<0.01$; correlation -0.613).

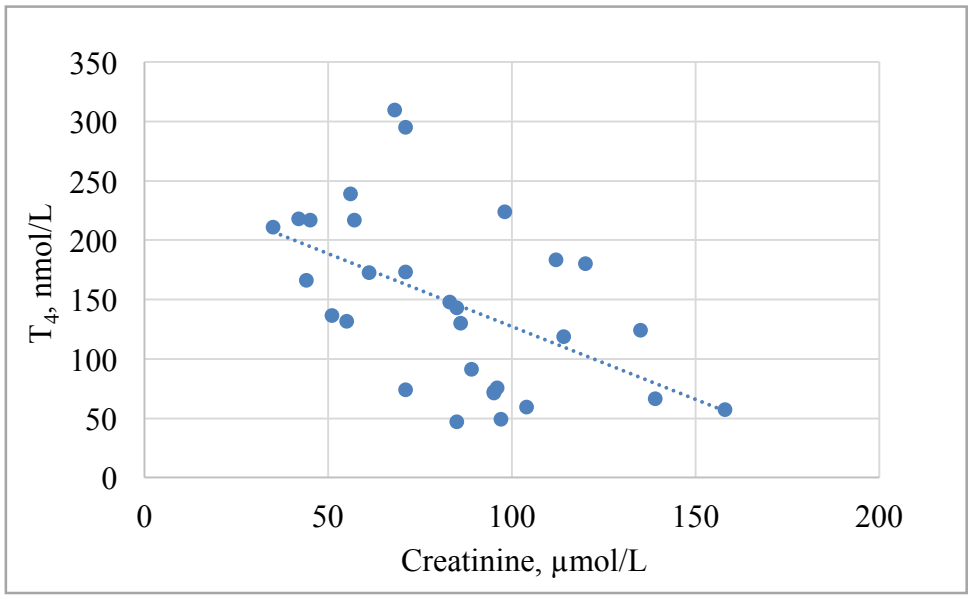

Figure 5. *The correlation between total thyroxine and creatinine in hyperthyroid cats (n=30) at the time of diagnosis, P<0.01, correlation -0.516*

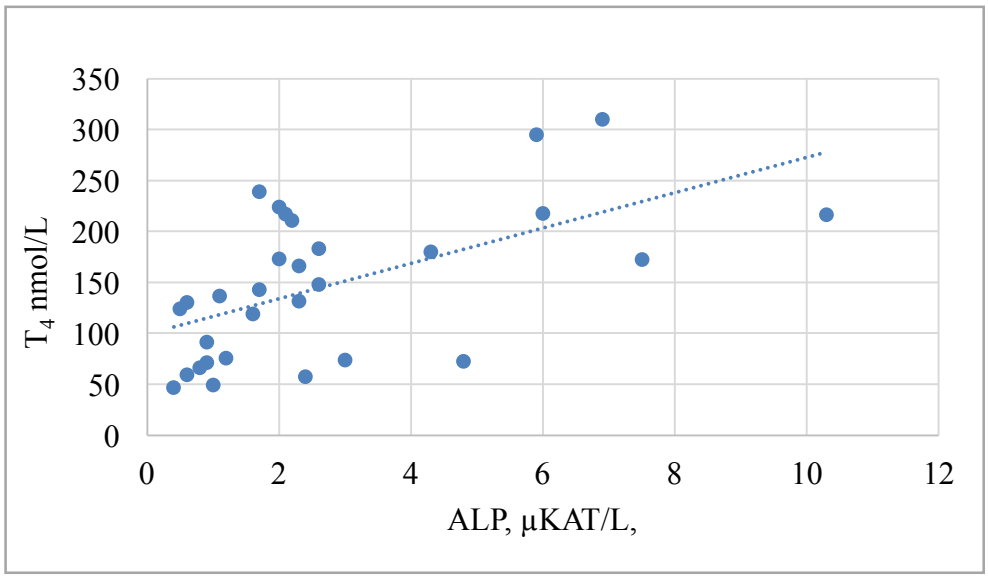

Figure 6. *The correlation between total thyroxine and alkaline phosphatase in hyperthyroid cats (n=30) at the time of diagnosis, P<0.01, correlation 0.572*

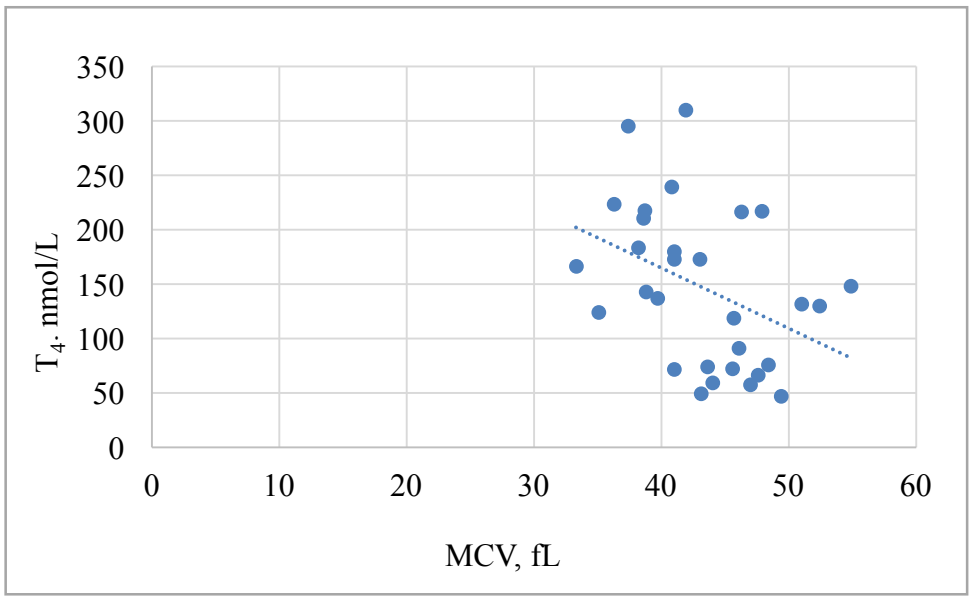

Figure 7. *The correlation between total thyroxine and mean corpuscular volume in hyperthyroid cats (n=30) at the time of diagnosis, P<0.05, correlation -0.40*

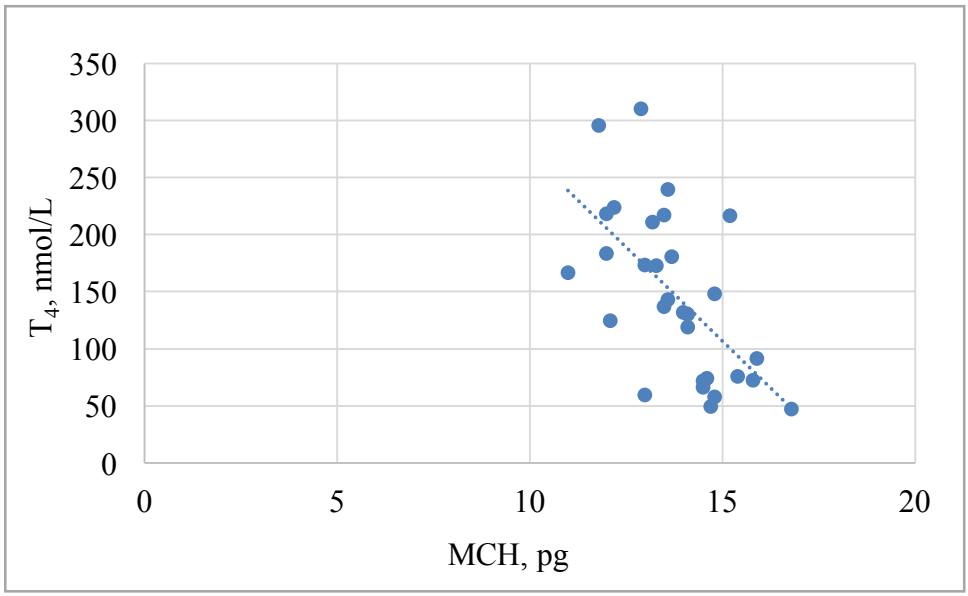

Figure 8. *The correlation between total thyroxine and mean corpuscular hemoglobin in hyperthyroid cats (n=30) at the time of diagnosis, P<0.01, correlation -0.613*

3.3 Development of azotemia

Fig. 9 demonstrates the level of creatinine at the time of diagnosis prior to treatment and 6-12 (mean = 7.53) months following the beginning of treatment. The creatinine concentration had increased in 29 (96.7%) of the cats' post-treatment. The mean value of the post-treatment concentration of creatinine was 67.4% higher than the pre-treatment concentration of creatinine ($p<0.001$).

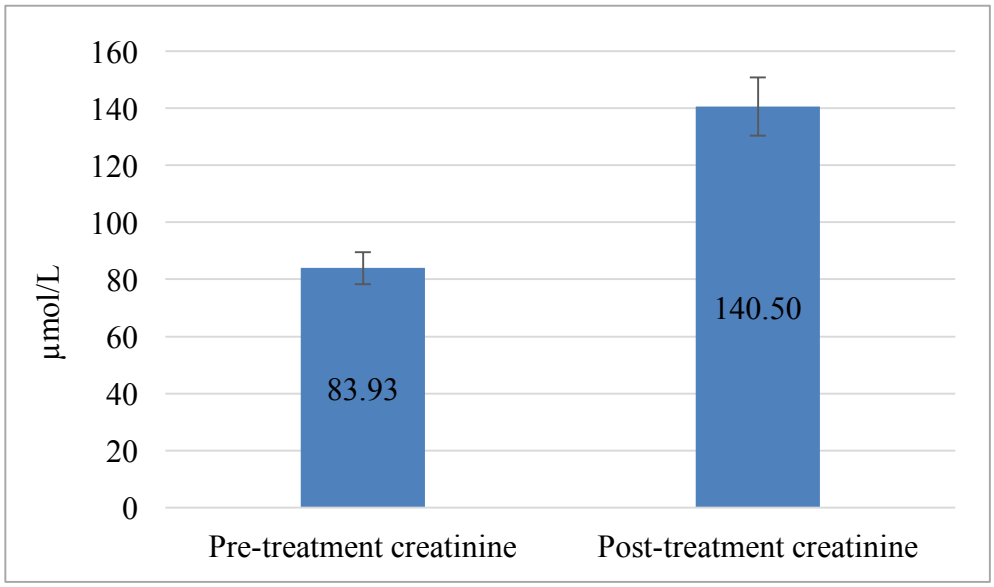

Figure 9. *Standard error of mean and mean creatinine concentration pre-treatment and post-treatment in hyperthyroid cats (n=30)*

The number of cats identified as azotemic pre-treatment and post-treatment are presented in Figure 10. Azotemia was defined as the serum creatinine concentration demonstrating levels > 170.00 µmol/L. No cats were identified as azotemic at diagnosis prior to the initiated treatment. The first follow-up was performed after an average period of 7.53 months following treatment at which eight cats (27%) were identified as azotemic. The mean creatinine concentration for these eight cats was 210.8 µmol/L. The second follow-up was performed after an average period of 12.8 months in order to confirm azotemia. Only six cats (20%) remained azotemic at the second follow-up and these six cats had a mean creatinine concentration of 229.8 µmol/L.

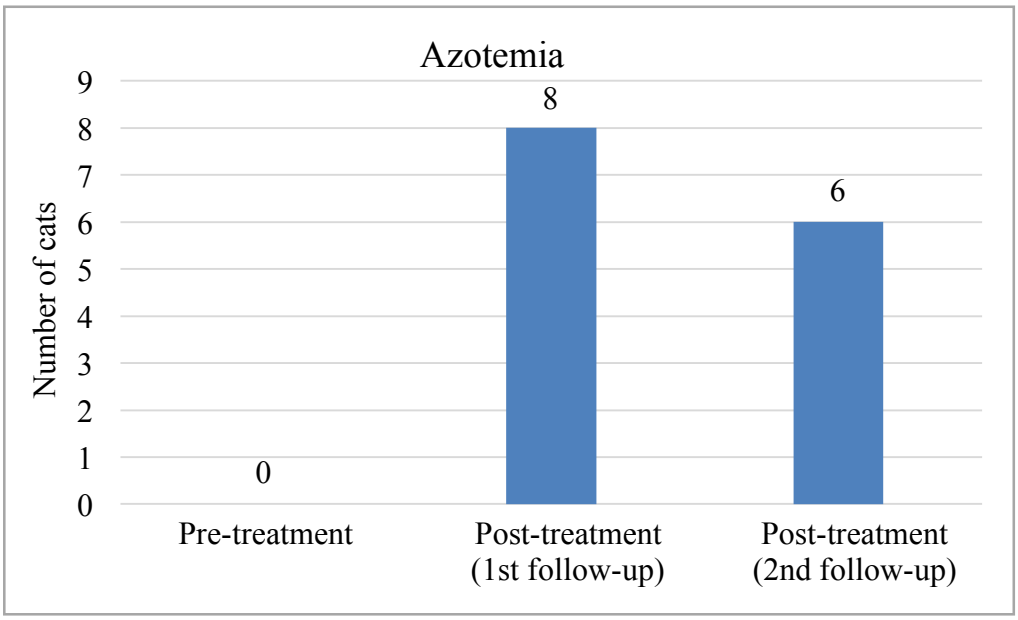

Figure 10. *Identification of number of hyperthyroid cats with azotemia*

Results of serum total thyroxine concentrations measured 6-12 (mean = 7.53) months following treatment are presented in Figure 11. Out of the 30 cats, 14 cats (46.7%) were euthyroid (TT_4=15.00-45.00 nmol/L). The hyperthyroid state (TT_4 >45 nmol/L) was present in 12 cats (40%) and 4 of the cats (13.3%) were hypothyroid (TT_4 <15 nmol/L).

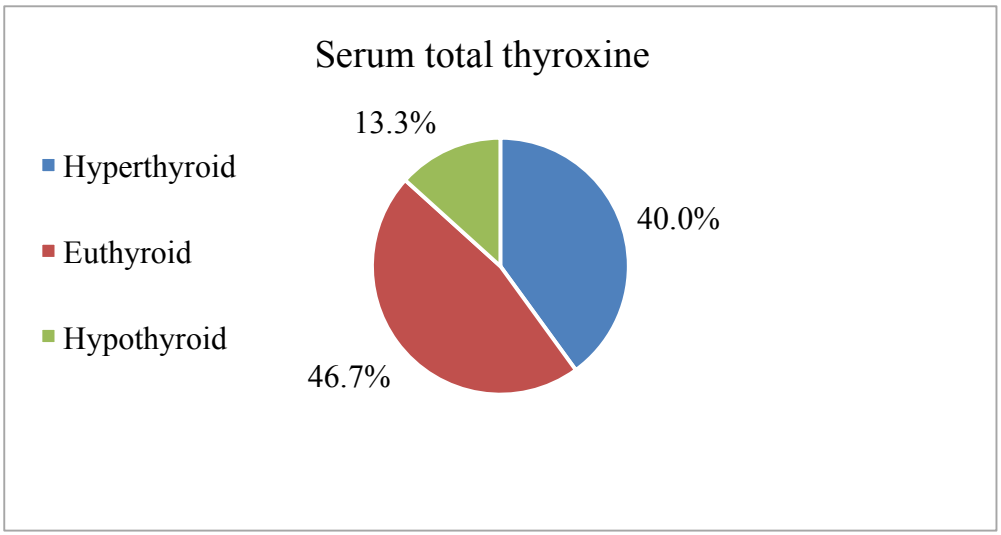

Figure 11. *Serum total thyroxine concentration after 6-12 months of treatment in hyperthyroid cats (n=30)*

Clinical signs and physical examination findings at diagnosis in azotemic (n=6) and non-azotemic (n=24) cats are presented in Figure 12. Two variables, weight loss and polyphagia had a mean difference between azotemic and non-azotemic cats which was statistically significant ($p<0.05$). A mean difference of 16.7% for weight loss was measured between azotemic and non-azotemic cats (chi-square = 4.138, df = 1, $p<0.05$). For polyphagia, a mean difference of 58.3% was measured

between azotemic and non-azotemic cats (chi-square = 6.563, df = 1, p<0.01). Other clinical signs and physical examination findings did not have a significant mean difference between azotemic and non-azotemic cats: 12.5% vomiting (chi-square = 0.305, df = 1, p>0.05), 29.2% vocalizing (chi-square = 2.283, df = 1, p>0.05), 8.4% hyperactivity (chi-square = 0.370, df = 1, p>0.05), 4.2% polydipsia/polyuria (chi-square = 0.036, df = 1, p>0.05), 4.1% diarrhea (chi-square = 0.052, df = 1, p>0.05), 4.2% decreased activity (chi-square = 0.259, df = 1, p>0.05), 4.2% decreased appetite (chi-square = 0.072, df = 1, p>0.05), 12.5% dyspnea (chi-square = 0.072, df = 1, p>0.05), 20.9% palpable thyroid gland (chi-square = 1.205, df = 1, p>0.05), 12.5% tachycardia (chi-square = 0.305, df = 1, p>0.05), 29.2% heart murmur (chi-square = 1.663, df = 1, p>0.05) and 12.5% hair changes (chi-square = 0.305, df = 1, p>0.05).

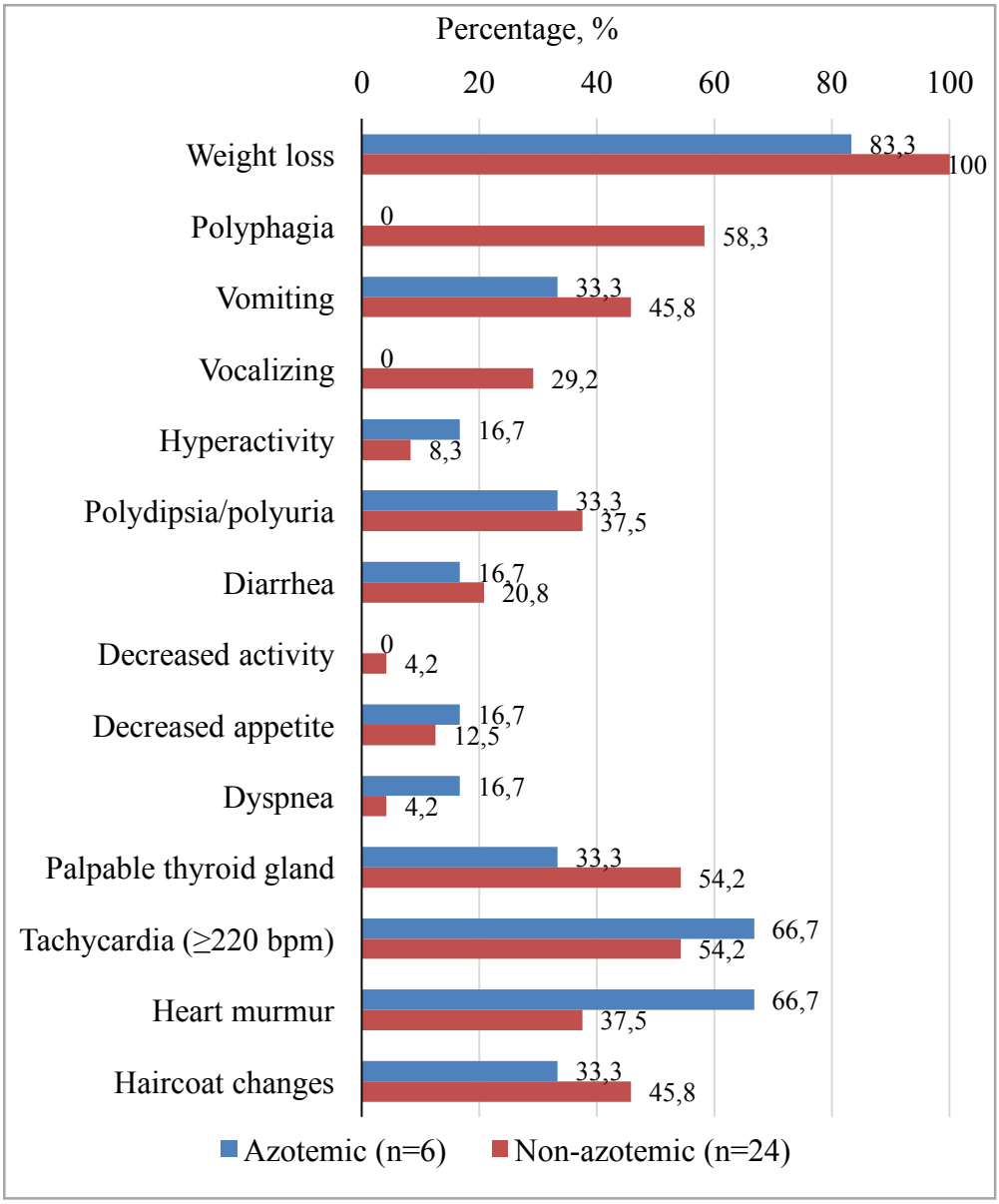

Figure 12. *Clinical signs and physical examination findings in azotemic (n=6) and non-azotemic (n=24) cats*

Blood biochemical (Fig. 13) and hematological (Fig. 14) parameters at diagnosis in azotemic (n=6) and non-azotemic (n=24) cats were analyzed. No parameters had a mean difference between azotemic and non-azotemic cats which were statistically significant. The mean difference of the hormone TT_4 was higher by 3.15% (p>0.05) in azotemic cats compared to non-azotemic. The largest mean differences of biochemical parameters between azotemic and non-azotemic cats were measured for liver and kidney function parameters. The mean difference of ALT was greater 62.33% (p>0.05) and of ALP 76.47% greater (p>0.05) in non-azotemic cats compared to azotemic. For creatinine and urea, the mean differences were 27.89% higher (p>0.05) and 20.61% higher (p>0.05), respectively, in azotemic cats compared to non-azotemic. Other biochemical parameters had very low mean difference between the investigated groups. The mean difference of TP was greater by 2.24% (p>0.05) in azotemic cats compared to non-azotemic. Mean differences were greater by 0.82% for ALB (p>0.05), by 0.51% for Na (p>0.05), by 7.07% for K (p>0.05) and by 0.4% for Ca (p>0.05) in non-azotemic cats compared to azotemic. (Fig. 13)

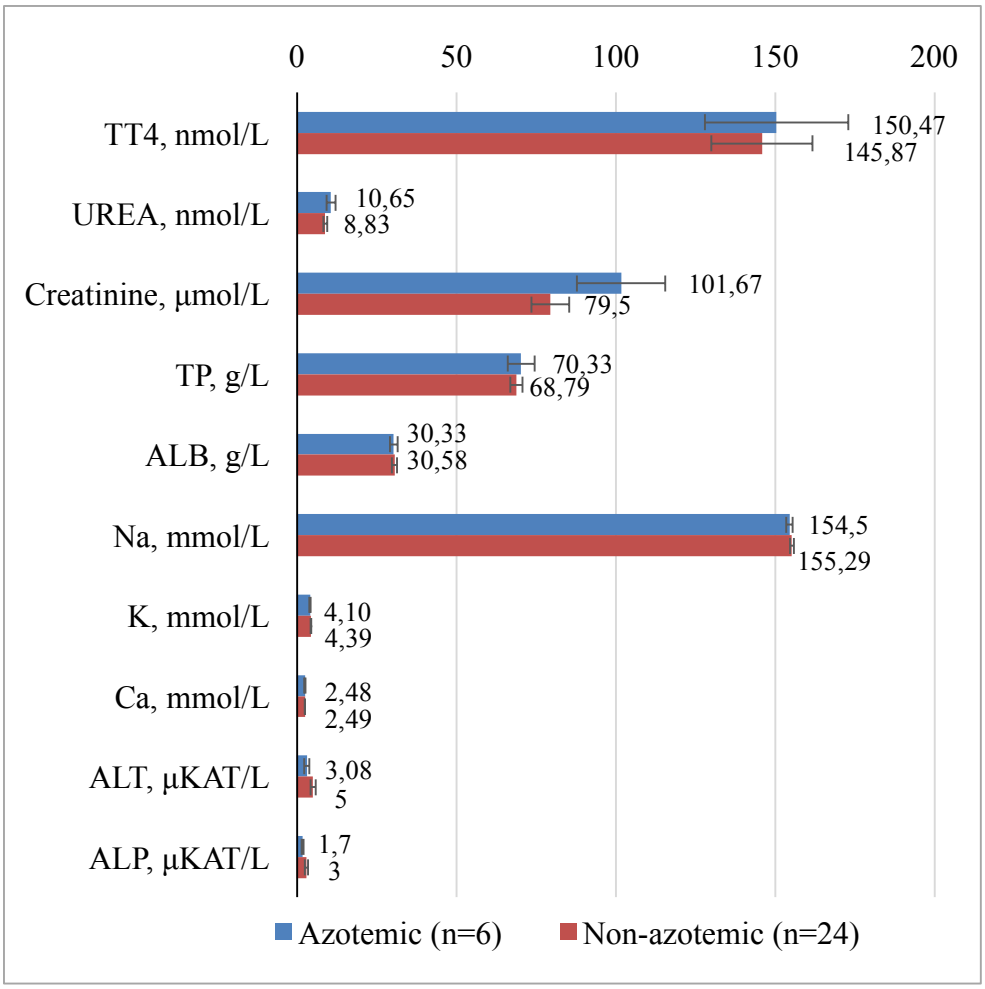

Figure 13. *Standard error of mean and mean value of total thyroxine and biochemical parameters in azotemic (n=6) and non-azotemic (n=24) cats*

TT4= Total T_4, TP= total protein, ALB= Albumin, Na= Sodium, K= Potassium, Ca= Calcium, ALT = Alanine aminotransferase, ALP= Alkaline phosphatase

The leading mean differences of hematological parameters were measured in LYMPH, MONO, NEU and EOS. The mean difference of LYMPH was greater by 154.02% (p>0.05) and of EOS greater by 85.71% (p>0.05) in non-azotemic cats compared to azotemic. For MONO and NEU, the mean difference was 75.75% higher (p>0.05) and 35.93% higher (p>0.05), respectively, in azotemic cats compared to non-azotemic. The mean difference for SEG NEU between azotemic and non-azotemic cats was not significant (p>0.05). Other hematological parameters had a very low mean difference between the investigated groups. The mean difference of HCT was higher by 2.8% and of WBC higher by 9.46% (p>0.05) in azotemic cats compared to non-azotemic. Mean differences were higher by 5.52% for Hb (p>0.05), by 4.15% for MCV (p>0.05) and by 7.86% for MCHC (p>0.05) in non-azotemic cats compared to azotemic. (Fig. 14)

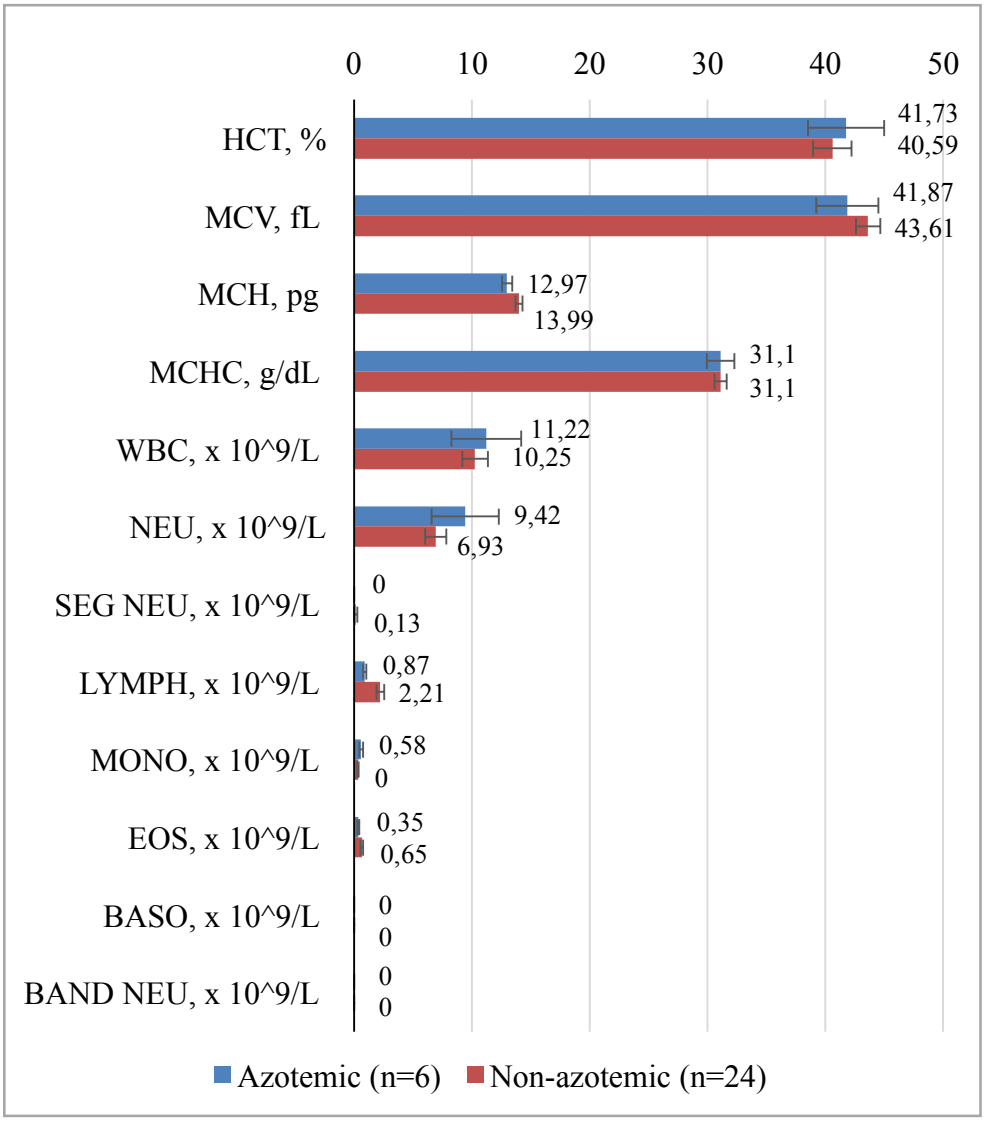

***Figure 14**. Standard errror of mean and mean value of hematological parameters in azotemic (n=6) and non-azotemic (n=24) cats*

Hb= Hemoglobin, HCT= Hematocrit, MCV= Mean corpuscular volume, MCH= Mean corpuscular hemoglobin, MCHC= Mean corpuscular hemoglobin concentration, WBC= white blood cell, NEU=Neutrophil, SEG NEU= Segmented neutrophil, LYMPH= Lymphocyte, MONO= Monocyte, EOS=Eosinophil, BASO= Basophil, BAND NEU= Band neutrophil

4. DISCUSSION OF RESULTS

The most common clinical signs, physical examination findings, biochemical and hematological parameters were identified in 30 cats diagnosed with feline hyperthyroidism. Hyperthyroid cats were followed-up with after a minimum of 6 months and maximum of 12 months in order to identify if azotemia had been unmasked. In order to remain categorized as azotemic, cats had to be azotemic on two consecutive occasions. The investigated parameters were then compared to both azotemic and non-azotemic cats to evaluate if any of these parameters could be a predictor for the development of azotemia.

According to several published studies, weight loss is the most common clinical sign and is present in 87-98% of cats with hyperthyroidism (9,10,24). That finding was supported in this study with 96.7% of cats presenting weight loss.

A palpable thyroid gland can be found in approximately 80% of cats diagnosed with hyperthyroidism (10,22,24). In this study, only 50% were found to have a palpable thyroid gland. The reason for could be that cats were diagnosed at an earlier disease stage in which the thyroid gland was not enlarged enough. Other reasons could be ectopic thyroid tissue, affected thyroid lobes have descended into the thoracic cavity or an inexperienced practitioner (22).

In the present study, the prevalence of tachycardia (56.7%), polyphagia (46.7%), vomiting (43.3%), auscultation of a heart murmur (43.3%), PU/PD (36.7%), diarrhea (15%) and dyspnea (6.7%) were in accord with a published article by Broussard et al. 1995 (10).

Hair changes (30%) were reported at a higher percentage than previous studies which is probably due to the fact that our study referred to excessive shedding patterns, unkempt coats and alopecia as hair changes while other studies presented prevalence of cats with alopecia only (9,10).

Apathetic hyperthyroidism is an unusual form of hyperthyroidism represented by decreased appetite and apathy (9). This study confirmed it as an unusual form and found a decreased appetite in 13.3% and decreased activity in 3.3% of the cats.

Hyperactivity (10%) was reported in a lower percentage than previous studies (9,10), however, vocalization, which is similar to hyperactivity, was present in 23.3% of the cats.

The most common biochemical abnormalities were increased concentrations of both ALT and ALP, by 90% and 46.7%, respectively, which is supported by Broussard et al. 1995 (10) and Petersson et al. 1983 (9). Increased liver enzyme activity may suggest liver damage but in most hyperthyroid cats the liver function is normal and liver values return to within reference range following treatment (9,10,12). A close relationship between high activity of liver enzymes and high total thyroxine concentration has been measured (10). A similar joint relationship was measured in this study in the form of a strong positive correlation between total thyroxine and ALP ($p>0.01$, correlation 0.572).

Azotemia in regards to creatinine levels were not present as in previous studies (9,10), in fact, creatinine was decreased below the reference range in 26.7% of cats. The more the total thyroxine increased, the lower the creatinine value ($p<0.01$, correlation -0.516). The reason for decreased creatinine production could be due to a large reduction in muscle mass and/or large increases of GFR (13).

Lymphopenia was present in 53.3% of the cats with hyperthyroidism and was thus the most common hematological abnormality. Both Broussard et al. 1995 (10) and Petersson et al. 1983 (9) found lymphopenia as a common hematological finding.

Petersson et al. 1983 (9) reported increased activities of MCV and MCH to occur in 44% and 18%, respectively, of hyperthyroid cats. In contrast, no increased activities of MVC and MCH were detected in this study and TT_4 had a strong negative correlation with both MCV ($p<0.05$; correlation -0.4) and MCH ($p<0.01$; correlation -0.613). A possible explanation for this finding could be concurrent diseases that mimic hyperthyroidism which can interfere with results or just simply the fact that hyperthyroidism may cause disturbances of several different organ systems which can be reflected in blood results (10).

An increase in creatinine concentration is expected to occur post-treatment as cats begin to gain weight in addition to GFR levels decreasing (13,14). Creatinine concentration was increased in 96.7% of the cats following 6-12 months of treatment. The mean creatinine concentration was 67.4% higher post-treatment compared to pre-treatment ($p<0.001$).

CKD frequently occurs concurrently with feline hyperthyroidism but the presence of azotemia is often not unmasked until following treatment. Post-treatment azotemia has been reported to occur in approximately 15-49% of hyperthyroid cats and creatinine may continue to increase for 6 months following the achievement of euthyroidism (13,14). In this study, 20% of hyperthyroid cats became azotemic. Euthyroidism was achieved in 46.7% of cats with hyperthyroidism which means many cats were insufficiently treated. A hyperthyroid state despite treatment can suggest GFR is not yet normalized sufficiently for azotemia to occur (14).

Clinical findings and blood parameters at diagnosis in azotemic (n=6) and non-azotemic (n=24) cats were compared. Two clinical findings, weight loss and polyphagia, had a statistically significant mean difference between azotemic and non-azotemic cat. Weight loss was present in 100% of the non-azotemic cats and in 83.3% of the azotemic cats which is a mean difference of 16.7% (chi-square = 4.138, df = 1, $p<0.05$). Polyphagia was present in 58.3% of the non-azotemic cats and in 0% of the azotemic cats which is a mean difference of 58.3% (chi-square = 6.563, df = 1, $p<0.01$). No research could be found on the use of clinical findings to predict azotemia but it is clear that even if a statistically significant mean difference was detected, clinical signs overlap between non-azotemic and azotemic cats which is why they cannot be used reliably. Riensche et al.

2008 (38) compared pre-treatment hematologic and biochemical blood results between cats that developed post-treatment renal insufficiency and those that did not. No significant differences were detected. Renal insufficiency involved azotemia and inadequate urine concentration. This study involved only azotemia but no significant mean differences for pre-treatment hematological and biochemical blood results between azotemic and non-azotemic cats were detected. Williams et al. 2010 (14) found urea and creatinine to be positively correlated with the development of azotemia post-treatment but it is important to remember that more than 75% of functional nephrons must be lost for a significant elevation of urea and creatinine to occur which makes them a poor sensitivity and specificity indicator (38).

CONCLUSIONS

1. The most common clinical sign or physical examination finding was weight loss (96.7%) followed by tachycardia (56.7%) and a palpable thyroid gland (50%).

2. The most common biochemical abnormalities included high activities of alanine aminotransferase and alkaline phosphatase which were increased above the reference range in 90% and 46.7%, respectively, of cats diagnosed with hyperthyroidism. The most common hematological abnormality included lymphopenia which was present in 53.3% of cats with hyperthyroidism.

3. Post-treatment azotemia was detected in 20% of the cats. A statistically significant mean difference between azotemic and non-azotemic cats was found for weight loss and polyphagia. Between the investigated groups, a mean difference of 16.7% for weight loss (chi-square = 4.138, df = 1, $p<0.05$) and of 58.3% for polyphagia (chi-square = 6.563, df = 1, $p<0.01$) was measured.

4. This study suggest that the results of pre-treatment blood parameters and clinical findings cannot be used to reliably predict the development of azotemia following treatment.

SUGGESTIONS AND RECOMMENDATIONS

1. Since pre-treatment blood parameters and clinical findings cannot be used to reliably predict the development of azotemia in hyperthyroid cats it is recommended to use a reversible treatment option (oral antithyroid drug or dietary management) to assess the renal response to treatment prior to thyroidectomy or radioiodine therapy.

2. One limitation in this study is the small number of azotemic cats. If a larger study group was included more subtle differences that may be considered insignificant in this study may become significant.

3. Older cats can have concurrent diseases which might influence the results.

4. The retrospective nature of the study is another limitation since clinical findings were limited to the completeness of medical records.

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