Universidade de Évora - Escola de Ciências e Tecnologia

Mestrado Integrado em Medicina Veterinária

Relatório de Estágio

Feline Hyperthyroidism

Inês Silva Coelho

Orientador(es) | Maria Dias
Luís Miguel Lourenço Martins
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Évora 2024

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O relatório de estágio foi objeto de apreciação e discussão pública pelo seguinte júri nomeado pelo Diretor da Escola de Ciências e Tecnologia:

Presidente	|	Sónia Lucena (Universidade de Évora)
Vogais	|	Maria Dias (Universidade de Évora) (Orientador) Maria Teresa Oliveira (Universidade de Évora) (Arguente)

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Abstract

Regarding the Master's degree in Veterinary Medicine from the University of Évora, the present report is a result of the six-month period traineeship held at Priory Veterinary Surgeons, in the United Kingdom. Structurally, it is divided into three parts. The first englobes a brief descriptive analysis of the clinical cases observed during the traineeship period. The second, corresponds to a monograph about Feline Hyperthyroidism, where, as a bibliographic revision, the following topics are addressed: anatomy and physiology of thyroid and parathyroid glands; pathophysiology and epidemiology of the disease; diagnostic and treatment approaches available; potential ways of avoiding its development; and potential comorbidities and complications associated. Finally, a clinical case accompanied by the author during the traineeship, about a hyperthyroid cat treated surgically, is presented and discussed.

Keywords: comorbidities; feline; hyperthyroidism; senior; thyroid

Resumo – Hipertiroidismo Felino

No âmbito do Mestrado Integrado em Medicina Veterinária da Universidade de Évora, o presente relatório surge no seguimento do estágio curricular de seis meses realizado no hospital Priory Veterinary Surgeons, no Reino Unido. Estruturalmente, este encontra-se dividido em três partes. Na primeira é realizada uma breve análise descritiva dos casos clínicos observados durante o período do estágio. A segunda, apresenta uma monografia sobre o tema Hipertiroidismo Felino, onde, em forma de revisão bibliográfica, são abordados a anatomia e fisiologia da tiroide e da paratiroide; a patofisiologia e epidemiologia da doença; abordagens diagnóstica e terapêutica; como prevenir o seu desenvolvimento; e as possíveis comorbidades e complicações associadas. Por fim, é apresentado e discutido um caso clínico acompanhado pela estagiária durante o estágio sobre um gato com hipertiroidismo que foi tratado cirurgicamente.

Palavras-chave: comorbilidades; felino; hipertiroidismo; sénior; tiroide

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List of acronyms and abbreviations

^{123}I or ^{131}I: Isotopes of radioactive iodine

$^{99m}TcO_4^-$: Pertechnetate

ACP: Acepromazine

AFAST: Abdominal focused assessment with sonography for trauma

AHC: Animal health certificates

ALP: Alkaline phosphatase

ALT: Alanine aminotransferase

ANA: Antinuclear antibodies

AST: Aspartate aminotransferase

ATP: Adenosine triphosphate

BAR: Bright, alert and responsive

BID: Twice daily

BOAS: Brachycephalic obstructive airway syndrome

BP: Blood pressure

BPA: Bisphenol A

BUN: Blood urea nitrogen

Ca^{2+}: Calcium

CaG: Calcium gluconate

CaGP: Calcium gluconate powder

cAMP: Cyclic adenosine monophosphate

CBC: Cell blood count

CEIAs: Chemiluminescent enzyme immunoassays

CHF: Congestive heart failure

CKD: Chronic kidney disease

CRT: Capillary refill time

CT: Computed tomography

cTSH: Canine-specific TSH assay

DD: Differential diagnoses

DIT: Diiodotyrosine

DM: Diabetes *mellitus*

EIA: Enzyme immunoassay

ELISA: Point-of-care enzyme-linked immunosorbent assay

EPI: Exocrine pancreatic insufficiency

FeC: Feline comprehensive panel

FEL4: Thin cat A panel

FHT: Feline hyperthyroidism

Fi: Absolute frequency

Fip: Absolute frequency by species

Fr (%): Relative frequency

fT4: Free thyroxine

fTSH: Feline-specific TSH assay

GFR: Glomerular filtration rate

Gi: Inhibitory G proteins

GI: Gastrointestinal

Gs: Stimulatory G proteins

HCM: Hypertrophic cardiomyopathy

HPTa: Hypothalamic-pituitary-thyroid axis

HR: Heart rate

HT: Hyperthyroidism

I^-: Iodide

I_2: Iodine

IBD: Inflammatory bowel disease

iCa: Ionized calcium

IH: Iatrogenic hypothyroidism

IM: Intramuscular

IMHA: Immune-mediated haemolytic anaemia

IRIS: International Renal Interest Society

ITP: Immune-mediated thrombocytopenia

IV: Intravenous

LDLs: Low density lipoproteins

MIT: Monoiodotyrosine

MM: Mucous membranes

MMI: Methimazole

n: Total of cases

NAD: Nothing abnormal discovered

NIS: Na+/I- symporter

NTI: Non-thyroidal illness

PBDEs: Polybrominated diphenyl ethers

PE: Physical examination

PLO: Pluronic lecithin organogel

PO: oral route (from latin, *per os)*

PO_4^{3-}: Phosphate

PTH: Parathyroid hormone

PTU: Propylthiouracil

PU/PD: Polyuria/polydipsia

PVS: Priory Veterinary Surgeons

QoL: Quality of life

RBF: Renal blood flow

RI: Reference interval

RIA: Radioimmunoassay

RR: Respiratory rate

rT3: Reverse triiodothyronine

SBP: Systolic blood pressure

sCr: Serum creatinine

SDMA: Symmetric dimethylarginine

SEFEU: Senior wellness feline panel

SHIM-RAD: Severe, Huge, Intrathoracic, Multifocal disease, Refractory to antithyroid drugs

SID: Once daily

SQ: Subcutaneous

T/S.r: Thyroid; salivary ratio

T3: Triiodothyronine

T4: Thyroxine

TFAST: Thoracic focused assessment with sonography

TP: Thyroperoxidase

TRH: Thyrotropin-releasing hormone

TSH: Thyroid-stimulating hormone or Thyrotropin

TSIs: Thyroid-stimulating immunoglobulins

TT4: Total thyroxine

TTR: Transthyretin

UK: United Kingdom,

USG: Urine specific gravity

UTI: Urinary tract infection

WFI: Water for injection

I. Introduction

In order to conclude the Master's degree in Veterinary Medicine from the University of Évora, the present report has been developed following the traineeship about clinical and surgical medicine in small animals, at Priory Veterinary Surgeons (PVS), in the United Kingdom (UK), under the Dr. Margarida Correia Dias' internal guidance, the professor Luís Martins' internal co-guidance and the external supervision of the Dr. Stephen Carter.

The mentioned traineeship started on the 1st of October 2022 and finished on the 31st of March 2023, making a total of six months and a workload of approximately 972 hours. During the six-month period, the author was able to shadow the clinicians freely. Most of the mornings were spent assisting on the surgical procedures while the afternoons were dedicated to observing and helping with internal medicine consults; the former, being the area that most attracted the trainee's interest.

Throughout the curricular training period, the student was constantly encouraged to be involved in both surgical and internal medicine areas. That allowed her to develop clinical reasoning and to deepen the theorical and practical knowledge acquired previously, in addition to prepare her for the reality of the veterinary labour market.

Structurally, this report is divided into three parts. The first comprises a brief descriptive analysis of the clinical cases observed by the author during the six-month period. The second, corresponds to a bibliographic revision about Feline Hyperthyroidism (FHT), whereas the last part includes a presentation and discussion of one clinical case accompanied by the trainee, about a hyperthyroid cat submitted to a thyroidectomy.

II. Traineeship report

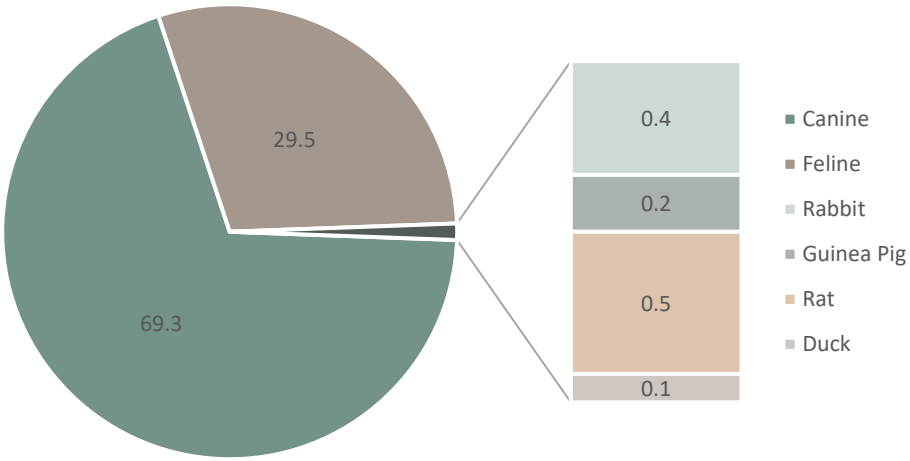
The following traineeship report represents a descriptive analysis of the cases observed and accompanied by the author during the six-month period at PVS. Primarily, the data is divided into five categories, including preventive medicine, clinical medicine, surgical medicine, imaging procedures and medical procedures, which are then divided into subcategories. Such information is visually organized into graphics and tables with the absolute frequency by species (Fip), the absolute frequency (Fi) (i.e., the sum of the Fip), and the relative frequency [Fr (%)] in representation of the percentage of Fi in the totality of the cases (n).

Please note that the total number of the reported cases does not reflect the true inflow of the practice as not every patient that visited PVS was recorded, because multiple consults and procedures happen at the same time throughout the working day. Besides it should be considered that animals with multiple problems or submitted to multiple procedures were included in more than one category and subcategory.

1. Case distribution by species and clinical areas

Statistically evaluating the distribution of the animals presented to the practice, there were

1034 in total within the six-month period. The overwhelming majority of patients were dogs (*Canis lupus familiaris*) and cats (*Felis catus*), representing 69.3% (n = 717) and 29.50% (n = 305) of the species observed, respectively. Of the remaining, five patients were domestic rats (*Rattus norvegicus*), four were rabbits (*Oryctolagus cuniculus domesticus*), two were guinea pigs (*Cavis porcellus*), and one a duck (*Anas platyrhynchos domesticus*) (Graphic 1).



Graphic 1 *– Distribution of the animals presented to the practice by patient species, expressed in Fr (%)*

Regarding the distribution of the observed cases illustrated in Table 1, cases related to clinical medicine were the most frequent (36.4%%), followed by those of surgical medicine (21.8%) and of preventive medicine (19.6%). Of the remaining 22.2%, 159 (12.1%) imaging procedures and 131 (10.1%) medical procedures were also recorded.

Table 1 *– Distribution of the observed cases by clinical area and patient species*

Clinical area	Fip canine	Fip feline	Fip exotic	Fi	Fr (%)
Preventive medicine	152	104	0	256	19.6
Clinical medicine	342	129	4	475	36.4
Surgical medicine	203	77	5	285	21.8
Imaging procedures	106	52	1	159	12.1
Medical procedures	89	39	3	131	10.1
Total	892	401	13	1306	100.0

In all clinical areas canine was the specie with the greatest representation, while the category of exotics, which includes the rabbits, guinea pigs, domestic rats and the duck, was the least.

It is worth nothing that the number of animals presented to the practice (n=1034) is less than the recorded cases (n=1306) because multiple patients were directed to more than one clinical area.

2. Preventive medicine

The category of preventive medicine includes six-month health checks, completion of animal health certificates (AHC), internal and external deworming, microchipping and vaccination (Table

2). Overall, the canine species is the one with the greatest representation in this category, in opposition to cases in relation to exotics, which were not registered.

Table 2 *– Distribution of the cases related to preventive medicine by procedure and patient species*

Preventive Medicine	Fip canine	Fip feline	Fi	Fr (%)
AHC completion	5	0	5	2.0
Internal and external deworming	19	17	36	14.1
Microchipping	2	26	28	10.9
Vaccination	101	57	158	61.7
6-Month health check	25	4	29	11.3
Total	152	104	256	100.0

Since 2021, in the UK, owners who want to travel with their dog, cat or ferret to a European Union country or Northern Ireland need to contact the practice to obtain an AHC. This certificate, with microchip information and vaccination history, allows their pet to travel to such destinations (Department for Environment, 2023; *Taking your pet dog, cat or ferret abroad*, [s.d.]). During the six-month period, five (2.0%) AHC's were issued, all for dogs.

Internal and external parasite control methods are an important aspect of the preventive medicine. At PVS, these are also included in the pet preventive plan, which means most of the adult dogs and cats receive their dewormers every six months, including imidacloprid and moxidectin, and praziquantel. Imidacloprid and moxidectin administered monthly ensure protection against fleas, lice, mite, heartworm, gastrointestinal nematodes and lungworm; whereas praziquantel is used against tapeworm in a dosage rate of 5 mg/kg every six months. During spring and summer, the animals covered by the plan receive a collar permeated with flumethrin and imidacloprid as well, which offers protection against ticks, besides also having anti-flea properties. Once applied around the animal's neck its effect lasts seven to eight months (*Seresto Flea and Tick Control collar*, 2015). For animals that develop side effects to the options already mentioned or whose owners have other preferences, tablets with febantel, praziquantel and pyrantel embonate; or praziquantel and pyrantel embonate; or with milbemycin oxime and praziquantel may be alternative internal dewormers. Chewable tablets with lotilaner are usually presented as a substitute to imidacloprid and moxidectin, despite targeting only fleas and ticks. Despite the overwhelming majority of animals presented at PVS being dewormed routinely, the percentage of the registered cases is relatively low (14.1%; n=36) (Table 2) because most owners are able to deworm their animals at home and only the ones performed in consult were counted.

Preventive medicine also comprises microchipping, which is crucial to ensure animals' safety and to increase the likelihood of being reunited with their family in the event of going missing. Besides, this allows owners to be held responsible in the event of animal abandonment. According to Table 2, of the 10.9% (n=28) cases regarding microchipping, the overwhelming majority were cats (n=26) with only two microchips applied to dogs. While dogs microchipping has been compulsory since 2016 in the UK (*Compulsory dog microchipping comes into effect*, 2016), this has only become mandatory for cats in March of the present year, allowing until June 2024 for

owners to microchip their cats (*Treasured pets now safer as microchipping for cats becomes compulsory*, 2023). Such legislation might explain the increased number of cats microchipped in relation to dogs. Most of the cats' microchips were applied at the time of neutering while they were under general anaesthesia.

Representing 61.7% of the preventive medicine recorded cases, 158 vaccinations were administered during the traineeship. Animals' immunization is crucial in order to prevent them from developing major contagious diseases that otherwise would threaten their lives. Furthermore, from the public health point of view, it helps decreasing the incidence of zoonoses. At PVS, puppies are vaccinated at eight weeks against the canine parvovirus type 2 and four strains of *Leptospira* (Novibac® L4). Despite being considered a non-core vaccine (i.e., may be used in those dogs or cats whose risk of infection is greater due to their lifestyle or geographical location), in the UK, L4 is seen by veterinarians as essential for dogs (i.e., core vaccine) (Day, 2017), therefore, all the dogs tend to receive this vaccine. Two weeks later they receive a core-vaccine called Novibac® DHP that provides immunisation against canine distemper virus, canine adenovirus and canine parvovirus. At 12 weeks, exactly four weeks after the first dose, Novibac® L4 must be administered again. From the first annual booster onwards, Novibac® DHP is given every three years whereas Novibac® L4 is annual. Depending on the owners' preferences, dogs can also receive an annual booster of Novibac® KC non-core vaccine, against *Bordetella bronchiseptica and* canine parainfluenza. In turn, kittens receive their first core vaccine at eight to nine weeks of age against feline parvovirus, feline herpesvirus type 1 and feline calicivirus, called Novibac® Tricat Trio. At the same time, they can receive the non-core vaccine against feline leukaemia (Novibac® FeLV). Three to four weeks later a second set of the same vaccines is administered, which is equally repeated at the first annual booster. Adult cats are immunized every three years with Novibac® Tricat Trio and Novibac® FeLV and every two years with Novibac® Ducat vaccine, which only contains feline herpesvirus type 1 and feline calicivirus. In the UK, small animals are only required to be vaccinated against the rabies virus in the event of leaving the country on holidays (*Bringing your pet dog, cat or ferret to Great Britain*, [s.d.]), unlike Portugal where it is compulsory to vaccinate all dogs against this virus (*Portaria n.º 264/2013 | DR*, [s.d.]).

Finally, at PVS most patients are under a pet preventive health plan that includes health checks every six months. These are important because they allow routine assessment of patients and also increase the likelihood of diagnosing early signs of illness that owners would otherwise not recognise as concerning. Such consults represent 11.3% (n=29) of the registered cases related to preventive medicine.

3. Clinical medicine

The cases regarding clinical medicine were subcategorized into 16 specialities (Table 3). Of them, dermatology and allergology, with 72 (15.2%) records, was the area with the greatest representation. Also, above 10% of the clinical cases, are those of stomatology and odontology (13.1%; n=62) and gastroenterology (11.2%; n=53). In opposition, the least frequent cases were

related to haematology and immunology (0.4%; n=2).

In this category, albeit non-uniformly, all canine, feline and exotics are represented. The reduced number (n=4) of clinical medicine cases recorded in exotics, is explained by the fact that very few exotic patients were presented to the practice during the six-month traineeship.

***Table 3** - Distribution of the cases related to clinical medicine by specialty and patient species*

Clinical Medicine	Fip canine	Fip feline	Fip exotic	Fi	Fr (%)
Cardiology	24	10	0	34	7.2
Dermatology and allergology	59	12	1	72	15.2
Endocrinology	4	12	0	16	3.4
Gastroenterology	37	15	1	53	11.2
Haematology and immunology	2	0	0	2	0.4
Infectiology and parasitology	17	10	0	27	5.7
Laryngology, rhinology and pulmonology	18	6	2	26	5.5
Neurology	10	1	0	11	2.3
Oncology	31	3	0	34	7.2
Ophthalmology	25	5	0	30	6.3
Orthopaedics	33	9	0	42	8.9
Stomatology and odontology	39	23	0	62	13.1
Theriogenology	9	1	0	10	2.1
Toxicology	10	0	0	10	2.1
Traumatology and emergency	8	4	0	12	2.5
Urology	16	18	0	34	7.2
Total	342	129	4	475	100.0

3.1. Cardiology

Cardiology is the area of clinical medicine responsible for the diagnosis and treatment of cardiovascular disorders, including the ones affecting the heart and blood vessels. As illustrated in Table 4, cardiac disease was only encountered in dogs and cats, with the former being the specie most commonly affected.

Myxomatous mitral valve disease represents almost 50% of the cardiac cases recorded. This was also the most prevalent disorder in dogs (n=14). In turn, cats suffered more from hypertrophic cardiomyopathy (HCM) (n=8), which was the second most frequent cardiac disorder (26.5%; n=9) at PVS. Other than that, three (8.8%) cases of dilated cardiomyopathy, all in dogs were identified. Both of the species are representative of congestive heart failure (CHF), that was the third most frequent (14.7%; n=5) cardiac disease encountered in the patients assessed.

***Table 4** - Distribution of the cases related to cardiology by disorder and patient species*

Cardiology	Fip canine	Fip feline	Fi	Fr (%)
CHF	3	2	5	14.7
Dilated cardiomyopathy	3	0	3	8.8
HCM	1	8	9	26.5
Left atrial enlargement	3	0	3	8.8

Myxomatous mitral valve disease	14	0	14	41.2
Total	24	10	34	100.0

3.2. Dermatology and allergology

The category of dermatology and allergology comprises the observed cases related to disorders of the skin and respective annexes, including allergy reactions.

Regarding the distribution of the cases (Table 5), external otitis was the most prevalent skin condition observed (16.7%; n=12), followed by contact dermatitis and pyoderma, which were found in 10 cases each (13.9% each), by skin laceration (12.5%; n=9) and by atopic dermatitis (11.1%; n=8). Of the remaining observed diseases, the least represented were greasy seborrhoea and lip fold dermatitis, existing one case of each (1.4% each).

Regarding the patient species, external otitis was also the most prevalent (n=12) in dogs, while a third (n=4) of the skin disorders developed by cats were cutaneous abscesses. Of the exotic species presented to the practice, only a guinea pig had skin problems, due to excessive greasy gland's secretion which led to the development of greasy seborrhoea.

Table 5 *- Distribution of the cases related to dermatology and allergology by disorder and patient species*

Dermatology and allergology	Fip canine	Fip feline	Fip exotic	Fi	Fr (%)
Atopic dermatitis	7	1	0	8	11.1
Contact dermatitis	9	1	0	10	13.9
Cutaneous abscesses	2	4	0	6	8.3
Ear polyps	2	0	0	2	2.8
Eosinophilic granuloma complex	0	2	0	2	2.8
External otitis	12	0	0	12	16.7
Flea allergy dermatitis	1	0	0	1	1.4
Food allergy dermatitis	3	0	0	3	4.2
Greasy seborrhoea	0	0	1	1	1.4
Lip fold dermatitis	1	0	0	1	1.4
Periocular dermatitis	1	2	0	3	4.2
Pododermatitis	4	0	0	4	5.6
Pyoderma	8	2	0	10	13.9
Skin laceration	9	0	0	9	12.5
Total	59	12	1	72	100.0

3.3. Endocrinology

Endocrinology is the area of clinical medicine responsible for the diagnosis and treatment of disorders resultant of the endocrine glands' dysfunction. This area represents only 3.4% (n=16) of the total cases recorded regarding clinical medicine.

Half (n=8) of the endocrine cases were of diabetes *mellitus* (DM), followed by hyperthyroidism (HT) (31.3%; n=5). Addison's disease and Cushing's disease were the least common disorders in this subcategory, with one (6.3%) and two (12.5%) cases respectively, both in dogs. Interestingly, the feline species was the one with the greatest representation, regarding that three

quarters (n=12) of the registered cases were found in cats, of which seven developed diabetes and five HT (Table 6).

***Table 6** - Distribution of the cases related to endocrinology by disorder and patient species*

Endocrinology	Fip canine	Fip feline	Fi	Fr (%)
Addison's disease	1	0	1	6.3
Cushing's disease	2	0	2	12.5
DM	1	7	8	50.0
HT	0	5	5	31.3
Total	4	12	16	100.0

3.4. Gastroenterology

The sub-category of gastroenterology comprises the disorders affecting the gastrointestinal (GI) tract, liver, pancreas and gallbladder.

Of the 53 recorded cases in Table 7, anal glands impaction or infection and foreign body ingestion were the most prevalent ones, being each represented in eight cases (15.1%), mostly in dogs. Next, both dietary indiscretion and pancreatitis were recorded six times, which together represent 22.6% (n=12) of the gastroenterological cases. Cholelithiasis, oesophageal stricture, megacolon and pyloric stenosis were diagnosed only once (1.9%).

***Table 7** - Distribution of the cases related to gastroenterology by disorder and patient species*

Gastroenterology	Fip canine	Fip feline	Fip exotic	Fi	Fr (%)
Anal glands impaction or infection	8	0	0	8	15.1
Cholelithiasis	0	1	0	1	1.9
Colitis	2	0	0	2	3.8
Dietary indiscretion	6	0	0	6	11.3
Oesophageal stricture	1	0	0	1	1.9
Faecaloma	0	3	0	3	5.7
Foreign body ingestion	7	1	0	8	15.1
Gastric dilatation	2	0	0	2	3.8
Gastritis	2	3	0	5	9.4
Haemorrhagic gastroenteritis	4	0	0	4	7.5
Ileus	1	0	1	2	3.8
Inflammatory bowel disease	1	2	0	3	5.7
Megacolon	0	1	0	1	1.9
Pancreatitis	2	4	0	6	11.3
Pyloric stenosis	1	0	0	1	1.9
Total	37	15	1	53	100.0

Regarding the canine specie, the most prevalent disorder was related to anal glands, followed by haemorrhagic gastroenteritis (n=4). In turn, cats were mostly diagnosed with pancreatitis (n=4), faecaloma (n=3) and gastritis (n=3). Besides, a rabbit was presented to the practice with signs of ileus.

3.5. Haematology and immunology

Regarding the haematology and immunology clinical area, only two cases were observed. One of immune-mediated haemolytic anaemia (IMHA) and one of immune-mediated thrombocytopenia (ITP), both in dogs (Table 8), and which required blood transfusions. The first case was continuously followed by the author and the patient was really well medically managed and made a full recovery.

It is worth nothing that for this area, only animals presenting primary haematologic disorders and/or coagulopathies were considered.

***Table 8** - Distribution of the cases related to haematology and immunology by disorder and patient species*

Haematology and immunology	Fip canine	Fi	Fr (%)
IMHA	1	1	50.0
ITP	1	1	50.0
Total	2	2	100.0

3.6. Infectiology and parasitology

Regarding the cases related to infectiology and parasitology (n=27), the majority were associated with Giardia spp. infection (40.7%; n=11) and flea infestation (33.3%; n=9) (Table 9).

Two (7.4%) cases of feline infectious peritonitis, whose treatment was not pursued, and two (7.44%) cases of kennel cough in dogs were also observed. In opposition to Portugal, leishmaniosis is not a common disease in the UK. According to the veterinarians at PVS, usually the patients seen with leishmaniosis are the ones adopted from a European country, which was the case of the infected dogs observed during the traineeship. Other than that, faecal analysis revealed an overgrowth of *Clostridium perfringens* in a cat with loss of weight and profuse diarrhoea for weeks (3.7%).

It is worth nothing that for this area, only animals presenting primary infections were considered.

***Table 9** - Distribution of the cases related to infectiology and parasitology by disorder and patient species*

Infectiology and parasitology	Fip canine	Fip feline	Fi	Fr (%)
Clostridiosis	0	1	1	3.7
Feline infectious peritonitis	0	2	2	7.4
Pulicosis	5	4	9	33.3
Giardiasis	9	2	11	40.7
Kennel cough	2	0	2	7.4
Leishmaniosis	2	0	2	7.4
Total	18	9	27	100.0

3.7. Laryngology, rhinology and pulmonology

Laryngology, rhinology and pulmonology is the area of clinical medicine responsible for the diagnosis and treatment of disorders of the respiratory system, affecting the larynx, the nose and lungs. This area represents 5.5% (n=26) of the total cases recorded regarding clinical medicine.

Approximately 35% (n=9) of the problems affecting the respiratory system (Table 10) were related to the brachycephalic obstructive airway syndrome (BOAS), being elongated soft palate diagnosed six (23%) times and stenotic nares four (15.4%). Likewise, upper respiratory tract infections represent 19.2% (n=5) of the registered cases and the presence of nasopharyngeal foreign bodies 15.4% (n=4). Furthermore, three (11.5%) cases of bronchopneumonia, two (7.7%) of reverse sneezing, one (3.8%) of bronchitis, and one (3.8%) of rhinitis were recorded.

While respiratory problems were mostly caused by elongated soft palate in dogs, cats were particularly affected by grass blades lodged in the nasopharynx (n=3). In turn, the two only records in exotics are with regard to two rats presented to the clinic with signs of upper respiratory tract infection.

Table 10 *- Distribution of the cases related to laryngology, rhinology and pulmonology by disorder and patient species*

Laryngology, rhinology and pulmonology	Fip canine	Fip feline	Fip exotic	Fi	Fr (%)
Bronchitis	1	0	0	1	3.8
Bronchopneumonia	3	0	0	3	11.5
Elongated soft palate	6	0	0	6	23
Nasopharyngeal foreign body	1	3	0	4	15.4
Reverse sneezing	2	0	0	2	7.7
Rhinitis	1	0	0	1	3.8
Stenotic nares	4	0	0	4	15.4
Upper respiratory tract infection	1	2	2	5	19.2
Total	18	6	2	26	100.0

3.8. Neurology

The sub-category of neurology includes disorders where animal's nervous system was somewhat affected, either due to dysfunction of the brain, spinal cord or peripheral nerves.

Of the eleven neurologic cases observed in Table 11, only the Horner's syndrome was diagnosed in the feline specie. Of the remaining, all in dogs, the most common were canine cognitive dysfunction and idiopathic epilepsy (36.4%; n=4 each). Only one case of laryngeal paralysis and one of meningitis (9.1% each) were recorded, otherwise.

Table 11 *- Distribution of the cases related to neurology by disorder and patient species*

Neurology	Fip canine	Fip feline	Fi	Fr (%)
Canine cognitive dysfunction	4	0	4	36.4
Horner's syndrome	0	1	1	9.1
Idiopathic epilepsy	4	0	4	36.4
Laryngeal paralysis	1	0	1	9.1
Meningitis	1	0	1	9.1
Total	10	1	11	100.0

3.9. Oncology

Of all the clinical medicine cases, oncology is one of the least represented areas, with a total

of 34 cases (7.2%) observed.

As observed in Table 12, apart from the diagnosed benign tumours (i.e., cutaneous histiocytoma, lipomas, perianal adenoma and trichoblastomas), which together represent 58.8% of the registered cases, hemangiosarcoma (14.7%; n=5) and alimentary lymphoma (11.8%; n=4) were the most prevalent oncologic disorders. The former was only seen in dogs, while the latter affected one dog and three cats during the period of the traineeship. Otherwise, a severe case of cutaneous lymphoma, a case of mammary gland tumour, one of mast cell tumour, one of ovarian papillary adenocarcinoma and one case of urothelial carcinoma were diagnosed (2.9%; n=1 each).

***Table 12** - Distribution of the cases related to oncology by disorder and patient species*

Oncology	Fip canine	Fip feline	Fi	Fr (%)
Alimentary lymphoma	1	3	4	11.8
Cutaneous histiocytoma	5	0	5	14.7
Cutaneous lymphoma	1	0	1	2.9
Hemangiosarcoma	5	0	5	14.7
Lipoma	12	0	12	35.3
Mammary gland tumour	1	0	1	2.9
Mast cell tumour	1	0	1	2.9
Ovarian papillary adenocarcinoma	1	0	1	2.9
Perianal adenoma	1	0	1	2.9
Trichoblastoma	2	0	2	5.9
Urothelial carcinoma	1	0	1	2.9
Total	31	3	34	100.0

3.10. Ophthalmology

The sub-category of ophthalmology comprises the cases related to ocular diseases (6.3%; n=30).

As illustrated in Table 13, conjunctivitis was the most prevalent disorder, in both dogs and cats, by representing 40.0% of the ophthalmic cases. Moreover, corneal ulcers were diagnosed in six animals and other six presented with scleritis (20% each). Besides the three (10.0%) cases of cataracts in dogs; lens luxation, retinal detachment, and retrobulbar abscess were also recorded (3.3%; n=1 each). All the animals received treatment accordingly, apart from the one with the retinal detachment that was euthanised.

***Table 13** - Distribution of the cases related to ophthalmology by disorder and patient species*

Ophthalmology	Fip canine	Fip feline	Fi	Fr (%)
Cataracts	3	0	3	10.0
Conjunctivitis	9	3	12	40.0
Corneal ulcers	6	0	6	20.0
Lens Luxation	1	0	1	3.3
Retinal detachment	1	0	1	3.3
Retrobulbar abscess	1	0	1	3.3

Scleritis	5	1	6	20.0
Total	26	4	30	100.0

3.11. Orthopaedics

The specialty of orthopaedics consists of disorders that affect the animal's skeletal system (8.9%; n=42).

The big proportion of the animals with advanced age at PVS suffered from osteoarthritis, as such some consults were scheduled with the only specific purpose of the administration of a monoclonal antibody (Librela® for dogs or Solensia® for cats). Therefore, it is not a surprise that these cases represent almost 60% (n=25) of the orthopaedic instances, being dogs the most affected specie (n=18). Next, cranial or medial cruciate ligament rupture was diagnosed seven times, representing 16.7% of the presented disorders in Table 14. Apart from that, six (14.4%) bone fractures were diagnosed (one in a cat and five in dogs), two (4.8%) dogs showed evidence of lateral or medial patellar luxation, one (2.4%) had patellar subluxation and other (2.4%) elbow dysplasia.

***Table 14** - Distribution of the cases related to orthopaedics by disorder and patient species*

Orthopaedics		Fip canine	Fip feline	Fi	Fr (%)
Cranial or medial cruciate ligament rupture		7	0	7	16.7
Elbow dysplasia		1	0	1	2.4
Fracture	Humerus	0	1	1	2.4
	Pelvis	1	0	1	2.4
	Rib	0	1	1	2.4
	Scapula	1	0	1	2.4
	Tarsus	1	0	1	2.4
	Tibia	1	0	1	2.4
Osteoarthritis		18	7	25	59.5
Lateral or medial patellar luxation		2	0	2	4.8
Patellar subluxation		1	0	1	2.4
Total		33	9	42	100.0

3.12. Stomatology and odontology

The sub-category of stomatology and odontology, includes the cases associated with diseases that affect oral mucous membranes, the structure and viability of the teeth, and the salivary glands.

Of the 62 recorded instances in Table 15, 50% (n=31) were of periodontal disease, followed by gingivitis (37.1%; n=23). While the former was also the most prevalent problem in dogs (n=26), the latter was the most prevalent disorder in cats (n=15). Besides, four (6.5%) tooth fractures, two (3.2%) tongue lacerations, one (1.6%) malar root abscess, and one salivary mucocele (1.6%) were observed.

***Table 15** - Distribution of the cases related to stomatology and odontology by disorder and patient species*

Stomatology and odontology	Fip canine	Fip feline	Fi	Fr (%)
Gingivitis	8	15	23	37.1
Malar root abscess	1	0	1	1.6
Periodontal disease	26	5	31	50.0
Salivary mucocele	1	0	1	1.6
Tongue laceration	0	2	2	3.2
Tooth fracture	3	1	4	6.5
Total	39	23	62	100.0

3.13. Theriogenology

Theriogenology is the area of clinical medicine responsible for the diagnosis and treatment of disorders of the reproductive system. This area represents 2.1% (n=10) of the total cases recorded regarding clinical medicine.

As illustrated in Table 16, the most prevalent reproductive disorder observed was pseudo-pregnancy (30.0%; n=3), followed by pyometra and cryptorchidism (20%; n=2 each). Other than that, one female dog was diagnosed with polycystic ovaries and other with vaginitis, whereas one severe case of prostatic hyperplasia was found in a male dog (10.0%; n=1 each).

***Table 16** - Distribution of the cases related to theriogenology by disorder and patient species*

Theriogenology	Fip canine	Fip feline	Fi	Fr (%)
Cryptorchidism	1	1	2	20.0
Polycystic ovaries	1	0	1	10.0
Prostatic hyperplasia	1	0	1	10.0
Pseudo-pregnancy	3	0	3	30.0
Pyometra	2	0	2	20.0
Vaginitis	1	0	1	10.0
Total	9	1	10	100.0

3.14. Toxicology

During the six months, only 10 cases of toxicology were observed (Table 17), which represent 2.1% of the clinical medicine instances. No cases of ingestion of toxic substances were found in cats. In opposition, chocolate and raisin intoxication were registered in five dogs each. Not surprisingly, these became more common around Christmas holidays.

***Table 17** - Distribution of the cases related to toxicology by disorder and patient species*

Toxicology	Fip canine	Fi	Fr (%)
Chocolate ingestion	5	5	50.0
Raisin ingestion	5	5	50.0
Total	10	10	100.0

3.15. Traumatology and emergency

The cases observed in the context of traumatology and emergency are illustrated in Table 18.

Of all the 12 cases, 50% were in relation to polytraumatized patients, of which two cats and three dogs were involved in road traffic accidents and one cat was found inside a tumble dryer that had been turned on without the owner being aware of his presence. Besides, three (25.0%) animals were registered with serious bite wounds, which were either medically or surgically managed. A case of hemoperitoneum in a dog (8.3%), possibly due to rupture of the gastric or splenic vasculature, was identified as well. Besides, as an emergency, one (8.3%) dog was presented with signs compatible with ischaemic stroke, which was directed to the nearest referral hospital with computed tomography (CT) where the diagnosis was confirmed. Also, as an emergency, a female dog with cognitive canine dysfunction, that had laid on a bonfire still hot, was presented with serious burn lesions throughout the body. At first, she was sedated and the wounds cleaned, treated medically and bandaged, but on the second day of treatment the owners decided to euthanize her.

Table 18 *- Distribution of the cases related to traumatology and emergency by disorder and patient species*

Traumatology and emergency	Fip canine	Fip feline	Fi	Fr (%)
Bite wound	1	2	3	25.0
Burns	1	0	1	8.3
Hemoperitoneum	1	0	1	8.3
Ischaemic stroke	1	0	1	8.3
Polytraumatized	3	3	6	50.0
Total	7	5	12	100

3.16. Urology

The sub-category of urology comprises 34 cases (Table 19) associated with diseases of the urinary tract, which represents 7.2% of the clinical medicine cases recorded.

Table 19 *- Distribution of the cases related to urology by disorder and patient species*

Urology	Fip canine	Fip feline	Fi	Fr (%)
CKD	4	4	8	23.5
Non-obstructive idiopathic cystitis	0	3	3	8.8
Renal cyst	0	1	1	2.9
Urinary incontinence	5	0	5	14.7
Urinary tract infection	7	6	13	38.2
Urolithiasis	0	4	4	11.8
Total	16	18	34	100.0

Almost 40% (n=13) of the cases observed, are related to urinary tract infection, which was simultaneously the most prevalent disease in both canine (n=7) and feline (n=6) species. The second most frequent urinary disorder diagnosed was chronic kidney disease (CKD), with eight (23.5%) cases registered, followed by urinary incontinence (14.7%; n=5). Besides, 11.8% (n=4) of the urinary problems were originated from urolithiasis and 8.8% (n=3) caused by non-obstructive idiopathic cystitis. The remaining 2.9%, is in regard to a Maine Coon diagnosed with

a renal cyst prior to the traineeship, whose cyst was surgically drained once and constantly monitored throughout the six months. Unfortunately, the cyst refilled and his body condition became very poor at the time the author concluded her traineeship.

4. Surgical medicine

The category of surgical medicine is subdivided into: dentistry, minimally invasive surgery, neurosurgery, ophthalmic surgery, orthopaedic surgery and soft tissue surgery. Each of these sub-categories is then organized according to the procedures observed.

As illustrated in Table 20, a total of 285 surgical procedures were performed during the traineeship period. More than 50% (n=159) of them were related to soft tissue surgery. Of the remaining procedures, almost a quarter (n=71) were related to dentistry, 14% (n=40) to minimally invasive surgery, 3.5% (n=10) to orthopaedic surgery and a little bit less than 2% (n=5) to ophthalmic surgery. At PVS, cases that require neurosurgery were referred to a referral hospital capable of performing such surgeries, therefore, no cases of this area were recorded.

***Table 20** - Distribution of the cases related to surgical medicine by procedure and patient species*

Surgical Medicine	Fip canine	Fip feline	Fip exotic	Fi	Fr (%)
Dentistry	52	16	3	71	24.9
Minimally invasive surgery	40	0	0	40	14.0
Neurosurgery	0	0	0	0	0.0
Ophthalmic surgery	4	1	0	5	1.8
Orthopaedic surgery	7	3	0	10	3.5
Soft tissue surgery	100	57	2	159	55.8
Total	203	77	5	285	100.0

4.1. Dentistry

As the second most prevalent surgical medicine specialty, multiple dentistry procedures were observed during the traineeship (Table 21). Of those, tooth scale and polish (49.3%; n=35) most of the times accompanied by tooth extraction (33.8%:n=24), were the most prevalent procedures in this area. Together they represent around 83% (n=59) of the registered cases. Besides that, six (8.5%) ameloblastoma and four (5.6%) deciduous canines were removed in dogs. In terms of dentistry procedures performed in exotic species, two (2.8%) rabbits with molar spurs were presented to the practice so that they could be reduced. Overgrowth of sharp spikes on the edges of their teeth is not uncommon in this specie.

***Table 21** - Distribution of the cases related to dentistry by procedure and patient species*

Dentistry	Fip canine	Fip feline	Fip exotic	Fi	Fr (%)
Ameloblastoma removal	6	0	0	6	8.5
Crown height reduction	0	0	2	2	2.8
Deciduous canine tooth removal	4	0	0	4	5.6
Tooth extraction	15	9	0	24	33.8
Tooth scale and polish	27	7	1	35	49.3

Total	52	16	3	71	100.0

4.2. Minimally invasive surgery

During the traineeship at PVS, as illustrated in Table 22, minimally invasive surgery was only performed in dogs, in case of cryptorchidism whose testicle was retained intraabdominally (5.0%; n=2), and when owners showed their preference on spaying their pet through a keyhole surgery (95%; n=38). Due to the multiple advantages of laparoscopic ovariectomy (i.e., reduced risk of complications, reduced post-treatment recovery, less pain associated, etc [*Laparoscopic Neutering and Spaying*]), especially in larger dog breeds, multiple owners at PVS prefer this method over the standard midline ovariohysterectomy.

***Table 22** - Distribution of the cases related to minimally invasive surgery by procedure and patient species*

Minimally invasive surgery	Fip canine	Fi	Fr (%)
Abdominal cryptorchid orchiectomy	2	2	5.0
Ovariectomy	38	38	95.0
Total	40	40	100.0

4.3. Ophthalmic surgery

Ophthalmic surgery was the specialty with the least representation (n=5). This may be partially justified by the lack of ophthalmologic specialists at PVS, qualified to perform complex ocular surgical procedures. Of the surgical procedures observed (Table 23), 60% consist of eyelid lump removal (two in dogs and one in cats). The remaining 40% were attributed to the use of an alger brush to debride eye ulcers, one in a French Bulldog and one in a Shih Tzu.

***Table 23** - Distribution of the cases related to ophthalmic surgery by procedure and patient species*

Ophthalmic surgery	Fip canine	Fip feline	Fi	Fr (%)
Eyelid lump removal	2	1	3	60.0
Debride eye ulcer with alger brush	2	0	2	40.0
Total	4	1	5	100.0

4.4. Orthopaedic surgery

As described in Table 24, the author observed and assisted in 10 orthopaedic surgeries, whose distribution is fairly homogenous. In dogs, were registered three (30%) digit amputations, one amputation of a traumatized tail and three (30.0%) tibial tuberosity advancement. In turn, two tail amputations, both due to a broken tail, and one (10.0%) fracture repair in a polytraumatised cat were performed.

***Table 24** - Distribution of the cases related to orthopaedic surgery by procedure and patient species*

Orthopaedic surgery		Fip canine	Fip feline	Fi	Fr (%)
Amputation	toe	3	0	3	30.0
	tail	1	2	3	30.0
Fracture repair		0	1	1	10.0

Tibial Tuberosity Advancement	3	0	3	30.0
Total	7	3	10	100.0

4.5. Soft tissue surgery

At PVS, soft tissue surgery is performed daily, which explains the great number of procedures registered (n=159) in Table 25. Elective neutering represents 54,8% of soft tissue surgeries performed, with 40 (25.2%) castrations and 47 (29.6%) ovariohysterectomies and ovariectomies. As common practice in the UK, the overwhelming majority of feline patients were spayed through the flank, while midline spay in cats was only performed by an Australian veterinarian.

Skin mass removal was also commonly observed, particularly in dogs (6.3%; n=10). Furthermore, as described in Table 25, stich up skin laceration and surgical biopsy accounted for eight cases each (5.0% each). In addition, four (2.5%) exploratory laparotomies were performed either in cases of foreign body ingestion or in cases whose conventional means were unable to reach a diagnosis. In the same proportion (2.5%; n=4), three dogs and one cat with anal glands recurrent problems were submitted to anal sacculectomy. Other interesting procedures witnessed by the author include cystostomy (1.3%; n=2), enterotomy (1.3%; n=2), oesophagostomy feeding tube placement (1.3%; n=2), ovariohysterectomy due to pyometra (1.3%; n=2) and splenectomy (1.9%; n=3).

Regarding the least observed surgeries, the author was able to assist in surgeries like a caesarean section, a salivary mucocele removal, a tenotomy, all performed in dogs, and a perineal urethrostomy performed in a cat (0.6% each).

***Table 25** - Distribution of the cases related to soft tissue surgery by procedure and patient species*

Soft Tissue Surgery			Fip canine	Fip feline	Fip exotic	Fi	Fr (%)
Exploratory laparotomy			2	2	0	4	2.5
Anal sacculectomy			3	1	0	4	2.5
BOAS surgery			2	0	0	2	1.3
Caesarean section			1	0	0	1	0.6
Castration	Inguinal cryptorchidism		1	1	0	2	1.3
	Elective		23	16	1	40	25.2
Cystotomy			1	1	0	2	1.3
Drain abscess			0	2	1	3	1.9
Enterotomy			2	0	0	2	1.3
Oesophagostomy feeding tube placement			0	2	0	2	1.3
Hernia repair			2	1	0	3	1.9
Lumpectomy			3	0	0	3	1.9
Mastectomy			3	0	0	3	1.9
Spay	Elective	Midline	25	5	0	30	18.9
		Flank	0	17	0	17	10.7
	Pyometra		2	0	0	2	1.3
Perineal urethrostomy			0	1	0	1	0.6
Salivary mucocele removal			1	0	0	1	0.6

Skin mass removal	10	0	0	10	6.3
Splenectomy	3	0	0	3	1.9
Stitch up skin laceration	5	3	0	8	5.0
Surgical biopsy	6	2	0	8	5.0
Tenotomy	1	0	0	1	0.6
Thyroidectomy	0	3	0	3	1.9
Wound Debridement	4	0	0	4	2.5
Total	100	57	2	159	100.0

Apart from elective surgeries, the most frequent soft tissue surgery performed in dogs were skin mass removals (n=10), while in cats were thyroidectomies (n=3) and skin lacerations stich up (n=3). The single non-elective case regarding exotics, was a rat that was presented three times to the practice with recurrent accumulation of pus in the face after multiple surgical management, which required euthanasia.

5. Imaging procedures

As auxiliary tools of diagnosis, the author was able to observe and assist in a total of 158 imaging procedures. Of these, the most commonly performed were abdominal ultrasonography and radiography, representing, respectively, 38.6% (n=61) and 36.1% (n=57) of the imaging studies (Table 26). Echocardiography has also shown to be well represented in dogs (n=20) and cats (n=6), regarding its importance for the diagnosis of cardiac disease. Endoscopy was the third most performed imaging procedure (4.4%; n=7), where two cats were submitted to laryngoscopy, one dog and a cat to a rhinoscopy, two dogs to a gastroscopy and one dog to a bronchoscopy. Although less frequent (2.5%; n=4) dental radiographs were taken in some animals as part of the dental procedure, especially in cats, as an attempt to identify tooth resorption, which is a painful condition. In total, two (1.3%) abdominal focused assessments with sonography for trauma (AFAST) and one (0.6%) thoracic focused assessment with sonography (TFAST) were performed in animals that arrived as an emergency.

Table 26 *- Distribution of the cases related to the imaging procedures performed, regarding the type of procedure and patient species*

Imaging procedures	Fip canine	Fip feline	Fip exotic	Fi	Fr (%)
Dental radiography	1	3	0	4	2.5
Echocardiography	20	6	0	26	16.5
Ultrasonography	35	26	0	61	38.6
Endoscopy	4	3	0	7	4.4
AFAST	2	0	0	2	1.3
TFAST	0	1	1	1	0.6
Radiography	41	15	1	57	36.1
Total	103	54	1	158	100.0

6. Medical procedures

Table 27 illustrates 132 medical procedures encountered by the trainee, which were either

performed as complementary diagnostic tools or as a part of the treatment of specific diseases. Please note that the total listed, underestimates the real number of medical procedures observed and performed during the six-month traineeship, particularly because blood sampling and routine peripheral intravenous catheterization were left out of the records, considering they were performed multiple times daily and, therefore, were impractical to register.

Table 27 *- Distribution of the medical procedures performed, regarding the type of procedure and patient species*

Medical procedures	Fip canine	Fip feline	Fip exotic	Fi	Fr (%)
ACTH stimulation test	2	0	0	2	1.5
Anal glands flush	5	0	0	5	3.8
Arthrocentesis	1	0	0	1	0.8
Bandage and splint care	7	1	0	8	6.1
Blood transfusion	2	0	0	2	1.5
Cardiopulmonary resuscitation	4	2	0	6	4.5
Chemotherapy	1	1	0	2	1.5
Clip and clean lip folds	1	0	0	1	0.8
Ear cleaning	5	0	0	5	3.8
Emesis induction	12	0	0	12	9.1
Enema	0	2	0	2	1.5
Euthanasia	11	9	2	22	16.7
Fine needle aspiration	9	0	0	9	6.8
Gastric decompression	2	0	0	2	1.5
Glucose curve	1	3	0	4	3.0
Jaw wire removal	0	2	0	2	1.5
Laser therapy	3	2	0	5	3.8
Nail removal	8	0	0	8	6.1
Nasal swabbing	0	2	0	2	1.5
Nasal wash	1	1	0	2	1.5
Seroma drainage	1	0	0	1	0.8
Suture removal	4	1	0	5	3.8
Subcutaneous ureteral bypass flush	1	0	0	1	0.8
Thoracocentesis	0	2	0	2	1.5
Throat inspection for grass blade	1	3	0	4	3.0
Tracheal wash	0	1	0	1	0.8
Ultrasound-guided cystocentesis	0	5	0	5	3.8
Urinary catheterization	1	2	0	3	2.3
Wound exploration	7	0	1	8	6.1
Total	90	39	3	132	100.0

Of the listed procedures, the most commonly one was euthanasia, with 22 cases recorded (54.9%). The majority of the euthanized patients, had been chronically ill for a long time, had become terminally ill or had suffered an acute disorder incompatible with life. However, there were also some cases where factors related to the owners (i.e., lack of funds or capability to actively keep treating their animal) were the determinants for such decision to be made. In addition, in the

UK there is a phenomenon, recognised by the veterinarians, although not fully understood, around Christmas and Boxing Day, where the incidence of euthanised animals increases, which also contributes to the number of the cases registered.

Emesis induction was performed twelve times (9.1%), 10 of them in cases of toxicology and two in situations of foreign body ingestion. Fine needle aspiration was also one of the most frequent listed procedures (6.8%; n=9). Of the remaining, the most relevant medical procedures for the author learning were: cardiopulmonary resuscitation (4.5%; n=6); anal glands flush (3.8%; n=5) under sedation, due to anal gland infection; throat inspection for suspected grass blade (3.0%; n=4); urinary catheterization (2.3%; n=3); ultrasound-guided cystocentesis (2.3%; n=3); blood transfusions (1.5%; n=2); enema (1.5%; n=2); gastric decompression (1.5%; n=2); and thoracocentesis (1.5%; n=2).

The least performed procedures were arthrocentesis, clip and clean of painfully moist lip folds, drainage of a seroma formed post-operatively in the site of the surgical incision, subcutaneous ureteral bypass flush and tracheal wash (0.8%; n=1 each).

Regarding the distribution of the procedures listed by patient species, induction of emesis with apomorphine was the most common in dogs, while euthanasia in both cats and the exotics was indeed the predominant one.

III. Monograph – Feline Hyperthyroidism

1. Introduction

First described in the late 1970s (Peterson, 2012; Daniel & Neelis, 2014; Peterson, 2014; Carney *et al.*, 2016; Miller, 2022;), FHT is nowadays one of the most common diagnosed endocrinopathies in cats (Peterson, 2012; Daniel & Neelis, 2014; McLean, Lobetti & Schoeman, 2014; Peterson, 2014; Carney *et al.*, 2016; Yu, Lacorcia & Johnstone, 2022), being age the predominant risk factor (McLean, Lobetti & Schoeman, 2014; Peterson, 2014; Hoek, van, Hesta & Biourge, 2015; McLean *et al.*, 2017; Fossum, 2019; Nelson & Couto, 2019).

HT presents as a multisystemic disorder resulting from the overproduction and excessive circulation of hormones from an ill functioning thyroid gland (McLean, Lobetti & Schoeman, 2014; Nelson & Couto, 2019; Geddes & Aguiar, 2022; Yu, Lacorcia & Johnstone, 2022; Bugbee *et al.*, 2023). The diagnosis, briefly speaking, involves confirmation of persistently raised serum thyroid hormone levels, the presence of one or more HT typical signs (Shiel & Mooney, 2007; Carney *et al.*, 2016; Yu, Lacorcia & Johnstone, 2022) and, frequently but not mandatory, exclusion of concurrent non-thyroidal illness (NTI).

There are four treatment modalities available in feline medicine: radioiodine, thyroidectomy, antithyroid medication and iodine-restrictive diet (Birchard, 2006; Boland *et al.*, 2014; Geddes & Aguiar, 2022; Yu, Lacorcia & Johnstone, 2022). Therefore, treatment can be adapted to patients' medical condition and also attend their owners' preferences (Padgett, 2002; Fossum, 2019; Grossi *et al.*, 2019; Peterson, 2020). Overall prognosis for cats with controlled HT is good to

excellent for the majority of patients, if underlying comorbidities are successfully controlled and malignant thyroid tumour is absent (Birchard, 2006; Daniel & Neelis, 2014; Nelson & Couto, 2019; Peterson, 2020).

Because the exact cause of FHT is not fully understood, disease prevention can be demanding, but there are some prophylactic measures that can be taken, such as: avoiding cat foods with soy, choosing diets with balanced iodine content, avoiding pop-top canned food and wiping the cat daily with a wet cloth or towel, to name a few (Peterson, 2012).

2. Thyroid gland and adjacent structures

2.1. Thyroid gland

2.1.1. Anatomy

The thyroid is an endocrine gland, located adjacent to the trachea and just distal to the larynx (Birchard, 2006), whose morphology varies slightly among species. In all domestic mammals, except swine, it is divided in two lobes (Konig & Liebich, 2016), which lie on either side of the trachea, midway down the neck (Peterson, 2014).

In cats, the lobes are characterized by being dark red or brown, depending on the degree of vascularization (Fossum, 2019; Miller, 2022), and are approximately one to two centimetres long, three to five millimetres wide and one millimetre thick (Padgett, 2002; Fossum, 2019). They are connected caudally by a band of connective tissue, called isthmus, that extends to the ventral aspect of the trachea (Konig & Liebich, 2016). The normal thyroid gland is not palpable and is located slightly ventral to the fifth to eighth cartilage rings of the trachea (Petroff & Greco, 2020). The left lobe is usually slightly more caudal in relation to the right lobe (Figure 1) (Birchard, 2006).

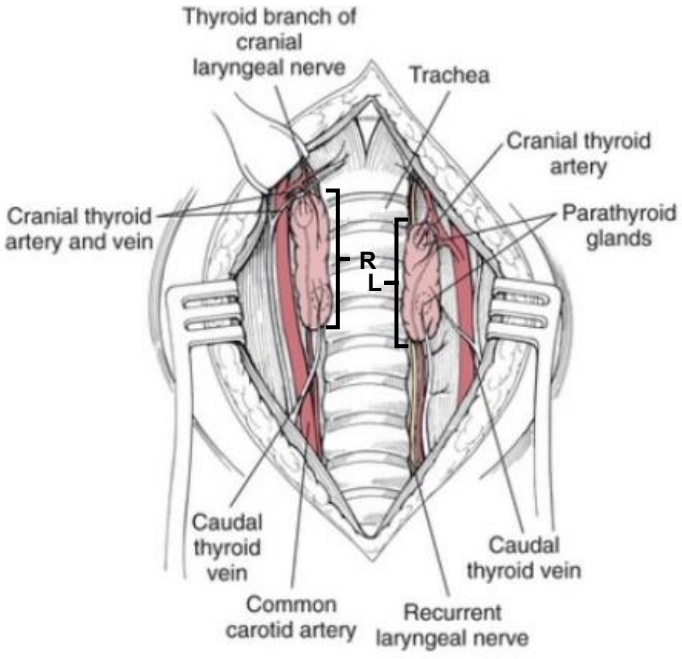


Figure 1 *– Thyroid gland anatomy. The cats' thyroid gland is anatomically divided in two lobes which lie on either side of the trachea, being the left lobe (L) usually slightly more caudal than the right lobe (R). Each thyroid lobe is irrigated by a*

cranial thyroid artery, drained by the cranial and caudal veins and innervated by laryngeal nerves. Each thyroid lobe has two parathyroid glands associated. Adapted from (Fossum, 2019)

The gland's blood supply is provided by the cranial and caudal thyroid arteries, branches of the common carotid and brachiocephalic arteries, respectively (Fossum, 2019), while venous drainage happens through the cranial and caudal thyroid veins (Figure 1) (Birchard, 2006). Particularly in this specie the caudal thyroid arteries may be absent (Fossum, 2019). In turn, lymphatic drainage occurs in the deep cervical lymph nodes or directly from the trunk of the trachea (Konig & Liebich, 2016).

Besides, both sympathetic and parasympathetic systems innervate the gland: the former via fibres from the cranial ganglion and the latter through branches of the caudal and cranial laryngeal nerves (Figure 1), descendants of the vagus nerve, which then form the thyroid nerve (Konig & Liebich, 2016; Fossum, 2019).

2.1.2 Physiology

Histologically, the thyroid gland lobes are organized in lobules, which are arranged in thyroid follicles (or thyrocytes), parafollicular cells (also named C cells) and interfollicular connective tissue (Figure 2).

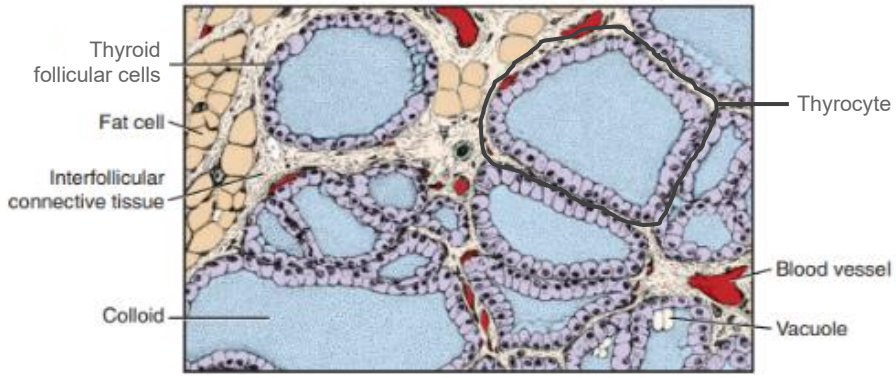


Figure 2 *– Representation of the thyroid gland histology: Each thyroid lobule is organized in thyrocytes surrounded by interfollicular connective tissue, fat cells and blood vessels. In turn, each thyrocyte is lined with a single layer of epithelium made of thyroid follicular cells which surrounds an extracellular storage site filled with a substance called colloid. Adapted from (Petroff & Greco, 2020)*

The thyrocytes are lined with a single layer of epithelium, that can either be cuboidal, when the secretion is basal, or elongated, when stimulated to release hormones, and are filled with a substance called colloid which is considered the main extracellular storage site for the hormones (Figure 2), allowing the gland to function as a large reservoir (Petroff & Greco, 2020). The most abundant and important epithelial cells are the thyroid follicular cells, responsible for the production of thyroid hormones (i.e., thyroxine [T4] and triiodothyronine [T3]), and an important protein implied on that process, called thyroglobulin.

The C cells can be found in the epithelium of the thyroid follicles or in the connective tissue and are responsible for the production of calcitonin, an important hormone for the regulation of calcium (Petroff & Greco, 2020).

2.1.2.1. Thyroid hormones

A. Production

Regarding T4 and T3 production, tyrosine and iodine (I_2) are the most important molecules (Petroff & Greco, 2020). While tyrosine is part of the thyroglobulin amino acid sequence (Petroff & Greco, 2020), I_2 has to come from the animal's diet (Peterson, 2006; Vaske, Schermerhorn & Grauer, 2016). So, although tyrosine is already found inside the thyroid cell, I_2 needs to be converted throughout the GI tract into iodide (I^-) and then absorbed into circulation in order to reach the thyroid. Here, it is actively transported, by a Na^+/I^- symporter (NIS), into the intracellular space, against its concentration gradient (Miller, 2022). Next, I^- is pumped into the colloid where it is further converted into I_2, through a process of oxidation (Peterson, 2006) promoted by an enzyme called thyroperoxidase (TP) (Figure 3). TP also catalyzes thyroglobulin's iodination, which brings about iodine's attachment to thyroglobulin that in the meantime was also exported to the colloid. So, the binding of one I_2 molecule with tyrosine forms a monoiodotyrosine (MIT) molecule; if two I_2 molecules are involved then it is called diiodotyrosine (DIT) (Petroff & Greco, 2020). The coupling of two DIT results in a tetraiodothyronine hormone, known as T4, whereas one MIT plus a DIT creates the T3 hormone (Petroff & Greco, 2020) (Figure 4). By this step, thyroglobulin has attached to it MIT, DIT, T4 and T3 molecules (Figure 3). Therefore, for the hormones to be released they must be cleaved from thyroglobulin. Hence, the large molecule returns to the cytoplasm by endocytosis and is hydrolysed by lysosomal enzymes. Finally, T4 and T3 molecules are free to diffuse through the basal cell membrane into circulation, while the remaining MIT and DIT molecules are deiodinated and its components recycled (Petroff & Greco, 2020) (Figure 3).

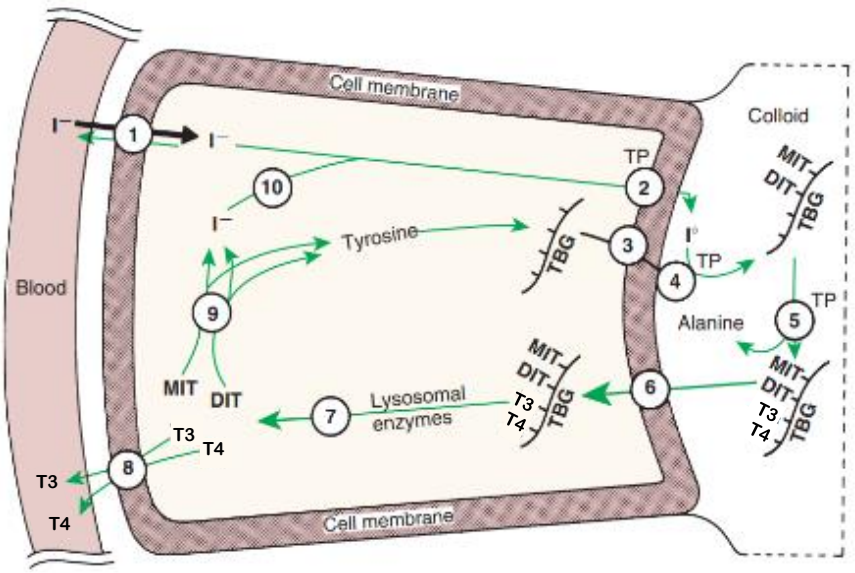


Figure 3 *– Representation of the synthesis and release of T4 and T3 inside a thyroid follicle. The numbers identify the major steps: 1, trapping of iodide; 2, oxidation of iodide; 3, exocytosis of thyroglobulin; 4, iodination of thyroglobulin; 5, coupling of iodotyrosines; 6, endocytosis of thyroglobulin; 7, hydrolysis of thyroglobulin; 8, release of T3 and T4; 9, deiodination of monoiodotyrosine (MIT) and diiodotyrosine (DIT); and 10, recycling of iodide. TBG, Thyroglobulin; TP, thyroperoxidase. Adapted from (Petroff & Greco, 2020)*

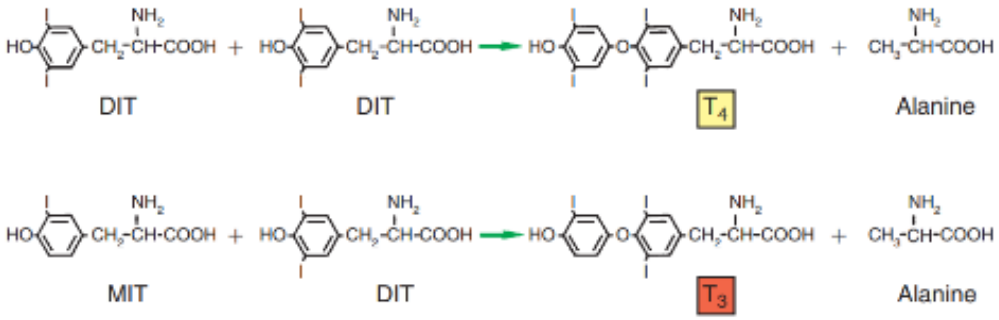


Figure 4 *– Production of tetraiodothyronine (thyronine, T4) and (triiodothyronine, T3) by the coupling of iodinated tyrosyl residues with thyroglobulin molecule. DIT, Diiodotyrosine; MIT, monoiodotyrosine. From (Petroff & Greco, 2020)*

B. Transport

Lipophilic hormones, like T4 and T3, have limited solubility in aqueous solutions including blood (Petroff & Greco, 2020). Thus, in order to be carried through the vascular system, they must be coupled to a specific binding protein (Petroff & Greco, 2020). In cats, albumin or transthyretin (TTR) are the carrier proteins, with albumin being the most important (Jones, Engdahl & Weiss, 2019; Petroff & Greco, 2020). However, only the free and unbound hormone can interact with the cell's receptors. Therefore, thyroid hormones must quickly dissociate from carrier proteins before penetrating target cells (Petroff & Greco, 2020). This unbound fraction represents only around one percent of the total amount of hormones in the plasma (Petroff & Greco, 2020; Yu, Lacorcia & Johnstone, 2022).

C. Action

Due to their multisystemic effect (Table 28), thyroid hormones are considered the most important metabolic hormones (Petroff & Greco, 2020).

Interestingly, even though T4 accounts for around 90% of total thyroid hormone production, it is T3 that is the most responsible for the overall hormonal activity (Syme, 2007; Petroff & Greco, 2020). In fact, T4 is considered the inactive form of the thyroid hormone, whereas T3 is the active form (Syme, 2007; Petroff & Greco, 2020) and the most potent of the two (Vaske, Schermerhorn & Grauer, 2016; Yu, Lacorcia & Johnstone, 2022). This happens because T4 is deiodinated, as soon as it enters the cell, by a 5′-deiodinase or a 5-deiodinase enzyme, into T3 or reverse triiodothyronine (rT3), respectively (Vaske, Schermerhorn & Grauer, 2016; Petroff & Greco, 2020). From there, the T3 formed at the cellular level, or the one in circulation, can induce its biologic effects or be metabolized into inactive hormones like, once again, rT3 (Syme, 2007), which has little biologic effect on cells (Petroff & Greco, 2020). Hence, not only the majority T3 is produced outside the thyroid gland, especially in the liver, kidney and muscle, but also thyroxine's half-life is really short, lasting less than 24 hours (Petroff & Greco, 2020).

At the cellular level, thyroid hormones can exert genomic and non-genomic effects. By biding to receptors in the nuclei, transcription of a large variety of genes across the multiple target cells is triggered, leading to a synthesis of many different proteins such as specific enzymes, structural

and transport proteins (Hall, 2011; Yu, Lacorcia & Johnstone, 2022). It has also been reported that mitochondria have T3 receptors (Petroff & Greco, 2020) that, when activated, prompt these organelles to increase in number and activity. As a consequence, there is an increase in the synthesis of adenosine triphosphate (ATP) (Hall, 2011). This is responsible for what is called the thyroid hormone calorigenic effect, since ATP production increases tissue oxygen consumption and heat production (Petroff & Greco, 2020).

As far as carbohydrate metabolism is concerned, almost all aspects are under thyroid hormonal influence (Hall, 2011). T4 and T3 production increases glucose cell uptake, facilitates glycogen formation in small doses, enhances glycolysis and gluconeogenesis by the liver (Table 28) and increases insulin secretion (Hall, 2011; Petroff & Greco, 2020).

Regarding lipid metabolism, lipolysis is the main consequence of T4 and T3 secretion. Other than that, they have a predisposition to reduce plasma cholesterol levels by increasing cell absorption of low density lipoproteins (LDLs) (Petroff & Greco, 2020) (Table 28), as a consequence of the induced multiplication of the LDL-receptors in the liver (Hall, 2011).

Some target tissues are influenced by the thyroid gland to become more responsive to catecholamines (i.e., epinephrine and norepinephrine) due to its induction of β-adrenergic receptors (Table 28). This happens with the nervous and cardiovascular systems, for instance, resulting in the stimulation of the sympathetic system, heart rate (HR) (Table 28) and cardiac contractility (Hall, 2011; Petroff & Greco, 2020).

As a result of the HR increase, cardiac output follows the same tendency, which ultimately causes blood pressure (BP) to rise (Table 28) (Hall, 2011; Petroff & Greco, 2020). Apparently no change is seen in diastolic blood pressure, only the systolic blood pressure (SBP) seems to increase (Petroff & Greco, 2020). Moreover, because of the calorigenic effect, already described, vasodilation is also promoted, especially in the skin (Table 28) (Hall, 2011).

Lastly, thyroid hormones are known for boosting the secretion of the digestive juices and the motility of the GI tract (Hall, 2011) and, particularly, for being important for normal foetus and neonate growth and development (Table 28) (Hall, 2011; Petroff & Greco, 2020).

Table 28 *– Thyroid hormones and their physiological multisystemic effects throughout the body*

Target tissue	Thyroid hormone physiological effects
Cardiovascular system	↑ HR (Hall, 2011; Petroff & Greco, 2020) ↑ Cardiac output (Hall, 2011; Petroff & Greco, 2020) ↑ BP (Hall, 2011; Petroff & Greco, 2020) Vasodilatation (Hall, 2011)
GI tract	↑ Release of GI secretions (Hall, 2011) ↑ GI motility (Hall, 2011) ↑ Intestinal glucose absorption (Petroff & Greco, 2020)
Nervous system	↑ Sympathetic system (Petroff & Greco, 2020) Important for normal development of nervous tissue in the foetus and neonate (Hall, 2011; Petroff & Greco, 2020)
Liver	Induces glycogenolysis (Hall, 2011; Petroff & Greco, 2020) Induces gluconeogenesis (Hall, 2011) ↑ LDLs uptake (Hall, 2011; Petroff & Greco, 2020)
Muscle	Balances protein catabolism and anabolism (Hall, 2011)

Adipose tissue	↑ Lipolysis (Petroff & Greco, 2020)
Skin	Vasodilation (Hall, 2011) ↑ Heat dissipation (Hall, 2011)

↑, *stimulates/increases*

Because both genomic and non-genomic effects result in a generalized increase in physiological activity throughout the body, thyroid hormones are usually characterized as being stimulatory (Peterson, 1984; Petroff & Greco, 2020). However, some authors prefer a more balanced approach where their action is just considered as important for the normal metabolic activity of all organs (Petroff & Greco, 2020). In fact, some defend that at the same time that protein synthesis is increased, under the physiological influence of these hormones, the rate of protein catabolism increases as well (Hall, 2011).

D. Regulation

Thyroid homeostasis is ensured by the hypothalamic-pituitary-thyroid axis (HPTa) (Norrgran *et al.*, 2015) (Figure 5), being the thyrotropin-releasing hormone (TRH), the thyroid-stimulating hormone (TSH), also named thyrotropin, and a TSH receptor-G protein-cAMP signalling the mediators of thyroid hormone production.

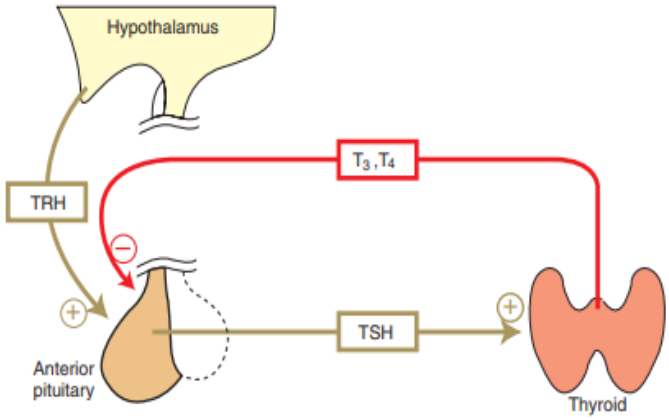


Figure 5 *– Hypothalamic-pituitary-thyroid axis. (+)Stimulation; (-) Inhibition. T3, Triiodothyronine; T4, thyronine; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone. Adapted from (Petroff & Greco, 2020)*

When the plasma concentration of thyroid hormone falls, TRH is synthetised by the hypothalamus in order to stimulate the pituitary gland to produce and secrete TSH. In turn, TSH acts upon its receptor on the surface of the thyroid follicular cells (Hoek, van, Hesta & Biourge, 2015; Norrgran *et al.*, 2015, 2015; Petroff & Greco, 2020; Yu, Lacorcia & Johnstone, 2022). The interaction between TSH and its receptor will promote the activation of stimulatory G proteins (Gs) (i.e., receptor-coupled guanosine triphosphate–binding proteins). These proteins exert a stimulatory effect on the adenylyl cyclase, an enzyme responsible for converting ATP into cyclic adenosine monophosphate (cAMP). Finally, there is an increase in the intracellular concentration of cAMP and, consequently, increased cell activation (Peterson & Ward, 2007; McLean, Lobetti & Schoeman, 2014; Peterson, 2014). Ultimately, thyroid hormone production increases by stimulation of iodide uptake, thyroglobulin's iodination, and T3 and T4 release into the vascular

system (Hoek, van, Hesta & Biourge, 2015; Norrgran *et al.*, 2015, 2015; Petroff & Greco, 2020; Yu, Lacorcia & Johnstone, 2022).

On the other hand, the secretion of TSH is controlled by rising concentrations of thyroid hormones, through a negative feedback mechanism (Figure 5) (Hoek, van, Hesta & Biourge, 2015), in which stimulation of inhibitory G proteins (Gi), instead of Gs, leads to a decrease in cAMP and consequent thyroid hormone production (Peterson & Ward, 2007; McLean, Lobetti & Schoeman, 2014; Peterson, 2014).

2.1.2.2 Calcitonin

Calcitonin, produced by the thyroid parafollicular cells, is one of the calcium metabolism's regulators (Petroff & Greco, 2020).

This hormone affects the mineral metabolism of the bone, by inhibiting osteoclastic activity, and consequently bone resorption, decreasing calcium movement from the bone to the extracellular fluid and increasing phosphate movement into the bone. Renal excretion of calcium (Ca^{2+}) and phosphate (PO_4^{3-}) is also stimulated by calcitonin. Therefore, hypocalcaemia and hypophosphatemia are induced (Table 29) (Petroff & Greco, 2020).

Table 29 *– Physiologic actions of the hormones that affect calcium and phosphate metabolism. Adapted from (Nelson & Couto, 2019)*

Hormone	Bone	Kidney	Intestine	Net effect	
				Serum Ca^{2+}	Serum PO_4^{3-}
PTH	↑ bone resorption	↑ Ca^{2+} absorption ↑ PO_4^{3-} excretion	No direct effect	↑	↓
Calcitonin	↓ bone resorption	↓ Ca^{2+} resorption ↓ PO_4^{3-} resorption	No direct effect	↓	↓
Vitamin D	↑ bone resorption	↓ Ca^{2+} resorption	↑ Ca^{2+} absorption ↑ PO_4^{3-} absorption	↑	↑

↑, increases; ↓, decreases

Physiologically, C cells are stimulated to secrete calcitonin in case of hypercalcemia, but GI hormones (like gastrin, cholecystokinin, secretin and glucagon) can also, at some level, promote that. In turn, its synthesis is inhibited in case of hypocalcaemia (Petroff & Greco, 2020).

2.2. Parathyroid glands

2.2.1 Anatomy

The parathyroid glands in cats are small and ellipsoidal organs (Fossum, 2019). Each thyroid lobe usually has two parathyroid glands associated (Birchard, 2006), one internally and other externally. On one hand, the internal parathyroid is usually located at the caudomedial pole of the thyroid lobe embedded within the thyroid parenchyma. On the other hand, the external parathyroid gland is located on the cranial dorsolateral surface of the thyroid lobe, just lying beneath its capsule (Fossum, 2019). This can be distinguished from the thyroid by its lighter colour and smaller and spherical shape (Birchard, 2006).

The blood supply to the parathyroid glands is provided by small branches of the cranial thyroid arteries that effectively perforate their capsule (Fossum, 2019). Innervation and lymphatic drainage are carried out by the same structures that perform those functions for the thyroid gland (Konig & Liebich, 2016).

2.2.2 Physiology

Microscopically, the parathyroid is very different from the thyroid (Figure 6). Instead of follicles, this gland is organized in cellular dense cords supported by connective tissue and the parenchyma has three types of cells: chief cells, oxyphil cells and adipocytes. While oxyphil cells are considered inactive and in degeneration, chief cells are responsible for the actual endocrine function by producing parathyroid hormone (PTH). Because of this hormone, the parathyroid gland is the main organ involved in the control of calcium and phosphate metabolism (Greco, 2012; Petroff & Greco, 2020).

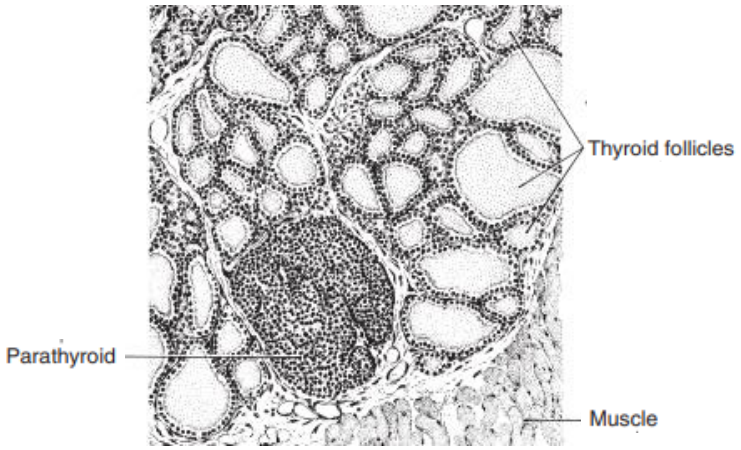


Figure 6 *- Histologically, the parathyroid gland is very different from the thyroid. Instead of follicles, this gland is organized in cellular dense cords supported by connective tissue. Adapted from (Petroff & Greco, 2020)*

PTH is rapidly metabolized by the liver and kidneys and has a relatively short half-life (five to ten minutes) in blood (Petroff & Greco, 2020).

PTH and calcitonin counterbalance each other's actions in order to provide calcium homeostasis. In hypocalcemic conditions, while calcitonin is inhibited, PTH secretion is stimulated in order to re-establish normal calcium concentrations (Petroff & Greco, 2020). In hypercalcemia, calcitonin is activated and PTH is inhibited.

Epinephrine, through stimulation of β-adrenergic receptors, and magnesium, by negative feedback just like calcium, can also stimulate chief cells to produce PTH. PTH values are the highest after waking, as well (Petroff & Greco, 2020).

PTH acts on the bone, by increasing osteoclastic activity and promoting bone resorption. Moreover, at the kidney level, it stimulates calcium absorption, decreases renal phosphate reabsorption (Table 29) and is involved in the activation of vitamin D (Greco, 2012). PTH-induced hypophosphatemia occurs due to its direct effect on the kidney, where phosphate excretion is increased (Petroff & Greco, 2020).

2.2.2.1. The importance of vitamin D

Despite not being considered a hormone, vitamin D is produced in one tissue and carried by the blood stream to a distant site of action via blood. Epithelial cells of the skin synthesize a vitamin D precursor that, when the skin is exposed to ultraviolet light, is cleaved into vitamin D (Greco, 2012; Petroff & Greco, 2020). An animals' diet can also be a source of vitamin D. This molecule, as such, has to be transformed by the liver and the kidney in order to become biologically active (Petroff & Greco, 2020).

Once activated, vitamin D is very important for the calcium and phosphate absorption in the GI system. In addition, it enhances PTH effects on bone metabolism of calcium, but decreases renal resorption of calcium (see Table 29) (Petroff & Greco, 2020).

2.2.2.2. The importance of calcium and phosphate

Calcium plays an important role in muscle contraction, nerve cell activity, exocytosis for hormone release, enzyme activation, blood coagulation, cell membranes stability, connectivity between cells and bone and teeth structural integrity (Greco, 2012; Petroff & Greco, 2020).

Around 99% of the body's calcium is part of the bone's structure as hydroxyapatite crystals, which are a mix of calcium, phosphate and water. Besides it can also be found intracellularly and a very small percentage is in the extracellular fluid (Petroff & Greco, 2020).

On top of being part of the bone and teeth structure, phosphate is a constituent of the phospholipid bilayer and intracellular components, such as nucleic acids, ATP and adenosine monophosphate (Petroff & Greco, 2020). Its production increases when PTH is secreted, as already stated, but decreases by negative feedback and in case of hyperphosphatemia (Petroff & Greco, 2020).

2.3 Other adjacent structures to the thyroid gland

Adjacent to the thyroid gland, on each side of the trachea there are important vessels and nerves, including those in the carotid sheath (i.e., vagosympathetic trunk, carotid artery, and internal jugular vein) and the recurrent laryngeal nerves (Figure 7). While the left recurrent laryngeal nerve is located dorsolateral to the trachea and ventral to the oesophagus, the right laryngeal nerve is located lateral to the trachea and dorsomedial to the sternothyroid muscle (Padgett, 2002). Once again, from some of this vessels and nerves, rise branches that irrigate and innervate the thyroid and parathyroid glands.

Interestingly, ectopic functional thyroid tissue can be found along the trachea, thoracic inlet, mediastinum and thoracic portion of the descending aorta (Fossum, 2019). Ectopic parathyroid tissue can also be found in the cranial mediastinum on a small percentage of cats (Birchard, 2006).

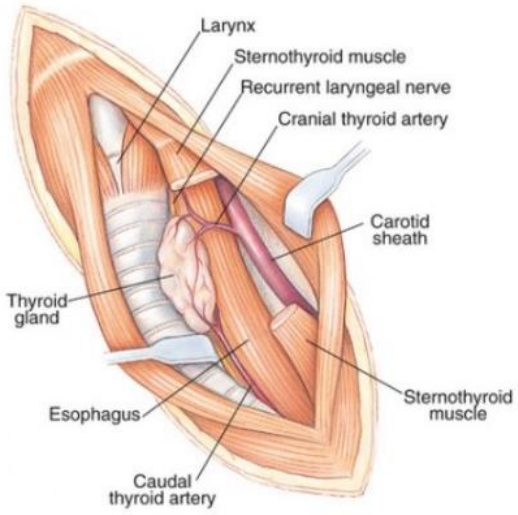


Figure 7 *– Each thyroid lobe is adjacent to important vessels and nerves, like those in the carotid sheath (vagosympathetic trunk, carotid artery, and internal jugular vein) and the recurrent laryngeal nerves. From (Fossum, 2019)*

3. Pathophysiology

FHT is a metabolic disease, which results from the overproduction and excessive circulation of thyroid hormones from an ill thyroid gland (McLean, Lobetti & Schoeman, 2014; Nelson & Couto, 2019; Geddes & Aguiar, 2022; Yu, Lacorcia & Johnstone, 2022; Bugbee *et al.*, 2023).

This disorder is the most common cause of thyrotoxicosis (i.e., any condition in which there is an excessive amount of circulating thyroid hormone, whether from excessive production and secretion from an overactive thyroid gland, leakage from a damaged thyroid gland, or an exogenous source) (Ward, 2007).

3.1. Aetiology

To date, the exact cause of FHT is yet to be fully understood. Many investigations have attempted to define the aetiology of the disease, however not a single factor was identified as the cause, which leads many to conclude that FHT is a multi-factorial disorder. A combination of molecular, nutritional, environmental, genetic, and factors related to the thyroid gland itself seem to partially explain the progress of such common disease (Peterson & Ward, 2007; Peterson, 2012; McLean, Lobetti & Schoeman, 2014; Chow *et al.*, 2015; Norrgran *et al.*, 2015; Carney *et al.*, 2016; Jones, Engdahl & Weiss, 2019; Nelson & Couto, 2019; Geddes & Aguiar, 2022; Yu, Lacorcia & Johnstone, 2022).

3.1.1. Thyroid autoimmunity and circulating stimulatory factors

When FHT aetiology was first studied, it was initially thought that it could have an autoimmune origin, like in humans with Graves' disease, in which thyroid-stimulating immunoglobulins (TSIs) mimic TSH, inducing not only T4 and T3 production and secretion, but also thyroid hyperplasia (Peterson & Ward, 2007; McLean, Lobetti & Schoeman, 2014; Peterson, 2014). However, subsequent studies disproved this theory. Although circulating TSIs have been found in some

hyperthyroid cats, no correlation was found between the antibodies and thyroid disfunction (Peterson & Ward, 2007; McLean, Lobetti & Schoeman, 2014; Peterson, 2014).

3.1.2. Molecular biology

Physiological thyroid hormone production depends on a balance between Gs and Gi activation (McLean, Lobetti & Schoeman, 2014); if this balance is in favour of Gs, by overexpression of Gs or Gi inhibition, then it would lead to an overproduction of cAMP and overstimulation of thyrocytes (Peterson & Ward, 2007). Therefore, similar to what has been investigated for toxic nodular goiter (i.e., other common hyperthyroid disorder in humans), pathologic mutations along the TSH receptor-G protein-cAMP pathway could lead to FHT (Peterson & Ward, 2007; Miller, 2022).

To date, mutations affecting TSH receptors and/or Gs have been reported in small groups of hyperthyroid cats (Peterson & Ward, 2007; McLean, Lobetti & Schoeman, 2014; Peterson, 2014; Miller, 2022). These gene mutations lead to very high levels of cAMP, unregulated cellular proliferation and excessive hormone production (Peterson & Ward, 2007; Peterson, 2014). Besides, significant decrease of the Gi expression is thought to contribute to the FHT pathogenesis (McLean, Lobetti & Schoeman, 2014; Petroff & Greco, 2020).

However, the importance of these abnormalities is yet to be fully understood, especially because they are not found in all thyrotoxic cats (Peterson & Ward, 2007).

3.1.3. Nutritional deficiencies or excesses in cat food

3.1.3.1. Dietary iodine

Iodine may be naturally present in some foods or be added to others as a supplement (i.e., iodized salt, sea salt, potassium iodide, calcium iodate, dry kelp, or ethylenediamine dihydriodide) (Edinboro, Scott-Moncrieff & Glickman, 2010; Peterson, 2012; Petroff & Greco, 2020). Depending on the organic ingredients used, some foods have higher I_2 content than others. For instance, those with ocean fishes tend to be richer in I_2 (Hoek, van, Hesta & Biourge, 2015).

As explained previously, I_2 plays a key role in normal thyroid gland function. Any change in I_2 intake could impair the production of thyroid hormones. However, there is no consensus on the role of I_2 in the development of HT (McLean *et al.*, 2017; Peterson, 2012).

Deficiency or excessive I_2 intake or even daily I_2 intake swings, have been hypothesised as possible thyroid dysfunction causal factors (Peterson, 2012; Daniel & Neelis, 2014; McLean, Lobetti & Schoeman, 2014; Peterson, 2014; Hoek, van, Hesta & Biourge, 2015; McLean *et al.*, 2017), although the mechanism is not clear (Peterson, 2012; McLean, Lobetti & Schoeman, 2014; McLean *et al.*, 2017).

When I_2 intake is low, synthesis of T3 might be preferred over that of T4, since the former requires less I_2 and is also more potent (Ferguson, 2018). Regardless, both T4 and T3 serum levels decrease, which, once again, induces TSH production (Peterson, 2012; Daniel & Neelis, 2014; Yu, Lacorcia & Johnstone, 2022). In some cases, I_2 deficiency may be enhanced by concurrent micronutrients deficiencies and/or act synergistically with other goitrogens (Miller,

2022; Peterson, 2012).

High I_2 intake decreases thyroid epithelial cells' receptivity to TSH, affects the capacity of the NIS to capture iodide into the follicular cell and inhibits the action of TP. These metabolic alterations will lead to an overall decrease of thyroid hormone production and secretion (Miller, 2022). Over time, such excess in I_2 intake may promote follicular cell hyperplasia due to continuous stimulation of TSH. Whether excess of dietary I_2 leads to HT or not, depends on the animal itself (Miller, 2022).

Basically, dietary I_2 must be both bioavailable and present in food in sufficient concentration to prevent thyroid disease (Edinboro, Scott-Moncrieff & Glickman, 2010). However, the amount of I_2 has been shown to be extremely variable between different commercial cat foods with most manufacturers including at least three to five times the minimum I_2 amount recommended (Ferguson, 2018). Nevertheless, that was not always the case. In the past, the manufacturers used much less supplemented I_2 and some authors suggest that it may have inadvertently contributed to the rising incidence of FHT (Edinboro, Scott-Moncrieff & Glickman, 2010; Ferguson, 2018; Peterson, 2012).

Furthermore, in a case control study cats fed commercial foods relatively deficient in I_2 were more than four times as likely to develop HT than cats consuming iodine-supplemented foods (Edinboro, Scott-Moncrieff & Glickman, 2010; Peterson, 2012).

3.1.3.2. Soy isoflavones

Soybeans, a component of many cat foods, contain isoflavones (such as daidzein, genistein and biochanin A), which are organic compounds capable of interfering with the physiological production of thyroid hormones. Isoflavones inhibit two important enzymes: TP and 5′-deiodinase. As a consequence, the pituitary will overproduce TSH, which chronically will lead to gland hyperplasia (Peterson, 2012; McLean, Lobetti & Schoeman, 2014; Carney *et al.*, 2016; McLean *et al.*, 2017).

Some authors suggest that dietary I_2 deficiency acts synergistically with the isoflavones' antithyroid effects (Peterson, 2012; Hoek, van, Hesta & Biourge, 2015) and that goiter induced by isoflavones only happens in animals consuming diets deficient in I_2 (Peterson, 2012).

Unfortunately, as a low-cost protein source (Peterson, 2012), soy is found in about 60% of cat foods with virtually every dry and semi-moist foods containing damaging concentrations of isoflavones (McLean, Lobetti & Schoeman, 2014).

3.1.3.3. Dietary selenium

Selenoproteins are selenium-containing antioxidant enzymes important to ensure thyroid's normal function (Peterson, 2012; Hoek, van, Hesta & Biourge, 2015). So, to some degree, the dietary selenium, may be part of the FHT aetiology. However, some authors disagree about its role. On one hand, deficiency of this mineral is hypothesized to increase T4 and T3 production, but on the other hand it also might supress the action of selonoprotein 5′-deiodinase, which will lead TSH to rise (Hoek, van, Hesta & Biourge, 2015).

Although it is not clear if dietary selenium deficiency results in hyper- or hypothyroidism (Peterson, 2012), high selenium intake seems to stimulate follicular epithelium autonomous growth (Hoek, van, Hesta & Biourge, 2015).

It is suggested that dietary selenium merely plays an additive and/or synergetic role in the development of feline thyrotoxic disease and that as a single factor barely contributes for the pathology (Peterson, 2012).

3.1.3.4. Type of can and flavours

Cats that are fed food from pop-top cans, oppose to pouches or sachets, have been demonstrated to be in greater risk of developing HT (Peterson, 2012; Daniel & Neelis, 2014; McLean *et al.*, 2017). On one hand, pop-top cans are suspected to contain the thyroid disruptor chemical bisphenol A (BPA) (Peterson, 2012; Daniel & Neelis, 2014). On the other hand, they could just represent a marker of cats that are more likely to live indoors and, consequently, tend to reach an advanced age, which, coincidently or not, represents the stage of life when FHT is more frequently diagnosed (Peterson, 2014).

Cats that prefer certain flavours, like fish, liver and giblets, have been demonstrated to be in greater risk of developing HT as well (Peterson, 2012; Daniel & Neelis, 2014; McLean *et al.*, 2017).

3.1.4. Thyroid-disrupting factors

3.1.4.1. Bisphenol A

Due to its structural similarity with thyroid hormones, BPA can act as a thyroid hormone receptor antagonist, which ultimately leads to stimulation of TSH production. The BPA capacity to bind directly to the thyroid hormone receptors and to inhibit the transcription of thyroid regulated genes by competing with T3 intracellularly, are the two responsible mechanisms for the pituitary gland stimulation (Peterson, 2012; McLean, Lobetti & Schoeman, 2014; Hoek, van, Hesta & Biourge, 2015; McLean *et al.*, 2017). Nonetheless, it is suggested that BPA would be a more important etiological factor for FHT if it was able to bind to the TTR (Jones, Engdahl & Weiss, 2019).

BPA has been found in water, air, floor dust, soil and food (Peterson, 2012). Its exposure occurs primarily through food ingestion (Peterson, 2012; McLean *et al.*, 2017). As BPA is regularly used for lining the interior of metal food cans, it is common overtime for it to migrate into the can contents (Peterson, 2012; Daniel & Neelis, 2014; McLean, Lobetti & Schoeman, 2014; Peterson, 2014; Fossum, 2019).

Once again, bisphenol goitrogenic effects may be potentiated by concomitant I_2 deficiency (Peterson, 2012).

3.1.4.2. Polybrominated diphenyl ethers

Polybrominated diphenyl ethers (PBDEs) are used as flame retardants in a wide range of consumer products (e.g.: plastics, textiles, furniture and electronics) (Hoek, van, Hesta & Biourge,

2015; Norrgran *et al.*, 2015). The first hypothetical correlation between PBDEs and FHT pathology was due to the temporal association of the introduction of PBDEs, in the 1970s, and FHT discovery (Peterson, 2012; Norrgran *et al.*, 2015). Nowadays, it is postulated that, due to their structural similarity to thyroid hormones, PBDEs are capable of interfering with thyroid physiology via inhibition of T4 action, negative feedback blockage and ultimately TSH stimulation (Mensching *et al.*, 2012; Carney *et al.*, 2016).

Although not actually proven, considering cats' grooming habits and being aware of these organic pollutants' tendency to leach out of the products and accumulate in household dust over time, ingestion seems to be cats' main source of PBDE contamination (Peterson, 2014; Chow *et al.*, 2015; Hoek, van, Hesta & Biourge, 2015; Norrgran *et al.*, 2015). In support of this, higher PBDEs dust levels have been found in hyperthyroid cats' households when compared to euthyroid cats' households. Simultaneously, cats living indoors have shown to have higher PBDEs serum levels in comparison to outdoor cats (McLean, Lobetti & Schoeman, 2014; McLean *et al.*, 2017). However, there are authors who are unable to obtain results that support the role of these ethers in the pathogenesis of FHT (Mensching *et al.*, 2012; Chow *et al.*, 2015).

PBDEs may interact synergistically with other thyroid-disrupting factors (Chow *et al.*, 2015).

3.1.4.3. Environmental pesticides or herbicides

Theories abound as to what factors may contribute for FHT development: exposure to fertilizers, herbicides, plant pesticides, topical flea products and others. However, no study was able to identify a specific product or component with an associated risk of developing FHT (Peterson & Ward, 2007; Peterson, 2012; Daniel & Neelis, 2014; McLean *et al.*, 2017; Fossum, 2019).

3.1.4.4. Other possible goitrogens or thyroid disruptors

Broccoli, rapeseed, cassava, lima beans and sweet potato all are mentioned by (Ferguson, 2018) as foods that contain compounds, which are metabolized into thiocyanate, an inhibitor of thyroid I_2 uptake and organification (i.e., addition of I_2 to a tyrosine residue of thyroglobulin, in order to form MIT's and DIT's [Ferguson, 2018]). However, no further information was found about their impact on the development of FHT.

Besides, other goitrogens and thyroid disruptors like perchlorates, PCBs, resorcinol, dioxins, fluoride, erythrosine and heavy metals (for instance mercury) have been briefly mentioned as possible contributors to the development of HT, either by directly reducing thyroid hormone production or by indirectly altering mechanisms of the gland or peripheral metabolism and excretion of the hormones. Cats may be exposed to such contaminants through their diet, drinking water or environment (Peterson, 2012; McLean, Lobetti & Schoeman, 2014; McLean *et al.*, 2017).

3.1.5. Intrinsic factors to the thyroid gland

The feline thyroid gland naturally contains a subpopulation of follicular cells genetically predisposed to proliferate, grow and form adenomatous nodules (Figure 8), with the ability to

eventually secrete thyroid hormone independently of the TSH regulation (Peterson & Ward, 2007; Peterson, 2012, 2020;). Therefore, HT may be a late manifestation of this natural phenomenon (Peterson, 2020).

In FHT-prone animals, this susceptibility to develop adenomatous nodules is even more enhanced under the influence of the already mentioned genetic, nutritional and environmental pathogenic factors (Peterson, 2020).

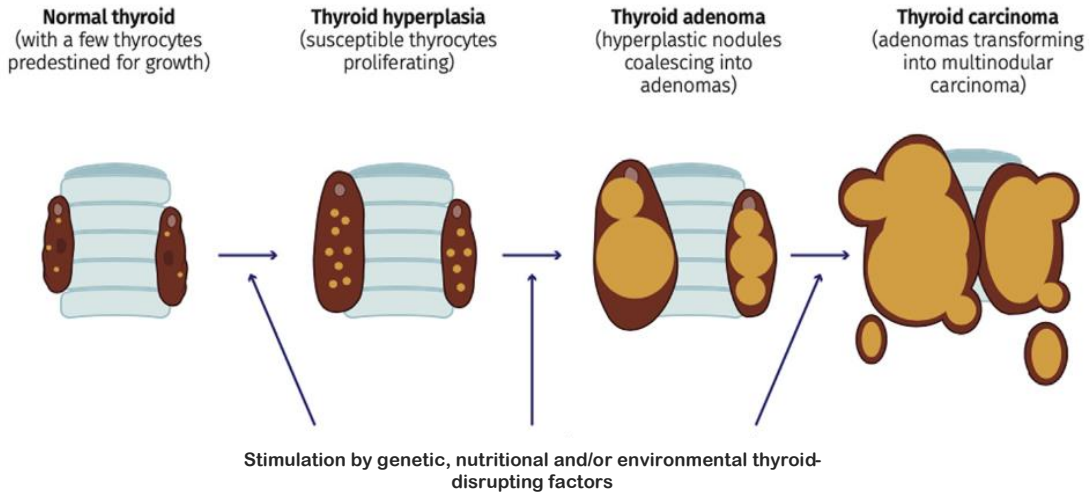


Figure 8 *– Etiopathogenesis of thyroid adenoma and carcinoma in cats with HT. In all likelihood, feline thyroid gland naturally contains a subpopulation of follicular cells genetically predisposed to proliferate, grow and form adenomatous nodules, with the ability to eventually secrete thyroid hormone independently of the TSH regulation. In FHT-prone animals, this susceptibility to develop adenomatous nodules is even more enhanced under the influence of genetic and nutritional factors and/or environmental thyroid disruptors. Adapted from (Peterson, 2020)*

3.2. Thyroid morphological changes

Although the underlying causes of FHT are poorly understood, the pathologic changes associated with a thyrotoxic thyroid gland seem to be well defined (Peterson & Ward, 2007).

Paradoxically, induction of low serum thyroid hormone circulation, described as the outcome of virtually every possible causal factor, triggers, in susceptible animals, autoregulatory mechanisms that might lead to disease onset (Figure 9). Regardless of what causes that hormone reduction, the HPTa responds by increasing the production and secretion of TSH. Thus, thyroid gland activity increases. When that hypermetabolic state becomes chronic, as if in response to an inability to secrete adequate amounts of hormone (Petroff & Greco, 2020), thyroid follicular cells start proliferating, especially those that are already genetically predisposed (Figure 8) or those that in the meantime become less sensitive to inhibitory factors or more susceptible to normally inactive factors. This promotes thyroid hyperplasia and a nonneoplastic enlargement of the gland, also defined as goiter, usually noticeable as a bulge in the cat's neck (Peterson, 2012; Hoek, van, Hesta & Biourge, 2015; Norrgran *et al.*, 2015; Miller, 2022). If the ongoing source of the problem is not corrected, the hyperplastic thyrocytes become autonomous (i.e., unresponsive to TSH regulation), leading to an adenomatous hyperplasia (Figure 9) (Peterson, 2012; Daniel & Neelis, 2014; Norrgran *et al.*, 2015). Once the adenoma is formed, the autonomous thyroid

function is set, causing an increased thyroid hormone secretion. That is when classic HT signs start to manifest (Hoek, van, Hesta & Biourge, 2015). As autonomous cells continue to proliferate, serum TSH levels decrease. Thus, the surrounding unaffected thyroid parenchyma with the TSH-dependent cells undergoes atrophy (Padgett, 2002; Nelson & Couto, 2019; Miller, 2022). As the cell modulation occurs, over time, the benign adenoma may turn into a carcinoma (Peterson, 2012; Miller, 2022). In fact, some thyrotoxic cats have areas of carcinoma coexisting with areas of adenoma within the same lobe (Peterson, 2012).

Since thyroid tumours are not static, either from a morphological, pathological and functional point of view, if left untreated, cats can reach a state where HT becomes incompatible to life (Peterson, 2020).

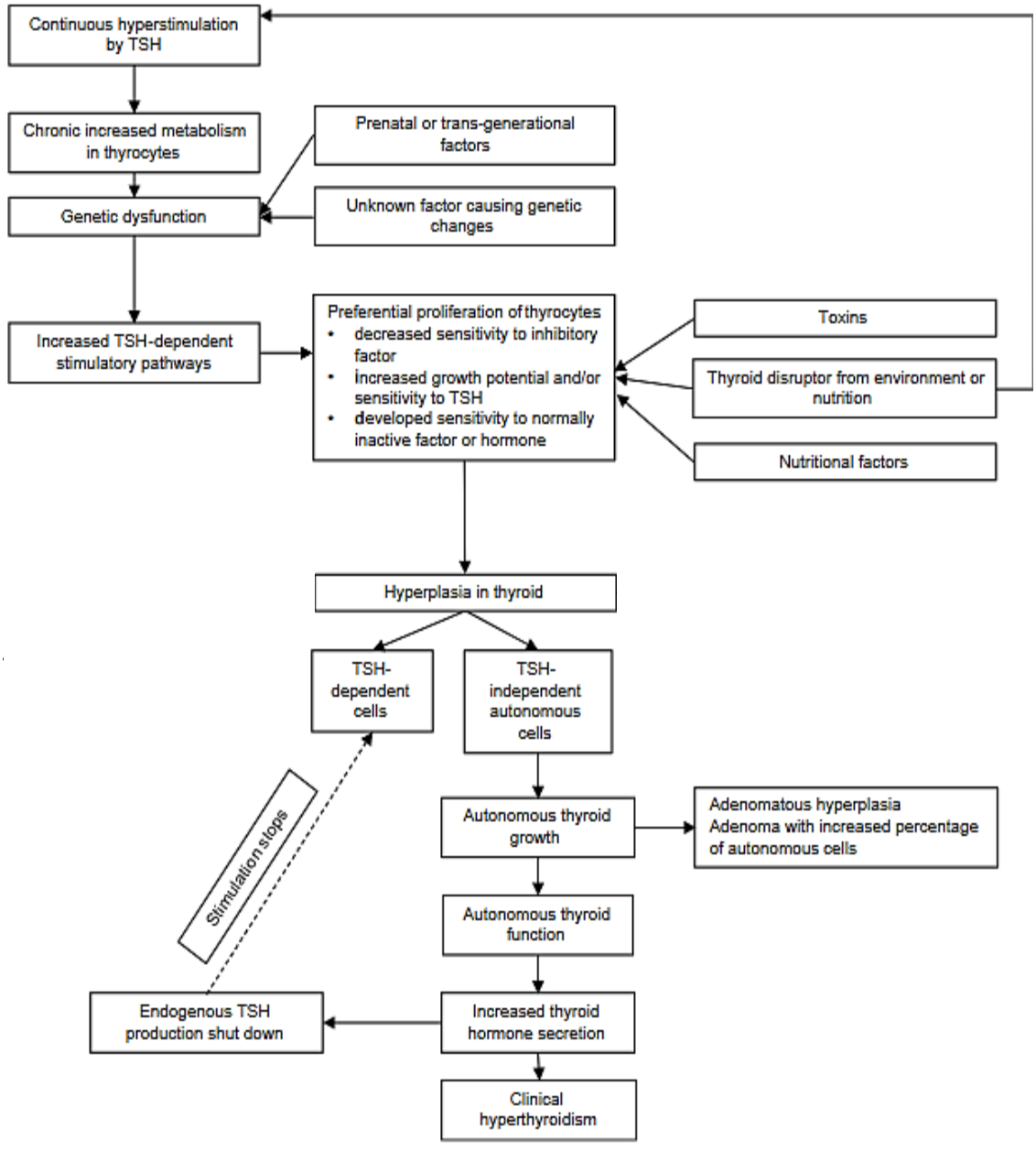


Figure 9 *- Causes and effects of preferential proliferation of thyrocytes. Several factors can cause increased thyroid-*

stimulating hormone (TSH)-dependent stimulatory pathways. These pathways or other factors like toxins, goitrogens or nutritional factors from the diet can cause preferential proliferation of certain thyrocytes or thyroid hyperplasia. Hyperplastic nodules of autonomous growing and functioning thyrocytes form, and clinical signs of HT develop. Solid lines: effect. Dashed lines: inhibition. Adapted from (Hoek, van, Hesta & Biourge, 2015)

3.2.1. Thyroid hyperplasia or goiter

Goiter is the term used to describe a nonneoplastic enlargement of the thyroid gland, caused by follicular hyperplasia. However, follicular hyperplasia does not necessarily lead to an appreciable enlargement of the gland (Miller, 2022).

This enlargement can be diffuse or multinodular. However, cats usually develop the latter, which is histologically characterised by the existence of nonencapsulated hyperplastic nodules (Miller, 2022).

Macroscopically, distinction between goiter and adenoma is very difficult. Besides, it is important to bear in mind that the thyroid gland can be palpably enlarged months to years before the development of clinical signs (Miller, 2022).

3.2.2. Thyroid adenomatous hyperplasia or adenoma

At the time of diagnosis, thyroid adenoma is responsible for the clinical manifestations of around 97-99% of FHT cases (Peterson & Ward, 2007; Shiel & Mooney, 2007; Peterson, 2012; McLean, Lobetti & Schoeman, 2014; Geddes & Aguiar, 2022; Yu, Lacorcia & Johnstone, 2022).

Compared to goiter, these benign tumours of epithelial origin, tend to be singular, larger and encapsulated nodules, coexisting with and compressing the atrophied thyroid parenchyma (Miller, 2022).

Once again, based solely on physical examination (PE), it is difficult to assess whether an enlarged thyroid gland is a goiter, adenoma or even a carcinoma, especially because the time course between each phase remains unknown (Peterson & Ward, 2007; Miller, 2022)

3.2.3. Thyroid carcinoma

Thyroid carcinoma accounts for only one to three percent of cats diagnosed with HT (Peterson, 2012; McLean, Lobetti & Schoeman, 2014; Carney *et al.*, 2016; Peterson, 2020; Peterson *et al.*, 2020; Geddes & Aguiar, 2022; Bugbee *et al.*, 2023).

Despite being rare, these malignant tumours of epithelial origin are generally invasive, with an associated metastatic rate of around 71% (Oramas, Boston & Wavreille, 2020), particularly to the lungs (Miller, 2022) and/or regional lymph nodes (Daniel & Neelis, 2014; Oramas, Boston & Wavreille, 2020).

Unfortunately, due to being well encapsulated and mobile with respect to adjacent tissue, thyroid carcinomas may be indistinguishable from thyroid adenoma, in both macroscopic morphology and clinical presentation. However, when the patient becomes rapidly debilitated and/or is refractory to standard approaches with reversible or definitive treatment, one should be more aware and concerned about an undiagnosed carcinoma (Yu, Lacorcia & Johnstone, 2022). In fact, it has been suggested that cats that manifest a SHIM-RAD (i.e., Severe, Huge, Intrathoracic, Multifocal disease, Refractory to antithyroid drugs) clinical presentation are most

likely suffering from severe HT or thyroid carcinoma. Therefore, these patients should undergo further investigation in order to exclude or confirm malignant thyroid disease (Yu, Lacorcia & Johnstone, 2022).

3.2.4. Unilateral vs Bilateral thyroid disease

The vast majority, around 85-90%, of the hyperthyroid cats have a palpable thyroid gland at the time of diagnosis (Peterson, 1984; Birchard, 2006; Daniel & Neelis, 2014; Nelson & Couto, 2019). Approximately two thirds of these cats suffer from bilateral disease (Geddes & Aguiar, 2022; Nelson & Couto, 2019), of which only 10-15% of the cases present symmetrically enlarged thyroid lobes (Nelson & Couto, 2019). The remainder, about 30% (Daniel & Neelis, 2014; Nelson & Couto, 2019), only have involvement of a single lobe, with the contralateral unaffected lobe atrophied and nonfunctioning (Padgett, 2002; Nelson & Couto, 2019).

3.3. Multisystemic effects of hyperthyroidism

Taking into account that thyroid hormones are the most important hormones of metabolism due to their multi systemic effect (Petroff & Greco, 2020) and that, physiologically, their action is generally stimulatory (Peterson, 1984; Petroff & Greco, 2020) (see Table 28), thyrotoxicosis from excessive activity of T4 and T3 will result in manifestation of a multisystemic disease characterized by a hypermetabolic and catabolic state (Peterson & Eirmann, 2014; Fossum, 2019; Petroff & Greco, 2020; Yu, Lacorcia & Johnstone, 2022).

Overall, clinical signs will be a reflection of the enhanced effects that thyroid hormones physiologically exert on multiple organ systems. The most clinically evident will be those resulting from: nervous and cardiovascular systems' increased sensitivity to catecholamines (Fossum, 2019; Petroff & Greco, 2020); increased energy demand that exceeds energy consumption and ultimately leads to increased protein catabolism (Peterson & Eirmann, 2014; Yu, Lacorcia & Johnstone, 2022); increased influence on the GI tract (Peterson, 1984; Matos *et al.*, 2022) and heat intolerance (Peterson, 1984). Although the kidney has not been listed as a physiological target tissue of thyroid hormones, the hemodynamic changes caused by HT may also affect the renal system (Peterson & Eirmann, 2014; Vaske, Schermerhorn & Grauer, 2016).

4. Epidemiology

HT is the most common endocrinopathy affecting cats (Peterson, 2012; Daniel & Neelis, 2014; McLean, Lobetti & Schoeman, 2014; Peterson 2014; Carney *et al.*, 2016; Yu, Lacorcia & Johnstone, 2022) and one the most frequently diagnosed disorders in small animal practice. Its prevalence ranges from 4-11% in regions like in the United States, Canada, UK, Europe, Australia, New Zealand and Japan (Daniel & Neelis, 2014; McLean, Lobetti & Schoeman, 2014; Peterson, 2014). Since the disorder was first discovered, FHT cases have continued to dramatically rise, due to: cat's longer life spans; changes in their husbandry with a higher percentage of cats living indoor or changes related to diet habits; increased owner awareness and willingness to treat their pets; improved diagnoses by clinicians and/or a true increase in disease prevalence (Peterson

& Ward, 2007; Peterson, 2014; Carney *et al.*, 2016).

Epidemiological studies have been carried out to identify risk factors associated with FHT. Advanced age has been consistently linked to the development of HT (McLean, Lobetti & Schoeman, 2014; Peterson, 2014; Hoek, van, Hesta & Biourge, 2015; McLean *et al.*, 2017; Fossum, 2019; Nelson & Couto, 2019). In fact, at the time of diagnosis, over 95% of hyperthyroid cats are senior (i.e., >10 years old [Quimby *et al.*, 2021]) (Peterson, 2014, 2020), with an average of 13 years old (Nelson & Couto, 2019). Thyroid dysfunction, however, seems to be rare in patients younger than eight years old (Nelson & Couto, 2019; Geddes & Aguiar, 2022). The old age at the time of diagnosis may be a reflection of chronic exposure to thyroid disruptors (Hoek, van, Hesta & Biourge, 2015).

No obvious breed predilection has been found in most epidemiologic studies (Peterson, 2012, 2014). However, domestic short-haired and long-haired cats seem to be the breeds more prone to develop HT (Peterson, 2014; Nelson & Couto, 2019). Furthermore, one article postulated that long-haired non-purebred cats are at more risk of thyrotoxicosis than short-haired ones. It is possibly due to greater exposure to goitrogens through grooming or an increased requirement for tyrosine, taking into account its role in melanin production (Yu, Lacorcia & Johnstone, 2022). On the other hand, some studies have consistently found that purebred cats have less risk of developing FHT (Peterson & Ward, 2007; Fossum, 2019), in particular Siamese and Himalayan breeds (Peterson & Ward, 2007; McLean, Lobetti & Schoeman, 2014; Peterson, 2014; Carney *et al.*, 2016; McLean *et al.*, 2017; Jones, Engdahl & Weiss, 2019; Nelson & Couto, 2019). Actually, a 10-fold risk of developing HT in non-Siamese breeds has been reported (Miller, 2022).

Regarding additional genetic factors that may influence cat's susceptibility to the disease, there is no consensus whether there is a sex-related predisposition. Some authors identify females as more susceptible to develop FHT (Peterson & Ward, 2007; Peterson, 2014; McLean *et al.*, 2017; Jones, Engdahl & Weiss, 2019), whereas other authors reported no gender predilection (Peterson, 2012; Nelson & Couto, 2019).

Finally, certain lifestyle factors (i.e., indoor housing [Peterson, 2014; Hoek, van, Hesta & Biourge, 2015; McLean *et al.*, 2017; Nelson & Couto, 2019; Miller, 2022] and the use of cat litter [Peterson & Ward, 2007; Peterson, 2012; McLean, Lobetti & Schoeman, 2014; Peterson, 2014; Hoek, van, Hesta & Biourge, 2015; McLean *et al.*, 2017; Nelson & Couto, 2019]), have been identified as potential risk factors related to FHT.

Regarding housing habits, the increased risk among indoor cats may reflect a greater exposure to thyroid-disruptors found indoors (Hoek, van, Hesta & Biourge, 2015). On one hand, outdoor cats, which usually are left outside unsupervised, are more likely to get injured, ill or even die (Peterson, 2012). On the other hand, cats living primarily indoors usually receive better care, enjoy longer lives and are more likely to reach the age at which the onset of HT is more susceptible to occur.

Regarding the use of cat litter, it can either be a potential risk factor due to the likelihood of containing goitrogens that may leach out to the environment over time, or a merely marker for

cats that indeed stay most of their time at home (Peterson & Ward, 2007; Peterson, 2012; McLean, Lobetti & Schoeman, 2014; McLean *et al.*, 2017).

5. Diagnosis

FHT definitive diagnosis is achieved by combining the presence of one or more typical clinical signs with laboratory confirmation of persistently elevated serum thyroid hormone levels or an elevated thyroidal radioisotope uptake (Shiel & Mooney, 2007; Carney *et al.*, 2016; Yu, Lacorcia & Johnstone, 2022).

Although relatively easy to diagnose in classically presenting cats, due to an increased awareness about FHT and its insidious progression, routine screening tests for HT became more frequent, which has had significant implications on the diagnostic accuracy (Shiel & Mooney, 2007; Peterson, 2013). While many years ago, diagnosis was done when there were evident clinical presentations, nowadays the search for HT is performed in cats with few, if any, clinical signs (McLean *et al.*, 2017). Consequently, at the time of diagnosis, hyperthyroid cats are far less symptomatic (Bucknell, 2000; Shiel & Mooney, 2007; McLean *et al.*, 2017), which also implies resorting to more means of diagnosis to confirm or rule out HT, particularly on those subclinical animals with different health problems that may or may not relate to thyroidal disease.

While diagnosing FHT, besides the medical history, a meticulous PE and the measurement of thyroid hormone levels, it is also important to obtain a complete blood count, biochemical profile and a complete urinalysis (McLean *et al.*, 2017; Peterson, 2020; Yu, Lacorcia & Johnstone, 2022). This is especially important because most hyperthyroid cats are senior and may have underlying concomitant diseases (Peterson *et al.*, 2020). In fact, some non-thyroidal disorders may resemble FHT (Peterson, 2013; Nelson & Couto, 2019) or even supress it. Therefore, with a complete patient database, situations where HT is misdiagnosed in euthyroid cats or where hyperthyroid cats are misdiagnosed as euthyroid, are avoided, which is essential, considering that none of the treatment choices is completely harmless and that this disease can be fatal if left uncontrolled (Peterson, 2013).

5.1. Patient assessment

Clinical manifestations of FHT range from mild to severe and are related to: duration of the thyrotoxic state; presence of concomitant disorders and the body's response, or lack thereof; and to the pathological effects caused by excessive thyroid hormone (Peterson, 1984). Hence, clinical signs and PE findings vary considerably among patients (Peterson, 1984; Shiel & Mooney, 2007; Carney *et al.*, 2016). Besides, no clinical presentation is considered pathognomonic for FHT (Carney *et al.*, 2016). In other words, the presence or absence of one sign can neither diagnose nor exclude HT (Peterson, 1984). Therefore, not all the clinical signs and findings described below are present in every hyperthyroid cat, especially when diagnosed in the early stages of the disease (Geddes & Aguiar, 2022).

5.1.1. Medical history and clinical signs

5.1.1.1. Classic presentation

Weight loss accompanied by a normal to increased appetite are two classic signs of FHT (Peterson, 2014; Geddes & Aguiar, 2022; Yu, Lacorcia & Johnstone, 2022). In fact, more than 80% of hyperthyroid cats present weight loss at the time of diagnosis (McLean *et al.*, 2017). So much so that, when owners say things like “The diet is finally working” or “My cat is starving all the time” (Carney *et al.*, 2016), especially in relation to a senior cat, HT must be one of the main differential diagnoses (DD).

Considering that hyperthyroid cats tend to eat voraciously and/or overeat, vomiting after food ingestion is not uncommonly reported (Peterson, 1984, 2014). Furthermore, diarrhoea, increased frequency of defecation and faeces volume are often consequences of the thyroid hormones in excess (Peterson, 1984, 2014; Nelson & Couto, 2019; Yu, Lacorcia & Johnstone, 2022).

Other expressions often uttered by the owners of hyperthyroid cats include: “I think my cat is senile”, “My cat feels great and is acting like a kitten again”, “My cat is losing weight because it is so much more active” or “I can’t believe this cat is 16 years old” (Carney *et al.*, 2016). These usually evidence such FHT common signs like hyperactivity, nervousness, restlessness and increased vocalization (Peterson, 1984; Daniel & Neelis, 2014; Peterson, 2014; Petroff & Greco, 2020; Geddes & Aguiar, 2022; Yu, Lacorcia & Johnstone, 2022). Excessive grooming has also been reported (Nelson & Couto, 2019). The stated behavioural changes are usually characteristic of severe cases (Peterson, 2014), which may also be associated with aggressive behaviour or seizures (Fossum, 2019).

Considering the excessive grooming, the hyperactivity, the increased sense of stress, and possibly other reasons, hyperthyroid cats often shed excessive amounts of hair or may become really matted (Ferguson, 2018; Nelson & Couto, 2019), which gives them a neglected appearance.

Polyuria and polydipsia (PU/PD) have been observed in up to 74% of hyperthyroid patients. However, as diagnosis are performed earlier, PU/PD becomes less prevalent (Syme, 2007). Therefore, more recently, only up to 50% of the patients present with PU/PD at the time of diagnosis (McLean *et al.*, 2017). Regardless, these are still two of the most common clinical features of FHT (Nelson & Couto, 2019; Geddes & Aguiar, 2022; Yu, Lacorcia & Johnstone, 2022), such that owners often refer that they need to clean the litter box more regularly and/or their pet is drinking water from unusual places (Carney *et al.*, 2016). Once PU/PD are identified, further investigation is required to understand if it is the result of a concurrent NTI or the result of heat intolerance from FHT (Peterson, 1984; Syme, 2007; McLean *et al.*, 2017). In case of the latter, these signs tend to resolve after successful treatment (Peterson, 1984; Syme, 2007).

5.1.1.2. Atypical presentation: Apathetic or masked hyperthyroidism

Although the classic presentation of FHT is a thin, insatiably hungry, restless and hyperactive cat (Bucknell, 2000; Birchard, 2006; Daniel & Neelis, 2014; Carney *et al.*, 2016; McLean *et al.*, 2017; Nelson & Couto, 2019; Petroff & Greco, 2020; Bugbee *et al.*, 2023), approximately 10% of

patients develop a “apathetic or masked hyperthyroidism”, characterized by a complete opposite panel of clinical signs (Peterson, 1984; McLean *et al.*, 2017; Yu, Lacorcia & Johnstone, 2022). Accordingly, animals present with reduced appetite or anorexia, depression, lethargy and weakness, besides the weight loss characteristic of nearly all hyperthyroid cats (Peterson, 1984; Birchard, 2006; Peterson, 2014; McLean *et al.*, 2017; Ferguson, 2018; Nelson & Couto, 2019; Geddes & Aguiar, 2022; Yu, Lacorcia & Johnstone, 2022).

Some authors wonder whether this atypical FHT may represent an end-stage form of the disorder (Ferguson, 2018), when patients might suffer from severe cardiac complications or even develop underlying neoplastic disease. Because of such problems, some patients may look overweight rather than thin (McLean *et al.*, 2017).

5.1.2. Physical examination findings (Classic presentation)

5.1.2.1. General appearance

Typically, hyperthyroid cats have an unkempt appearance with evidence of weight loss or sarcopenia and haircoat changes (Peterson, 1984, 2014; Carney *et al.*, 2016; Nelson & Couto, 2019; Geddes & Aguiar, 2022).

However, in the early stages of thyroid disease, patients can have an ideal or even higher body condition score. The majority of mildly thyrotoxic animals suffer an initial muscle mass loss in the lumbar paravertebral area while keeping their abdominal adipose tissue (Peterson & Eirmann, 2014). Besides, while there is an adequate compensation, at an initial stage, polyphagia may counterbalance the weight loss related to the high thyrotoxic metabolic rate (Hall, 2011). However, when that compensation becomes inadequate, weight loss becomes noticeable (Peterson, 1984).

As the matted hair and shedding worsens, some cats may develop other dermatologic changes like greasy hair coat (Peterson, 2014) and patchy alopecia (Nelson & Couto, 2019).

5.1.2.2. Patient handling

Hyperthyroid cats are usually hyperactive during the consult, difficult to examine and and/or become aggressive (Peterson, 1984; Nelson & Couto, 2019). Usually, this behaviour tends to resolve once successfully treated (Nelson & Couto, 2019).

5.1.2.3. Thyroid gland palpation

As a non-invasive and inexpensive auxiliary method of diagnosis, thyroid gland palpation should be performed as part of the routine PE of all cats, being particularly important in those animals where HT is more likely (Peterson, 2013).

(Peterson, 2013) presents two different palpation techniques that, in the author’s opinion, should complement each other instead of one replacing the other: the classic and the Norsworthy techniques (Figure 10). For the classic technique, one of the clinician’s hands tilts the cat’s head backward while promoting a slight extension of the neck, whereas the thumb and the index fingertip of the other hand gently passes within the jugular furrows, downwardly, on both sides of

the trachea (Peterson, 1984, 2013). For the Norsworthy technique, with the clinician directly behind the cat, with one hand raises and turns the cat's head 45º to the right or left, while the tip of the index or middle finger of the other hand moves along the groove created by the trachea and the sternothyroid muscle (Peterson, 2013). The downward movement, described on both approaches, should be continuous from the laryngeal area to the sternal manubrium, identified as the thoracic inlet (Peterson, 2013). While with the classic technique both thyroid lobes are evaluated at the same time, with the Norsworthy method, one lobe is looked at a time. To examine the left lobe, the patient's head must be turned to the right and to look at the right lobe, the head must face the left (Figure 10) (Peterson, 2013). An enlarged thyroid is generally perceived as a "somewhat mobile, subcutaneous mass or a "blip" that slides or slips under the fingertips", as described by (Peterson, 2013).

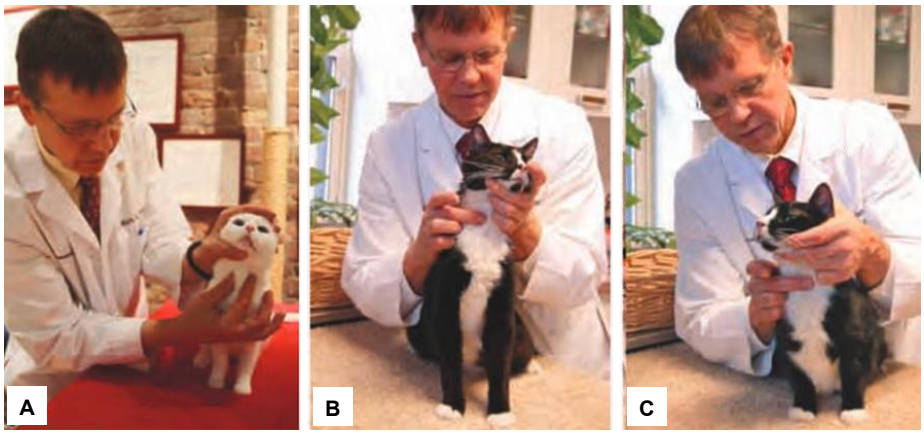


Figure 10 *– Thyroid palpation techniques: A – the classic technique; B and C – the Norsworthy technique. In B the cat's head is turned to the left so that the right thyroid lobe can be assessed, while in C the left thyroid lobe is the one being examined. From (Peterson, 2013)*

Thyroid palpation cannot always accurately distinguish between bilateral and unilateral thyroidal disease. Besides, as mentioned earlier, it is equally limited when it comes to differentiate goiter from adenoma or carcinoma (Peterson, 2014; Nelson & Couto, 2019). So, occasionally, when the term goiter is employed, it may solely mean that an enlarged thyroid was felt without excluding the presence of an adenoma or carcinoma.

On one hand, a palpable goiter is a highly sensitive test to diagnose FHT (Peterson, 2013) with very few cases where thyrotoxic animals do not present with it. However, false negatives should be considered: if the clinician presses too firmly, the gland may be pressed into the muscle and be mistaken for it (Peterson, 2013). Moreover, as the gland grows, it may migrate to the thoracic cavity where it can no longer be palpable (Peterson, 1984; Padgett, 2002; Peterson, 2013; Fossum, 2019; Nelson & Couto, 2019). This migration occurs in 10% of the affected lobes (Nelson & Couto, 2019). Other false negative results can be due to some thyrotoxic cats having ectopic glandular hyperactive tissue without a palpable goiter (Nelson & Couto, 2019). Animals in an early or subclinical stage, whose clinical signs are very mild, if existent, and the thyroid is very difficult to feel, are also candidates for misdiagnosis (Peterson, 2013).

On the other hand, a palpable goiter is a poorly specific test for FHT (Peterson, 2013; Yu,

Lacorcia & Johnstone, 2022) for two reasons: not all neck masses originate from the thyroid gland (Nelson & Couto, 2019) and goiter has been found in both clinically sound cats and those suffering from NTI (Yu, Lacorcia & Johnstone, 2022). However, there is a tendency among euthyroid cats with a “cold” goiter (i.e., the presence of a palpable thyroid mass without detectable HT) to develop clinical signs of FHT as the mass continues to grow morphologically and functionally (Peterson, 2013, 2014; McLean *et al.*, 2017). In fact, this period between the mass detection and the animal becoming clinically thyrotoxic is considered, by some authors, as subclinical HT or pre-hyperthyroidism and may last several years (Peterson, 2013, 2014; McLean *et al.*, 2017).

In summary, palpation of a cervical mass is not unquestionably indicative of HT. Therefore, a palpably enlarged thyroid gland is not pathognomonic for HT (Peterson, 2013; Carney *et al.*, 2016; Nelson & Couto, 2019), which means more diagnostic tools are required to confirm the suspicion.

5.1.2.4. Respiratory function assessment

Occasionally, thyrotoxic cats may present tachypnoea or even open-mouth breathing without an associated respiratory disorder (Nelson & Couto, 2019; Yu, Lacorcia & Johnstone, 2022). There may be multiple reasons for this (Syme, 2007): heat intolerance and increased cellular carbon dioxide production, both HT consequences, to name a few (Peterson, 1984; Hall, 2011; Veres-Nyéki, 2016). As these animals tend to get more stressed when handled, panting might be a reaction to the veterinary environment and the PE process itself (Syme, 2007).

5.1.2.5. Assessment of the cardiovascular system

Cardiac signs are very common in cats with HT (Peterson, 2014; McLean *et al.*, 2017), which, at some extent, may be related to the stimulatory effect that thyroid hormones exert on the cardiac tissue (Peterson, 1984; Birchard, 2006).

On PE, tachycardia is the most common cardiovascular abnormality (Syme, 2007; Peterson, 2014; Nelson & Couto, 2019), encountered in around 50% of FHT cases (Syme, 2007). Heart murmurs, arrythmias and gallop rhythms are often found as well (Padgett, 2002; Syme, 2007; Daniel & Neelis, 2014; Carney *et al.*, 2016; McLean *et al.*, 2017; Nelson & Couto, 2019; Peterson, 2020; Petroff & Greco, 2020; Geddes & Aguiar, 2022; Yu, Lacorcia & Johnstone, 2022). Moreover, detection of hyperkinetic femoral pulses and an increased left apical precordial beat is not uncommon (Syme, 2007; McLean *et al.*, 2017).

Since 25-87% of hyperthyroid cats develop hypertension (Trepanier, 2007; Geddes & Aguiar, 2022), usually clinically silent (Nelson & Couto, 2019), it is important to also look for signs of retinal haemorrhage and detachment (McLean *et al.*, 2017; Nelson & Couto, 2019), albeit uncommonly identified (Nelson & Couto, 2019). In most cats, such hyperthyroid-induced hypertension tends to resolve after treatment (Nelson & Couto, 2019).

5.1.2.6. Abdominal palpation

Usually, abdominal palpation in hyperthyroid cats is unremarkable. However, in some cases, it may be possible to detect kidneys or intestinal tract with abnormal size, shape or consistency.

This may suggest comorbidities or be a consequence of an advanced stage of thyroidal disease (Carney *et al.*, 2016).

5.2. Laboratory tests

5.2.1. Circulating hormones concentration measurement

5.2.1.1. Serum Total T4

In more than 90% of the old cats with classic clinical signs of FHT, serum total thyroxine (TT4) is clearly above the reference interval (RI) (Peterson, 2013; Daniel & Neelis, 2014; Peterson, 2014; Nelson & Couto, 2019). With such sensitivity and a specificity of 100% (McLean *et al.*, 2017; Yu, Lacorcia & Johnstone, 2022), considering its cheap price and that most of the times it is readily available, measuring TT4 has become the screening test of choice to confirm the diagnosis (Peterson, 2013, 2014; Peterson *et al.*, 2015).

Unfortunately, there are cases where a single TT4 test may not be enough to confirm or even rule out the diagnosis. For instance, HT may be suspected in cats with normal or even low Total T4 concentrations (Peterson, 2013), considering that approximately 10 percent of hyperthyroid cats, of which 30-40% with early to mild disease, have TT4 within the RI (Peterson, 2006, 2013; Peterson *et al.*, 2015;). These situations are related to the fact that serum T4 concentrations are influenced by concurrent illness and also randomly fluctuates within the RI (Peterson, 2006; Shiel & Mooney, 2007; Nelson & Couto, 2019; Geddes & Aguiar, 2022).

The greater the severity of the NTI, the greater is the degree of suppression of T4 serum concentration. Although mild concurrent disease seems to have little suppressive effect, moderate to severe sickness can mask early or mild HT by decreasing thyroid hormone values into the mid- to high-normal range (Peterson, 2006; Shiel & Mooney, 2007; Peterson, 2013; Daniel & Neelis, 2014; Peterson *et al.*, 2015). Low TT4 measurements are even detected in extremely ill cats (Peterson, 2006; Shiel & Mooney, 2007; Peterson, 2013). In these situations, such concomitant problems must be addressed first, and often, once managed, TT4 concentrations rise, which ultimately allows the correct assessment of the thyroid gland function (Peterson, 2013).

In addition, serum T4 nonspecific fluctuations, in and out of the RI, occur in all hyperthyroid cats. In severe thyrotoxic cats, TT4 fluctuations will not affect diagnosis. However, it can disturb the diagnosis in mild or moderately thyrotoxic animals (Peterson, 2006; Shiel & Mooney, 2007; Peterson, 2013).

T4 levels also tend to naturally decrease with age (Bugbee *et al.*, 2023). So, if a young cat is tested early on, the diagnosis is achieved more easily. In turn, this may justify why senior or geriatric hyperthyroid cats can be out of the diagnostic thyrotoxic range, despite being hyperthyroid (Bugbee *et al.*, 2023).

Other situations, where relying on a single TT4 test may be a mistake, are those in which a high serum T4 value is found in cats that lack clinical signs of HT (Peterson, 2013), because false positives may sometimes occur (Bugbee *et al.*, 2023). In fact, the method used to quantify serum

T4 can influence that.

5.2.1.2. Assay techniques for serum T4

There are four different ways to measure serum T4 levels: radioimmunoassay (RIA), chemiluminescent enzyme immunoassays (CEIAs), point-of-care enzyme-linked immunosorbent assay (ELISA) and enzyme immunoassay (EIA) (Peterson, 2013). None of them is 100% sensitive nor specific but all of them seem to provide good correlation with serum T4 concentrations (Peterson, 2013).

Briefly speaking, RIA and CEIAs use the same type of antibody. While the former measures the radioactive isotope bound to the hormone, the latter uses a photomultiplier tube that counts light emissions. In practical terms, RIA has several drawbacks: the use of radioactive reagents, lack of automation and expensive price. ELISA and EIA can be done in-house, are fully automated and are less expensive than RIA and CEIAs. As a matter of fact, EIA may be performed as part of the routine clinical chemistry testing (Peterson, 2013).

In terms of results, RIA is considered the gold standard, followed by the CEIAs that have been shown to provide very similar test results. Despite ELISA and EIA practical advantages, they seem to be not as reliable. ELISA has been found to overestimated T4 concentration in half of the cases, which leads some authors (Peterson, 2013) to disregard this as an accurate method to diagnose FHT. Moreover, EIA was reported to have a higher rate of false-negative and false-positive cases, when compared with CEIAs, and was considered inappropriate for situations of borderline high or low T4 values (Peterson, 2013).

The result should always be interpreted in the light of the animal's history, clinical signs and, if necessary, using complementary diagnostic procedures. If T4 levels are elevated but there are no clinical signs of HT, the clinician should repeat the test for TT4 using a different method, preferentially RIA or CEIA (Peterson, 2013).

5.2.1.3. Serum free T4

Non-thyroidal disease has less suppressive effect on serum free thyroxine (fT4) concentration than on TT4. Increased serum fT4 has been identified in cats with occult HT, whose TT4 levels where within the RI (Shiel & Mooney, 2007; Nelson & Couto, 2019). Taking this into consideration and that this technique has a higher sensitivity (98%) than TT4 (Shiel & Mooney, 2007; Peterson, 2013; Peterson *et al.*, 2015; McLean *et al.*, 2017; Geddes & Aguiar, 2022; Yu, Lacorcia & Johnstone, 2022), some authors feature fT4 as the hormonal test, which may better assess thyroid function (Peterson, 2013; Aldridge *et al.*, 2015; Nelson & Couto, 2019).

However, serum fT4 can never be the gold standard diagnostic technique for FHT (Peterson, 2013) due to its relatively poor specificity (Peterson, 2006; Shiel & Mooney, 2007; Peterson, 2013; Peterson *et al.*, 2015; McLean *et al.*, 2017; Yu, Lacorcia & Johnstone, 2022). False positives have been found in euthyroid animals with or without concurrent NTI (Peterson, 2006, 2006; Nelson & Couto, 2019;), albeit with no apparent reason associated (Peterson, 2006). For instance, some authors (Peterson, 2006; Yu, Lacorcia & Johnstone, 2022) report that up to 12% of euthyroid cats

with NTI may have elevated free thyroid hormone. Other authors (Geddes & Aguiar, 2022) expect that to be the case in 3-17% of non-thyrotoxic cats and a few report higher percentages of up to 30% euthyroid cats mistakenly diagnosed with HT regardless of the presence of concurrent disorder (Peterson, 2013; McLean *et al.*, 2017).

Therefore, on its own, fT4 is not a reliable tool to diagnose FHT and its results must always be interpretated in conjunction with TT4 levels (Peterson, 2006, 2006; Shiel & Mooney, 2007; Peterson, 2013; McLean *et al.*, 2017; Nelson & Couto, 2019; Geddes & Aguiar, 2022).

Despite its limitations, serum fT4 is currently the favoured option to try to identify hyperthyroid cats with nondiagnostic TT4 results (Shiel & Mooney, 2007; Peterson, 2013; Nelson & Couto, 2019). On one hand, a low or low-normal TT4 result allied to a high fT4 is usually indicative of non-thyroidal disease (Peterson, 2006; Shiel & Mooney, 2007; Peterson, 2013; Nelson & Couto, 2019). On the other hand, a high fT4 combined with a TT4 in the upper half of the RI is consistent with FHT (Peterson, 2006; Shiel & Mooney, 2007; Peterson, 2013; McLean *et al.*, 2017). However, this may not be enough to confirm FHT and, in equivocal cats, both fT4 and serum TSH might have to be combined with TT4 (Peterson *et al.*, 2015).

In turn, there is not much benefit from coupling a fT4 test with a markedly elevated TT4 result, because in virtually all those cases fT4 rises concurrently to TT4 and it is an expensive test (Peterson, 2006; Shiel & Mooney, 2007; Nelson & Couto, 2019). So, it is indeed more cost effective to initially measure Total T4 concentration alone and reserve fT4 for those cats with suspected HT in which TT4 values are nondiagnostic (Peterson, 2006; Nelson & Couto, 2019).

As always, regardless of the tests that were performed, the results must be interpreted in the light of the cat's clinical signs and PE findings (Peterson, 2013).

5.2.1.4. Serum TSH

Excessive thyroid hormones in circulation will supress TSH production (see Figure 5). Therefore, hyperthyroid cats are expected to have undetectable serum TSH levels (i.e., <0.03 ng/mL) (Peterson, 2014; Peterson *et al.*, 2015; Nelson & Couto, 2019).

Until recently, a canine-specific TSH assay (cTSH) was the only available commercial test to evaluate serum TSH concentration in hyperthyroid cats (Peterson, 2013; Peterson *et al.*, 2015; Nelson & Couto, 2019). But, according to (Bugbee *et al.*, 2023), a commercial feline-specific TSH assay (fTSH) has just been recently released. The need for a fTSH is linked to the subpar sensitivity of cTSH to clearly distinguish low-normal feline TSH concentration from undetectable TSH concentration (Peterson, 2013, 2014; Peterson *et al.*, 2015). So, hopefully, fTSH will be a more reliable tool.

Despite the cTSH limitations, measuring serum TSH has a diagnostic value in cats with early to mild HT, more so when measured in conjunction with TT4 and fT4 (Peterson *et al.*, 2015; Nelson & Couto, 2019; Bugbee *et al.*, 2023). This is verified on the grounds that when combined with TT4 and fT4 tests, in spite of decreasing in sensitivity from 98% to 97% (i.e., sensitivity remains high), the test specificity of TSH distinctly rises from approximately 70% (i.e., poor specificity) to almost

99% (Peterson *et al.*, 2015; Nelson & Couto, 2019). Therefore, although undetectable TSH results may occur in both euthyroid or hyperthyroid animals (Nelson & Couto, 2019), just like some thyrotoxic cats fail to completely supress serum TSH concentrations (Peterson, 2013; Peterson *et al.*, 2015; Yu, Lacorcia & Johnstone, 2022), the diagnosis of FHT is extremely unlikely in cases with high-normal TT4 and fT4 plus a TSH greater than 0.03 ng/mL (Peterson *et al.*, 2015; Nelson & Couto, 2019;). At the same time, a serum Total T4 concentration increased or within the upper third of the RI combined with high serum fT4 and suppressed TSH level is consistent with a diagnosis of HT (Peterson *et al.*, 2015)

In addition to being an useful tool to rule out the disease in ambiguous cases (Peterson, 2013; Peterson *et al.*, 2015; Nelson & Couto, 2019; Geddes & Aguiar, 2022), cTSH has been used as a biomarker to determine the risk of a patient developing HT. Undetectable TSH concentration in a euthyroid senior cat is associated with an increased risk for subsequent diagnosis of FHT (Wakeling, Elliott & Syme, 2011; McLean *et al.*, 2017; Morré *et al.*, 2018). Some authors relate such findings with the animal being in a phase of subclinical HT (Peterson, 2014; McLean *et al.*, 2017).

5.2.1.5. Serum T3

The measurement of serum T3 is not an appropriate method to diagnose FHT, because around one-third of thyrotoxic cats, that present clearly high TT4 and fT4, maintain serum T3 concentration within the RI (Peterson, 2013; Peterson *et al.*, 2015).

5.2.2. Dynamic thyroid function tests

Dynamic thyroid function tests, such as T3 suppression test and TRH stimulation test (Table 30), should be used as a last resort (Shiel & Mooney, 2007; Peterson, 2013; McLean *et al.*, 2017; Yu, Lacorcia & Johnstone, 2022). This includes situations where serum TT4 remains equivocal, even after repetition, and fT4 measurement is unavailable or not helpful or a goiter is not detected; or when thyroid scintigraphy cannot be afforded or is unavailable (Peterson, 2006; Shiel & Mooney, 2007; Peterson, 2013). However, these dynamic techniques require multiple samples and have several side effects, which hinder its usefulness (McLean *et al.*, 2017).

Table 30 *– Commonly used protocols for dynamic thyroid function tests in cats. Adapted from (Fossum, 2019; Peterson, 2013; Shiel & Mooney, 2007)*

		T3 suppression test	**TRH stimulation test**
Drug		Liothyronine	TRH
Dose		25 µg/cat q8h for seven doses	0.1 mg/kg
Route		Oral	Intravenous
Sampling times		0 and 2-4h after last dose	0 and 4h
Assay		TT4	TT4
Interpretation	Euthyroidism	<20 nmol/L (<1.5 µg/dL) with >50% suppression	>60% increase
	Hyperthyroidism	>26 nmol/L (>2.0 µg/dL) ± <35% suppression	<50% increase

5.2.2.1. Triiodothyronine suppression test

The T3 suppression test relies on the physiological thyroid hormone negative feedback control on hypothalamus-pituitary hormone secretion (Shiel & Mooney, 2007; Nelson & Couto, 2019). Therefore, upon administration of exogenous T3, T4 serum concentration, in euthyroid cats, suffers a marked fall of more than 50%, relative to the basal value (Table 30), due to the expected suppression of TRH and TSH production. In contrast, because in hyperthyroid patients the HPTa is chronically suppressed, TT4 remains high (Peterson, 2006; Fossum, 2019; Nelson & Couto, 2019).

Much of this procedure is implemented by the animal's owner, at home, via oral administration of a synthetic T3 (e.g., liothyronine) tablet, three times a day, for a couple of days, and a last dose on the morning of the third day. Besides that, two blood samples are required: one before the procedure to determine basal thyroid hormone concentration and, the other one, two to four hours after the seventh dose (Peterson, 2006; Fossum, 2019; Nelson & Couto, 2019). For a more accurate interpretation of the results, both samples, should be submitted together to the same laboratory, which implies that the serum from the first sample must be kept refrigerated or frozen, after having centrifuged the blood and extracted the serum (Peterson, 2006).

As a complement to T3 suppression test, T3 serum levels can be evaluated to assess owner's compliance. If the owner followed through with the protocol, T3 serum levels will increase regardless of diagnosis (Fossum, 2019; Nelson & Couto, 2019). So, test results should be questioned when TT4 suppression is poor and serum T3 levels do not rise as expected, in order to avoid treating false positive animals (Peterson, 2006).

In conclusion, multiple disadvantages are associated with this technique such as a three day wait period and the results dependence on owner's compliance, on the cat's ability to swallow the tablet and its adequate GI absorption, albeit no adverse reactions are described (Peterson, 2006; Shiel & Mooney, 2007; Peterson *et al.*, 2015).

5.2.2.2. Thyrotropin-releasing hormone stimulation test

The TRH stimulation test evaluates the serum T4 values in response to an intravenous (IV) administration of 0.1 mg/kg of TRH (Table 30). Thyroid hormone concentration has to be determined before and four hours after the injection (Peterson, 2006; Fossum, 2019).

Since the HPTa is persistently inhibited to a great extend in hyperthyroid animals, when this test is performed, TT4 will increase by less than 50% relative to the basal value (Peterson, 2006; Fossum, 2019). In turn, in clinically normal cats, TT4 concentration increases in more than 60% (Peterson, 2006). Results between 50% and 60% are ambiguous (Peterson, 2006).

With this stimulation test it is not possible to differentiate between healthy cats and hyperthyroid cats with severe NTI, because the rise of T4 levels in more than 60% occur in both conditions (Peterson, 2006; Shiel & Mooney, 2007). For this reason, this represents a disadvantage of the technique.

In addition, transient side effects to TRH administration, for instance hypersalivation, vomiting, tachypnoea and defecation, are consistently reported (Peterson, 2006; Shiel & Mooney, 2007).

Considering that this stimulation test comes up with identical diagnostic value as the previous suppression test, its two major advantages include not being influenced by owners' compliance and the fact that results take less time (Peterson, 2006).

5.2.3. Hemogram

Broadly speaking, a hemogram adds no great value to the diagnostic process because results of cell blood count (CBC) are usually normal (Nelson & Couto, 2019; Bugbee *et al.*, 2023). If hematologic abnormalities are found, they are of little diagnostic significance (Shiel & Mooney, 2007). Nevertheless, it might be worth listing below some of most common abnormalities.

As far as erythrocytes are concerned, macrocytosis and mild erythrocytosis, with consequently mildly increased packed cell volume, can be detected (Shiel & Mooney, 2007; Nelson & Couto, 2019; Petroff & Greco, 2020; Geddes & Aguiar, 2022). Occasionally, in cases of severe HT and/or comorbidities, the hemogram can show signs of anaemia (Shiel & Mooney, 2007; Bugbee *et al.*, 2023). Moreover, despite being present in less than 20% of FHT cases, changes in leukocytes parameters may include: neutrophilia, lymphopenia, eosinopenia or monocytopenia (Shiel & Mooney, 2007; Nelson & Couto, 2019).

Regarding platelets parameters, hyperthyroid cats have been identified with a higher mean platelet size. However, its relevance is not fully understood (Shiel & Mooney, 2007). Likewise, some patients have developed thromboembolism, but HT has not been shown to consistently alter platelet function (Hiebert *et al.*, 2020).

5.2.4. Biochemistry

In about 80 to 90% of thyrotoxic cats, at least one of the serum liver enzymes (i.e., alanine aminotransferase [ALT], aspartate aminotransferase [AST] and alkaline phosphatase [ALP]) is mild to markedly elevated (Shiel & Mooney, 2007; Nelson & Couto, 2019; Petroff & Greco, 2020; Bugbee *et al.*, 2023). Such common serum biochemical abnormalities, are mostly related to the boost in metabolic rate due to the excessive thyroxin in circulation. It actually induces liver hypermetabolism and increases hepatic clearance, which equally is responsible for the decline in overall serum cholesterol (Petroff & Greco, 2020). After successful management of FHT, these parameters tend to resolve. Otherwise, hepatic concurrent disease should be investigated (Shiel & Mooney, 2007; Nelson & Couto, 2019; Bugbee *et al.*, 2023).

Furthermore, as muscle catabolism worsens in thyrotoxic cats, elevation of the blood urea nitrogen (BUN) concentration and a decrease of serum creatinine (sCr) concentration may be detected (Syme, 2007; Petroff & Greco, 2020; Bugbee *et al.*, 2023). In addition, these biomarkers, more particularly sCr, can be affected by kidney dysfunction. So, if suspicion about such concurrent disease is raised, further investigation is required (Bugbee *et al.*, 2023).

Elevated glucose concentrations may be found in FHT cases but as a stress response (Shiel & Mooney, 2007; Peterson & Eirmann, 2014).

5.2.5. Urinalysis

Most hyperthyroid cats present a slightly decreased urine specific gravity (USG), due to PU/PD (Petroff & Greco, 2020; Bugbee *et al.*, 2023). In addition, although the mechanism behind it remains not well known (Vaske, Schermerhorn & Grauer, 2016), it is common to find proteinuria in these patients (Shiel & Mooney, 2007; Syme, 2007; Vaske, Schermerhorn & Grauer, 2016; Nelson & Couto, 2019), which tends to resolve upon HT treatment (Syme, 2007; Nelson & Couto, 2019). The remainder of the urinalysis is usually unremarkable, unless certain concurrent diseases (i.e., DM, urinary tract infection [UTI] or CKD) are present (Nelson & Couto, 2019; Bugbee *et al.*, 2023). However, the effect of thyroid hormone excess on the urinalysis can be extremely variable (Shiel & Mooney, 2007; Petroff & Greco, 2020; Bugbee *et al.*, 2023). Therefore, some authors suggest that performing routine urine tests in hyperthyroid cats may add no value to the diagnosis (Shiel & Mooney, 2007).

Although some authors have postulated that thyrotoxic cats are more prone to develop subclinical bacteriuria (i.e., testing positive for bacterial urine culture despite no clinical evidence of UTI), more recent studies have refuted such relation and, at the same time, instituted the idea that urine cultures should not be included as part of the routine evaluation of these patients (Peterson *et al.*, 2020).

5.3. Imaging

5.3.1. Scintigraphy

Although scintigraphy is not crucial for the FHT diagnosis (Shiel & Mooney, 2007), it provides both functional and anatomical information that no other single diagnostic method can (Daniel & Neelis, 2014). By providing a picture of all active thyroid tissue, the assessment of thyroid size, location and activity becomes more accurate (Peterson, 2014; Nelson & Couto, 2019): allowing the differentiation between unilateral and bilateral disease, and in case of the latter, distinguishing between symmetrical or asymmetrical distribution (Padgett, 2002; Shiel & Mooney, 2007; Daniel & Neelis, 2014; McLean *et al.*, 2017; Geddes & Aguiar, 2022; Xifra, Serrano & Peterson, 2022); identifying the presence of hyperfunctional ectopic thyroid tissue or an extension of the goiter into the thoracic inlet and mediastinum (Padgett, 2002; Shiel & Mooney, 2007; Daniel & Neelis, 2014; Peterson, 2014; Fossum, 2019; Nelson & Couto, 2019; Geddes & Aguiar, 2022; Yu, Lacorcia & Johnstone, 2022); helping, at some extent, to exclude thyroid carcinoma (Xifra, Serrano & Peterson, 2022; Yu, Lacorcia & Johnstone, 2022); and pinpointing metastasis in case of malignant thyroidal disease (Padgett, 2002; Shiel & Mooney, 2007; Peterson, 2014; Nelson & Couto, 2019). Besides, the results from a scintigraphy are less likely to be influenced by NTI (Shiel & Mooney, 2007).

Performing a scintigraphy requires specialist facilities and clinicians licensed to work with radioactive material. In addition, it is a very expensive procedure (Shiel & Mooney, 2007; Peterson, 2013; Daniel & Neelis, 2014). So, despite being considered the gold standard method for confirming or excluding FHT in mild or occult cases (Peterson, 2013; Peterson *et al.*, 2015), it

is not used as often as it could be (Peterson, 2013; Daniel & Neelis, 2014; Peterson *et al.*, 2015; McLean *et al.*, 2017).

The most commonly used radionuclides for this procedure are isotopes of radioactive iodine (^{123}I or ^{131}I) and pertechnetate ($^{99m}TcO_4^-$) (Peterson, 2014; Ferguson, 2018). Both reflect the iodine trapping mechanism of the thyroid gland, however while the former is actually incorporated into tyrosine amino acids of thyroglobulin and stored within the colloid, the latter is neither organified nor stored inside the gland (Shiel & Mooney, 2007; Peterson, 2014; Ferguson, 2018; Fossum, 2019; Nelson & Couto, 2019). Pertechnetate is the preferred radionuclide because of its better availability, lower cost, superior image quality, shorter half-life and increased safety (Shiel & Mooney, 2007; Peterson, 2014; Ferguson, 2018). Moreover, the peak uptake of $^{99m}TcO_4^-$ occurs within 20 minutes, as compared to eight hours for radioactive iodine, allowing faster imaging analysis after radionuclide administration (Peterson, 2014).

The protocol to use $^{99m}TcO_4^-$ is not very clear, inasmuch as different authors report different ways of administration, such as: intravenous (Shiel & Mooney, 2007; McLean *et al.*, 2017; Fossum, 2019; Xifra, Serrano & Peterson, 2022), intramuscular (IM) (Fossum, 2019) and subcutaneous (SQ) (Shiel & Mooney, 2007; McLean *et al.*, 2017). Regardless, thyroid imaging, typically using a gamma camera (Daniel & Neelis, 2014; Fossum, 2019), can be performed from 20 minutes up to 60 minutes after injection (Shiel & Mooney, 2007; Daniel & Neelis, 2014; McLean *et al.*, 2017; Xifra, Serrano & Peterson, 2022).

In euthyroid cats, two well-defined, with smooth and regular margins, elongated, symmetrical (in shape and size) thyroid lobes with a uniform distribution of radioactivity are expected to be found (Figure 11) (Daniel & Neelis, 2014; Peterson, 2013). In turn, hypersecretory thyroid lobes usually exhibit an heterogenous appearance with focal areas of increased radionuclide uptake. These areas may also be enlarged in either a portion of the gland or as a “string of pearls” (Figure 11) and, although scintigraphy cannot reliably differentiate benign from malignant illness, when associated with irregular and spiculated margins they are most likely carcinomas. Radioactive patterns where foci of uptake are seen outside the confines of the gland are equally indicative of carcinoma. Moreover, by looking at the distribution of radionuclide, it is possible to assess if the disease is bilateral, unilateral, symmetrical or asymmetrical. Typical unilateral disease is defined by increased uptake by one lobe and total suppression of the contralateral (Figure 11). However, in cats, the lobe exhibiting normal uptake will be almost certainly equally hyperplasic, therefore both lobes are usually considered abnormal (Padgett, 2002; Daniel & Neelis, 2014). On the other hand, areas with less radioactivity may be identified as the suppressed normal thyroid parenchyma. Ectopic thyrotoxic tissue and metastasis from malignant HT will be evident with increased uptake as well (Figure 11) (Daniel & Neelis, 2014).

In addition to visual inspection, based on the principal that $^{99m}TcO_4^-$ is also concentrated by salivary glands (Nelson & Couto, 2019), radioisotope uptake can be estimated by determining the thyroid:salivary ratio (T/S.r), where the intensity of thyroid gland uptake is compared with the zygomatic salivary tissue (Daniel & Neelis, 2014; McLean *et al.*, 2017; Yu, Lacorcia & Johnstone,

2022). In euthyroid cats, both tissues are expected to be equally bright, with a 1:1 ratio (Peterson, 2013, 2014; Nelson & Couto, 2019) (Figure 11). Therefore, a T/S.r greater than two is diagnostic of FHT (Fossum, 2019). Alternatively, the percentage thyroidal uptake of the radioactive tracer can be determined, because it also strongly correlates with serum TT4 concentration (Peterson, 2006, 2013; Daniel & Neelis, 2014; Peterson, 2014; Xifra, Serrano & Peterson, 2022). However, it is not routinely performed (Shiel & Mooney, 2007; Daniel & Neelis, 2014).

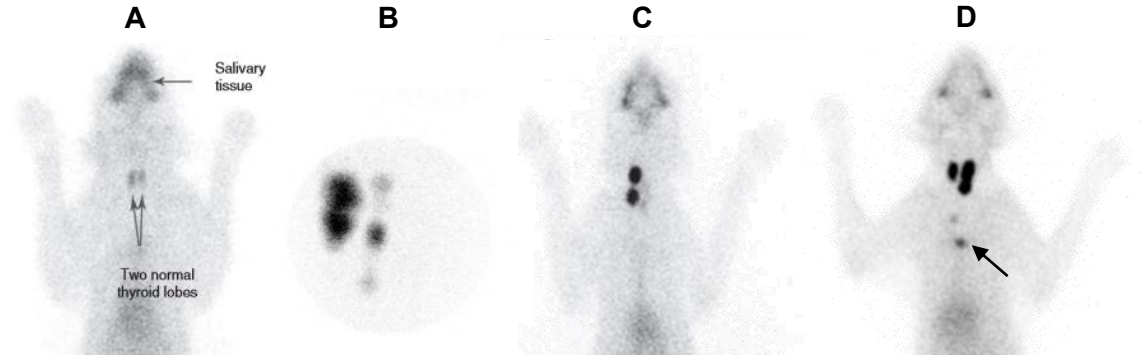


Figure 11 *– Thyroid scintigraphy in a euthyroid cat (A) and three hyperthyroid cats (B, C and D). A: Two well-defined, with smooth and regular margins, elongated, symmetrical (in shape and size) thyroid lobes with a uniform distribution of radioactivity and a 1:1 T/S.r are visualized. B: Scan of bilaterally thyrotoxic gland with left lobe enlarged in two different areas and the right one with the shape of a "string of pearls". C: Thyroid gland unilaterally hyper radioactive. D: Bilaterally thyrotoxic thyroid gland and ectopic tissue present in the cranial mediastinum (arrow). Adapted from (Daniel & Neelis, 2014)*

5.3.2. Ultrasonography

Despite not being recommended to establish the diagnoses of FHT (Nelson & Couto, 2019), an ultrasonographic evaluation of the thyroid gland might differentiate between unilateral and bilateral disease. In addition, it can help identify the origin of the cervical palpable mass and provide information about its morphology and tendency to spread (Shiel & Mooney, 2007; Nelson & Couto, 2019). In fact, this method seems to agree with scintigraphy on 85% of the cases when it comes to distinguish normal from abnormal thyroid lobes (Shiel & Mooney, 2007). However, thyroid ultrasonography cannot assess the functional status of the mass and does not identify metastases or ectopic hyperfunctional tissue, besides being technically challenging and operator and equipment dependent (Shiel & Mooney, 2007; Nelson & Couto, 2019).

Echocardiography, on the other hand, has great diagnostic value to rule out or confirm the existence of comorbidities, especially in hyperthyroid cats manifesting signs of cardiac disease (i.e., heart murmurs, arrhythmias, dyspnoea, etc.) (Peterson, 2006).

5.3.3. Computed tomography scan

CT scan may help shed light on the dimension, volume and invasiveness of the tumour. However, considering that it fails to provide functional information; that it may not accurately recognize ectopic thyroid tissue or carcinoma metastasis; its expensive cost; and its availability, CT is not being used to diagnose HT (Shiel & Mooney, 2007; McLean *et al.*, 2017).

5.3.4. Radiography

In terms of diagnosing FHT, radiography is even more limited than the previous methods. It may be useful to look for metastases, but even those need to be obvious in order to be identifiable (Padgett, 2002).

Other than that, it may be important for evaluation of concurrent NTI or to assess overall patients' health (Young *et al.*, 2022). In that sense, similar to echocardiography, chest radiography should be performed in hyperthyroid cats manifesting signs of cardiac disease (i.e., heart murmurs, arrhythmias, dyspnoea, etc.) (Peterson, 2006).

5.4. Differential diagnoses

When presented with a cat with clinical signs suggestive of HT, a number of DD should be equated, including: CKD, primary central nervous system deformities, acquired or congenital cardiac dysfunction, GI malabsorption or maldigestion (particularly inflammatory bowel disease [IBD]), neoplasia (particularly GI lymphoma), DM and parasitism (Carney *et al.*, 2016; Fossum, 2019; Bugbee *et al.*, 2023).

5.5. Recommendations on how to approach non-straightforward cases: possible scenarios

When FHT cases present with classic clinical signs of thyrotoxicosis, elevated TT4 and no comorbidities, the diagnosis of HT can be straightforward. However, concurrent NTI can often make the diagnosis ambiguous and difficult to achieve (Carney *et al.*, 2016; Bugbee *et al.*, 2023). Therefore, a systematic and categorical approach to diagnose suspected FHT has been devised (Carney *et al.*, 2016; Bugbee *et al.*, 2023). It uses the outcome of the physical exam, patient history and laboratory results to assign the patient to one of the diagnostic categories described below.

5.5.1. Cats with clinical signs of hyperthyroidism and normal TT4 values

When cats display clinical signs of HT and TT4 values are within the RI, clinicians should suspect of possible HT with probable NTI. In these cases, TT4 values should be reevaluated in two to four weeks after the initial blood screening and fT4 should also be looked at (Carney *et al.*, 2016; Bugbee *et al.*, 2023). If TT4 level is in the upper half of the RI and fT4 is elevated, the diagnosis of HT is supported (Peterson, 2013; Carney *et al.*, 2016; Nelson & Couto, 2019; Bugbee *et al.*, 2023); if both TT4 and fT4 remain normal, one should look for NTI. In case no concurrent illness is diagnosed but FHT is still suspected, then serum TSH, dynamic thyroid function tests and/or thyroid scintigraphy should be pursued (Peterson, 2006, 2013; Carney *et al.*, 2016; Fossum, 2019; Geddes & Aguiar, 2022; Yu, Lacorcia & Johnstone, 2022; Bugbee *et al.*, 2023).

5.5.2. Cats without clinical signs of hyperthyroidism, with palpable goiter and normal TT4 values

When cats present with an enlarged thyroid gland, no clinical signs of FHT and normal TT4, a

blood screening should be repeated within six months to reassess TT4 concentration and, in the meantime, close monitoring for the development of clinical signs is warranted (Peterson, 2013; Carney *et al.*, 2016; Geddes & Aguiar, 2022; Bugbee *et al.*, 2023).

5.5.3. Cats without clinical signs of hyperthyroidism, without palpable goiter and elevated TT4 values

When TT4 values are elevated in clinically normal cats without a palpable neck mass, suspicion should be raised upon false positive TT4 results. In those situations, TT4 should be reevaluated using the gold standard method, RIA. If RIA is not possible, CEIAs is the second most reliable test. Treatment for HT should be pursued in case TT4 remains elevated. However, if the TT4 re-evaluation comes back normal, treatment should be held off and the animal retested every six months or sooner if clinical signs develop (Carney *et al.*, 2016; Bugbee *et al.*, 2023).

5.5.4. Cats without clinical signs of hyperthyroidism, with physical examination findings suggestive of hyperthyroidism and elevated TT4 values

When TT4 values are elevated, there are no clinical signs of FHT but there are some PE findings that raise suspicion (i.e., palpable goiter), then the cat is most probably suffering from subclinical HT. In these cases, TT4 evaluation should be repeated in one to two weeks (Carney *et al.*, 2016; Bugbee *et al.*, 2023). If TT4 remains elevated, it is advisable to treat the patient for HT (Carney *et al.*, 2016; Geddes & Aguiar, 2022; Bugbee *et al.*, 2023). Otherwise, TT4 should be reevaluated in six months accompanied with a complete physical exam (Carney *et al.*, 2016; Bugbee *et al.*, 2023;).

6. Treatment

Due to the thyroid tumours' nature to keep growing over time, FHT is a progressive disease that left untreated will eventually be fatal (Peterson, 2020; Bugbee *et al.*, 2023). Therefore, treatment of HT is directed at limiting the excessive secretion of thyroid hormones (Peterson, 2006, 2020; Yu, Lacorcia & Johnstone, 2022) and consequently controlling the multisystemic effects of such excess.

There are four main treatment modalities for FHT: radioiodine, surgical thyroidectomy, antithyroid medication and iodine-restricted diet therapy (Birchard, 2006; Boland *et al.*, 2014; Geddes & Aguiar, 2022; Yu, Lacorcia & Johnstone, 2022). While the first two options are considered permanent, definitive or curative methods; the last two are labelled as reversible or palliative (Peterson, 2020). This is related to the fact that with radioactive iodine and surgery there is truly an ablation of the hyper-functional tissue or removal of the abnormal thyroid lobe(s) (Yu, Lacorcia & Johnstone, 2022), respectively, in opposition to the other two approaches that can only keep the circulating T4 within the RI when administered ongoing (Peterson, 2020).

Considering that no option is completely benign and that each has its advantages and disadvantages (Table 31), the treatment plan decision should take into account factors like: patient's medical condition, age, the presence of comorbidities, the likelihood of the thyroid tumour

becoming a carcinoma, therapy availability and aspects related to the owners themselves (Padgett, 2002; Fossum, 2019; Grossi *et al.*, 2019; Peterson, 2020). Regarding owners, it may be important to understand their preferences, tolerance for complications, ability to medicate the animal and their financial resources (Padgett, 2002; Grossi *et al.*, 2019).

Regarding the financial factor, dietary therapy may be thought to be the cheapest option. However, the lifelong cost of treating uncomplicated FHT is similar regardless the chosen method, because the cost of permanent methods is borne up front, whereas the cost of medical and nutritional management is separated over time (Carney *et al.*, 2016). Recently, it has been reported that the cost of ongoing therapy over a period of many months to years can exceed that of surgery or radioiodine (Peterson, 2020; Geddes & Aguiar, 2022).

Table 31 *– Considerations regarding treatment options for FHT*

	Radioiodine	Thyroidectomy	Antithyroid medication	Dietary Therapy
Indications	- Younger and senior cats without concurrent illness (Peterson, 2014, 2020) - Cats with more severe HT and larger goiters (Peterson, 2020) - Cats with ectopic thyroid tissue (Nelson e Couto, 2019) - Cats with thyroid carcinoma (Nelson e Couto, 2019)	- Younger and senior cats without concurrent illness (Peterson, 2014, 2020) - Cats with more severe HT and larger goiters (Peterson, 2020)	- Initial treatment to stabilize cat's condition and assess kidney function before definitive treatment (Nelson e Couto, 2019)	- Initial treatment to stabilize cat's condition and assess kidney function before definitive treatment (Nelson e Couto, 2019) - Cats enabled to receive definitive or medical treatment (Peterson, 2020)
Relative contraindications	- Renal insufficiency (Nelson e Couto, 2019)	- Ectopic thyroid lobes (Nelson e Couto, 2019) - Metastatic carcinoma (Nelson e Couto, 2019) - Bilateral, symmetrical large lobes (Nelson e Couto, 2019) - Severe systemic signs (Nelson e Couto, 2019) - Cardiac arrhythmias or failure (Nelson e Couto, 2019) - Renal insufficiency (Nelson e Couto, 2019)	- None (Nelson e Couto, 2019)	- Concurrent administration of antithyroid medication (Nelson e Couto, 2019)
Advantages	- Destroys thyroid tumoral tissue (Carney *et al.*, 2016; Peterson, 2020) - Treats all hyperfunctional tissue, regardless of anatomical location (Yu, Lacorcia e Johnstone, 2022)	- Removes thyroid tumour (Peterson, 2020; Yu, Lacorcia e Johnstone, 2022) - Allows histopathological evaluation of the thyroid tissue (Yu, Lacorcia e Johnstone, 2022) - Requires no special equipment (Carney *et al.*, 2016; Peterson *et al.*, 2020) - Can be performed by most general surgeons (Carney *et al.*, 2016; Peterson *et al.*, 2020)	- Widely available (Yu, Lacorcia e Johnstone, 2022) - Titratable and reversible (Carney *et al.*, 2016) - No hospitalization required (Carney *et al.*, 2016)	- Widely available (Yu, Lacorcia e Johnstone, 2022) - Titratable and reversible (Carney *et al.*, 2016) - No hospitalization required (Carney *et al.*, 2016)

Disadvantages	- Requires radiation safety expertise, licencing and specialty facilities (Carney *et al.*, 2016; Yu, Lacorcia e Johnstone, 2022) - Hospitalization and isolation time (Carney *et al.*, 2016; Nelson e Couto, 2019) - Patients are hazardous to humans (Nelson e Couto, 2019) - Not reversible (Carney *et al.*, 2016)	- Anaesthetic risk (Carney *et al.*, 2016; Nelson e Couto, 2019) - Requires hospitalization (Carney *et al.*, 2016) - Not reversible (Carney *et al.*, 2016)	- Thyroid tumour continues to grow and may become malignant (Carney *et al.*, 2016; Nelson e Couto, 2019; Peterson, 2020) - Need for ongoing and daily therapy (Carney *et al.*, 2016; Nelson e Couto, 2019; Yu, Lacorcia e Johnstone, 2022) - Dependence on owners's and cats' compliance (Peterson, 2020; Yu, Lacorcia e Johnstone, 2022)	- Thyroid tumour continues to grow and may become malignant (Carney *et al.*, 2016; Nelson e Couto, 2019; Peterson, 2020) - Need for ongoing therapy (Carney *et al.*, 2016; Yu, Lacorcia e Johnstone, 2022) - Dependence on owners's and cats' compliance (Peterson, 2020; Yu, Lacorcia e Johnstone, 2022) - Requires exclusive feeding (Carney *et al.*, 2016; Nelson e Couto, 2019; Peterson, 2020; Yu, Lacorcia e Johnstone, 2022) - Cat must be kept indoors (Nelson e Couto, 2019) - Problematic in multi-cat household (Nelson e Couto, 2019) - Poor palatability (Peterson, 2020)
Possible complications	- Hypothyroidism (Peterson, 2020; Yu, Lacorcia e Johnstone, 2022) - Recurrence or persistence of FHT (Peterson, 2020; Yu, Lacorcia e Johnstone, 2022)	- Hypothyroidism (Peterson, 2020; Yu, Lacorcia e Johnstone, 2022) - Hypoparathyroidism/hypocalcaemia (Carney *et al.*, 2016; Nelson e Couto, 2019; Peterson, 2020; Yu, Lacorcia e Johnstone, 2022) - Recurrence or persistence of FHT (Peterson, 2020; Yu, Lacorcia e Johnstone, 2022) - Horner's syndrome (Peterson, 2020; Yu, Lacorcia e Johnstone, 2022) - Laryngeal paralysis (Yu, Lacorcia e Johnstone, 2022) - Haemorrhage or death intra-op (Yu, Lacorcia e Johnstone, 2022)	- Hypothyroidism (Peterson, 2020) - Recurrence when off medication (Carney *et al.*, 2016; Peterson, 2020) - Commonly associated to multiple adverse reactions (Carney *et al.*, 2016; Nelson e Couto, 2019; Yu, Lacorcia e Johnstone, 2022)	- Recurrence of FHT when off diet (Carney *et al.*, 2016; Peterson, 2020) - Long-term consequences of iodine restriction are yet to be fully understood (Nelson e Couto, 2019)
Success rate	- Very high (>95%) (Carney *et al.*, 2016; Peterson, 2020; Yu, Lacorcia e Johnstone, 2022)	- High (>90%) (Carney *et al.*, 2016; Peterson, 2020)	- Fairly high (75%) (Peterson, 2020), in some cases high (>90%) (Yu, Lacorcia e Johnstone, 2022)	- Around 50% (Peterson, 2020)
Time to euthyroid	- Days to weeks (Peterson, 2020)	- Within 24-48 hours (Carney *et al.*, 2016; Peterson, 2020)	- Two to four weeks (Peterson, 2020)	- Very variable (Carney et al., 2016; Geddes & Aguiar, 2022; Bugbee et al., 2023)

6.1. Definitive treatment

Radioiodine and thyroidectomy are the only curative procedures available, because no other method is capable of permanently destroying or removing the hyperfunctioning thyroid tissue

(Boland *et al.*, 2014; Nelson & Couto, 2019; Peterson, 2020; Yu, Lacorcia & Johnstone, 2022).

Being mindful of that and that thyrotoxic cats never undergo spontaneous remission, definitive methods should be particularly carried out on those patients that are expected to live a long life (i.e., for instance longer than two to three years - time enough for the thyroid tumour to dramatically increase in size or undergo malignant transformation), in other words, younger or even healthy senior cats without concurrent illness (Peterson, 2014, 2020).

Permanent treatment may also be the best choice for cats with more severe HT and larger goiters, because they are more likely to become resistant to medical and nutritional management. In these cases, treatment must be performed before the cat ceases to be a good candidate due to overall poor body condition or worse complications like cardiac failure (Peterson, 2020).

6.1.1. Radioiodine

Radioactive iodine is considered the gold standard treatment for FHT (Boland *et al.*, 2014; Carney *et al.*, 2016; Morré *et al.*, 2018; Peterson & Rishniw, 2021; Geddes & Aguiar, 2022; Peak *et al.*, 2022; Xifra, Serrano & Peterson, 2022; Bugbee *et al.*, 2023). It is simple, effective and safe without significant morbidity and mortality (Padgett, 2002; Daniel & Neelis, 2014; Fossum, 2019; Nelson & Couto, 2019)

Because thyrocytes do not distinguish stable from radioactive iodine, the physiological dietary iodine-trapping mechanism by the thyroid gland is the foundation behind this treatment modality (Peterson, 2006). After administration, 10% to 24% of ^{131}I is actively concentrated by the hyperplastic or neoplastic thyrocytes. There, it produces both beta and gamma radiation to destroy the hyperfunctioning cells. Around 80% of tissue destruction results from the action of the beta particles, which travel a maximum of two millimetres. With such local action, adjacent structures like the parathyroid glands and other cervical structures are rarely damaged. Atrophic normal follicular cells are also preserved due to their inability to properly concentrate I_2, provided there is not an overdose. After the treatment they will eventually respond to TSH stimulation and resume thyroid hormone production (Peterson, 2006; Daniel & Neelis, 2014; Carney *et al.*, 2016; Ferguson, 2018; Fossum, 2019; Nelson & Couto, 2019; Peterson, 2020; Peak *et al.*, 2022; Yu, Lacorcia & Johnstone, 2022). The remainder radionuclide is excreted through saliva, urine and faeces (Peterson, 2006; Ferguson, 2018; Peak *et al.*, 2022).

Because of radiation concerns, due to ^{131}I biological (i.e.,1.5-4 days) and physical (i.e., eight days) half-lives (Peterson, 2006; Carney *et al.*, 2016; Ferguson, 2018; Nelson & Couto, 2019), patients submitted to radioiodine must be confined until they are no longer considered a human health hazard (Peterson, 2006; Daniel & Neelis, 2014; Fossum, 2019; Peak *et al.*, 2022). The duration of the hospitalization can range from three days to four weeks (Carney *et al.*, 2016), or even 40 days, albeit rare (Peak *et al.*, 2022). It will depend on the dose administered and the government regulations (Peterson, 2006; Boland *et al.*, 2014; Daniel & Neelis, 2014; Carney *et al.*, 2016; Fossum, 2019; Nelson & Couto, 2019; Peak *et al.*, 2022). The need for isolation and animal minimal contact somewhat justifies why cats must be relatively stable before the start of

the treatment and why animals with concurrent NTI subjected to complementary medication may not be good candidates (Peterson, 2006; Carney *et al.*, 2016; Fossum, 2019; Peterson, 2020).

In the early days of radioiodine therapy, no animal would be released without being individually assessed to ensure their radiation output had reached safe levels before discharge (Peak *et al.*, 2022). More recent approaches take into account that radiation protection measures can be put into practice at home and, thereby, helping to reduce hospitalization periods (Boland *et al.*, 2014; Peak *et al.*, 2022). Hence, cats are discharged knowing they will be excreting small amounts of the radionuclide for the next two to four weeks. During this period, cats must be kept indoors, children under 18 years old and pregnant women cannot be in contact with them, and the remaining household members must limit the amount of direct contact. Furthermore, one should use gloves to handle animal waste and follow proper disposal guidelines (Peterson, 2006; Daniel & Neelis, 2014).

In addition to the isolation requirement and potential human or animal health risk, the initial cost of the treatment, the limited availability of licensed centres with consequent long waiting periods for the treatment and the travel distance to the nearest one are other disadvantages related to this treatment modality (Birchard, 2006; Peterson, 2006, 2014; Boland *et al.*, 2014; Carney *et al.*, 2016; Ferguson, 2018; Fossum, 2019; Geddes & Aguiar, 2022; Padgett, 2002; Peak *et al.*, 2022). Interestingly, a survey about owners' perceptions and experiences of radioiodine therapy of FHT concluded that these limitations have low impact on owners' treatment choice (Boland *et al.*, 2014). In opposition, a moderate level of concern was indeed shown towards the confinement, but for reasons not related to the actual required isolation period length. Of the 158 respondents, 82.3% were concerned about the possibility of the cat being unhappy, around 62% were afraid they would miss the cat, a little bit more than 30% worried about their cat not eating while being apart from home, other owners wondered if the other pets at home would miss the cat (20.3%) and less than 20% of the respondents were apprehensive about the development of co-morbid disease or side effects while no visits were allowed. Therefore, when clinicians discuss radioiodine as a potential treatment option, these concerns should be addressed and the owners well informed and reassured (Boland *et al.*, 2014). In fact, although some cats may indeed become depressed if subjected to long periods of isolation (Peterson, 2006; Peak *et al.*, 2022), many centres address the environmental needs of the cats during that period of time with mental and physical stimulation. Hence, usually the cat is less stressed than the owners fear (Peterson, 2006; Carney *et al.*, 2016). Besides, it is noteworthy to fully explain to the owners that the amount of stress their cats may feel is similar to what they might experience when boarding while the owners are abroad and will always be much less than the stress of being ill or under other type of treatment. In other words, most cats tolerate the required post-treatment confinement fairly well (Carney *et al.*, 2016).

Despite the mentioned inconvenient characteristics, radioiodine therapy positively stands out from the others because: it has been repeatedly shown to be safe and effective with a single administration; it is the only option available with the potential to cure patients with metastatic or

nonresectable thyroid carcinomas; allows the destruction of ectopic hyperactive thyroid tissue; it is associated with a low prevalence of complications and longer survival time; it is non-invasive with no anaesthetic risk or risk of iatrogenic parathyroidectomy associated; avoids the inconvenience of daily, oral pharmacological management; and does not require the cat to have a restrictive diet (Padgett, 2002; Birchard, 2006; Peterson, 2006; Boland *et al.*, 2014; Daniel & Neelis, 2014; Carney *et al.*, 2016; Nelson & Couto, 2019; Peterson, 2020; Geddes & Aguiar, 2022; Peak *et al.*, 2022; Bugbee *et al.*, 2023).

6.1.1.1. Compatibility with other methods of FHT treatment

Some cats may benefit from a pre-treatment stabilization with administration of cardiac medications, β-adrenergic blocking agents or antithyroid drugs for a few weeks or one to two months (Peterson, 2006; Nelson & Couto, 2019). Even though β-adrenergic blocking agents do not interfere with the therapy outcome (Peterson, 2006), that may not be so true for thioureylenes.

Whether prior or concurrent therapy with antithyroid drugs affects the efficacy of this definitive method remains unclear, considering it has been variably proposed to worsen, enhance or have no influence on the outcome (Peterson, 2006; Fossum, 2019; Nelson & Couto, 2019). Overall, the majority of the treatment facilities recommend the discontinuation of the medication one to two weeks prior radionuclide administration and a subsequent TT4 evaluation to determine the actual severity of the cat's hyperthyroidism (Peterson, 2006; Nelson & Couto, 2019). However, animals with severe, life-threatening HT or concurrent disease may be advised to start radioactive therapy while still on antithyroid medication. In doubt, it is always best to discuss the cases with the radioiodine treatment centre (Peterson, 2006).

6.1.1.2. Treatment protocol

The purpose of radioactive iodine therapy is to restore euthyroidism without the development of post-treatment complications through administration of a single dose of radiation. Therefore, the optimal protocol is the one, which ensures that (Peterson, 2006; Carney *et al.*, 2016; Peterson & Rishniw, 2021; Xifra, Serrano & Peterson, 2022).

There are three methods of dosing the radioactive iodine to be administered: the fixed dose method, the variable dose method and the tracer technique (Peterson, 2006; Daniel & Neelis, 2014; Morré *et al.*, 2018; Matos *et al.*, 2022). With the fixed dose method, all hyperthyroid patients are administered with a relatively high dose, regardless of the severity of the disease or the size of the thyroid gland, which translates into animals severely thyrotoxic being undertreated or, more commonly, overtreatment of mildly affected cats (Peterson, 2006; Chow & White, 2022). The other two methods, albeit being more complex, allow an individual adjustment of the dosage. While the variable dose method uses a scoring system based on the severity of the clinical signs, the size of the goiter, either determined by PE or scintigraphy, and serum TT4 concentration (Peterson, 2006; Xifra, Serrano & Peterson, 2022); the tracer technique depends on the estimation of the percentage of iodine uptake, iodine biologic half-life and weight of the gland through thyroid imaging (Peterson, 2006; Daniel & Neelis, 2014). Unfortunately, the latter is not commonly used,

despite being the one that would theoretically produce the best results, because it seems to result in a marked difference between the calculated dose of radioiodine and the actual dose delivered to the cat's thyroid tissue (Peterson, 2006). In fact, due to the lack of consistent results associated with all three methods, there is no consensus on which one is the most appropriate (Peterson, 2006; Daniel & Neelis, 2014; Carney *et al.*, 2016; Morré *et al.*, 2018; Peterson & Rishniw, 2021; Matos *et al.*, 2022).

What seems to be agreed is that much larger doses of ^{131}I are required to destroy malignant thyroid cells. This is related to the fact that carcinomas are usually much bigger and their cells are less efficient at concentrating and retaining I_2 than adenomatous hyperplastic cells (Peterson, 2006; Carney *et al.*, 2016; Ferguson, 2018; Morré *et al.*, 2018; Fossum, 2019; Nelson & Couto, 2019). Obviously, the higher the dose, the longer the animal excretes radiation and the longer the isolation period will be (Peterson, 2006; Fossum, 2019). As an alternative to the administration of extremely high doses, the combination of surgical debulking prior administration of a high dose of iodine has been reported to be a successful strategy (Peterson, 2006; Carney *et al.*, 2016).

Radioactive iodine can be administered intravenously, orally or subcutaneously (Peterson, 2006; Nelson & Couto, 2019; Yu, Lacorcia & Johnstone, 2022). The latter is usually the preferred route, because it is not associated with GI effects, it has been shown to be as effective as the others, and it turns out to be safer for the staff (Peterson, 2006).

6.1.1.3. Possible post-treatment complications

A. Dysphagia and fever

During the first few days after treatment cats may develop, albeit very rarely, dysphagia and fever, probably due to radiation thyroiditis. Fortunately, such post-treatment complications are transient and resolve spontaneously (Peterson, 2006).

B. Hypothyroidism

Hypothyroidism is the most frequent complication of radioiodine therapy (Nelson & Couto, 2019), with up to 75% of patients becoming hypothyroid after treatment (Carney *et al.*, 2016; Peterson, 2014; Geddes & Aguiar, 2022). Nevertheless, making the distinction between the resolution of FHT and the onset of hypothyroidism may be demanding regarding that the clinical presentations are similar (Aldridge *et al.*, 2015).

Usually a three month-period of time is necessary for the pituitary to recover its function and for the re-establishment of the physiological feedback mechanisms to happen (Yu, Lacorcia & Johnstone, 2022). After that, the majority of patients tend to recover thyroid function without ever developing signs of hypothyroidism (i.e., lethargy, weight gain, poor appetite [Peterson, 2006; Yu, Lacorcia & Johnstone, 2022]) (Peterson, 2006; Geddes & Aguiar, 2022). However, in up to 30% of patients, TT4 levels remain low after those three months (Carney *et al.*, 2016; Geddes & Aguiar, 2022), of which around 50% are expected to require thyroid hormone supplementation due to development of permanent hypothyroidism (Carney *et al.*, 2016).

Because of the difficulty in determining which cats will develop hypothyroidism, monitoring of the patient is crucial for at least three and six months post-treatment (Vaske, Schermerhorn & Grauer, 2016; Geddes & Aguiar, 2022), preferably with evaluation of TT4 with fT4, to determine any euthyroid sick syndrome, and, if possible, serum TSH concentration. Findings of a low TT4 and fT4 concentration with a high serum TSH levels are indicative of iatrogenic hypothyroidism (IH) (Peterson, 2006; Vaske, Schermerhorn & Grauer, 2016; Ferguson, 2018). If that is indeed verified, therapy with levothyroxine (75–100 µg/cat PO BID) is warranted (Nelson & Couto, 2019). Because of this potential, radioiodine should be carefully discussed with owners whose cats do not tolerate oral medication (Peterson, 2020). After the cat is stable and has become euthyroid, monitoring should follow at least once a year (Peterson, 2006).

Fortunately, there are factors that can somewhat help predicting which cats are more prone to such complication and, therefore, should be more closely monitored after the procedure. The treatment dose protocol instituted is one of the factors, inasmuch higher doses of ^{131}I are more susceptible to damage normal thyroid tissue and, consequently, are associated to a greater risk of IH, that will require subsequent management (Carney *et al.*, 2016; Nelson & Couto, 2019). This can be the case of hyperthyroid cats with thyroid carcinomas (Carney *et al.*, 2016). Moreover, somewhat following the same reasoning, patients with bilateral hyperfunctional thyroid are expected to be twice as likely to develop ^{131}I-induced hypothyroidism than cats with unilateral dysfunction (Geddes & Aguiar, 2022). Likewise, a more recent approach has suggested that cats with measurable serum TSH concentration before the procedure are at much higher risk of subsequently becoming hypothyroid. In fact, considering such risk, pursuing ^{131}I therapy is contraindicated if serum TSH is not undetectable before the procedure (Geddes & Aguiar, 2022; Bugbee *et al.*, 2023).

C. Persistent or recurrent hyperthyroidism

Approximately five percent of cats fail to achieve euthyroidism with a single dose of radioactive iodine (Peterson, 2006; Carney *et al.*, 2016; Nelson & Couto, 2019). Such cases are usually those with a more severe clinical presentation, higher TT4 values, larger palpable goiter or with malignant thyroid tumour (Peterson, 2006; Carney *et al.*, 2016; Nelson & Couto, 2019; Yu, Lacorcia & Johnstone, 2022). Overall, these tend to respond positively to a second dose of ^{131}I. Cats with carcinomas may be the exception, though (Peterson, 2006; Carney *et al.*, 2016; Peterson, 2006).

In less than five percent of cats, HT recurrence may happen one year or longer after successful therapy (Nelson & Couto, 2019). This may be suggestive of reactivation of the initial tumour or of the development of new nodules arising from the remaining normal thyroid tissue, particularly if relapses occur three or more years after treatment (Peterson, 2006).

Similar to the monitoring for IH, after ^{131}I injection, clinicians should also be alert for signs of persistent or recurrent HT. This means that even after euthyroidism has been restored the cat should keep being periodically monitored at least once a year (Peterson, 2006).

6.1.1.4. Expected outcome

Radioiodine is curative in more than 95% of the cases (Peterson, 2014; Carney *et al.*, 2016; Peterson, 2020; Chow & White, 2022; Geddes & Aguiar, 2022; Peak *et al.*, 2022; Bugbee *et al.*, 2023), with the euthyroid status generally returning within one week to six months following treatment, depending on the protocol instituted (Peterson, 2006; Daniel & Neelis, 2014; Peterson, 2014; Carney *et al.*, 2016; Ferguson, 2018; Nelson & Couto, 2019; Yu, Lacorcia & Johnstone, 2022).

Besides the prognosis being good to excellent, the overwhelming majority of patients achieve better quality of life (QoL) when submitted to radioiodine (Peterson, 2020). Actually, in a survey about owners' perceptions and experiences of radioiodine therapy of FHT, on a scale of one (i.e., very poor) to ten (i.e., excellent), owners reported that their animal's QoL improved from four, prior ^{131}I injection, to a nine, post-treatment. Besides, around 92% of the 132 respondents considered they had made the best decision in choosing radioiodine over other treatment modalities (Boland *et al.*, 2014).

Regarding median survival times, overall uncomplicated hyperthyroid cats treated with ^{131}I, live approximately more two to five years, which tends to be greater than cats managed with other therapy modalities, even when additional post-treatment is needed (Chapman, 2011; Fossum, 2019; Nelson & Couto, 2019; Chow & White, 2022).

6.1.2. Surgical thyroidectomy

Surgical removal of the dysfunctional thyroid gland (i.e., thyroidectomy) (Fossum, 2019) is the treatment of choice when ^{131}I is not available or is declined by the owner (Peterson, 2020). This is especially true for uncomplicated cases.

However, performing surgery in thyrotoxic cats has associated risks and may be contraindicated in the following situations: cats with cardiac or kidney disease; when postoperative hypocalcaemia is more likely to develop; in case inoperable ectopic glandular tissue has been identified; and when malignant HT is associated to metastases (Nelson & Couto, 2019; Bugbee *et al.*, 2023).

On the other hand, in addition to being an effective curative method, thyroidectomy is the only approach that enables routine histopathological evaluation of the hyperfunctional thyroid gland (Yu, Lacorcia & Johnstone, 2022). So, the opportunity to submit the resected tissue for histopathologic examination should be taken whenever possible (Padgett, 2002; Nelson & Couto, 2019).

6.1.2.1. Preoperative care

Cases of mild FHT (i.e., cats with good body condition, TT4 only mildly elevated and non-severely tachycardic), can be operated without pretreatment (Birchard, 2006).

In opposition, patients with higher anaesthetic risk should be stabilised prior to surgery. This involves controlling TT4 levels, until a euthyroid state is attained, with reversible modalities of treatment, so that tachycardia, arrhythmias and other cardiac and metabolic complications are

minimised during surgery (Padgett, 2002; Birchard, 2006; Syme, 2007; Trepanier, 2007; Veres-Nyéki, 2016; Fossum, 2019; Geddes & Aguiar, 2022; Yu, Lacorcia & Johnstone, 2022; Bugbee *et al.*, 2023).

The ideal period of pretreatment with antithyroid medication has varied over time. Stabilization periods of two to four weeks (10–15 mg/kg PO of methimazole) (Padgett, 2002), seven to ten days (Tapazole® - 5mg *per os* [PO] twice daily [BID]) (Birchard, 2006), one to three weeks (1.25–2.5 mg/cat PO BID for 7–14 days and then increase dose by 2.5 mg/d until control is achieved up to 5–10 mg/cat PO BID) (Fossum, 2019) or, more recently, one to two months (no dose specified) (Nelson & Couto, 2019), have been suggested. To really ensure that the TT4 values are within the range of euthyroidism, there is nothing better than to measure it before the surgery (Fossum, 2019).

β-adrenergic blocking agents (such as propranolol, metoprolol and atenolol) (Fossum, 2019) may also help decrease HR and other cardiac alterations (Padgett, 2002; Veres-Nyéki, 2016; Fossum, 2019). They can be instituted in addition to methimazole (MMI) (Peterson, 2006) or as an alternative to it in case of adverse reaction (Padgett, 2002; Fossum, 2019). When preoperative therapy with β-blockers is required, propranolol seems to be the most frequently used, with a suggested dose of 2.5–5 mg/cat (0.4–1.2 mg/kg) PO q8–12h during one to two weeks before surgery (Fossum, 2019). Care must be taken with this β-blocker since it may cause sudden death in hypokalemic hyperthyroid cats (Ferguson, 2018; Miller, 2022), and because when discontinued 24 to 48 hours before the intervention the risk of tachycardia and hypertension increases, particularly at induction (Fossum, 2019). Metoprolol and atenolol are other possible choices, but their administration may be accompanied with antihypertensive therapy, like amlodipine, until the morning of the surgery (Fossum, 2019). The suggested preoperative dose of amlodipine is 0.625–1.25 mg/kg orally or rectally q12–24h (Veres-Nyéki, 2016).

If possible and not performed during the diagnostic process, preoperative ultrasound examination of the ventral neck or, still, scintigraphy are beneficial in order to try to classify thyroid morphological changes and ectopic tissue, that otherwise would likely be missed during thyroid palpation (Daniel & Neelis, 2014; Fossum, 2019; Nelson & Couto, 2019; Geddes & Aguiar, 2022; Yu, Lacorcia & Johnstone, 2022). This may also give some insight into the probability of complications postoperatively (Carney *et al.*, 2016; Nelson & Couto, 2019). Some findings may compromise thyroidectomy success or even lead the surgeon to change the approach.

Due to the likelihood of cats with FHT developing cardiac abnormalities, surgery should not be carried out without excluding thyrotoxic heart disease with a thoracic radiograph and/or echocardiography. Electrocardiogram and BP measurement prior to the intervention can equally aid diagnosing complications that left unidentified would represent a higher anaesthetic risk (Padgett, 2002; Fossum, 2019).

6.1.2.2. Anaesthesia

When choosing the best drugs to ensure a good anaesthesia during surgery, it is important to

remember that hyperthyroid cats are often patients with increased catecholamine production, underlying hypovolemia, masked renal insufficiency, masked anaemia, abnormal cardiac output, tachyarrhythmias and/or increased metabolic rates, drug metabolism and oxygen consumption (Fossum, 2019).

FHT patients may be premedicated with diazepam (0.2 mg/kg IV) or midazolam (0.2 mg/kg IV or IM) plus buprenorphine (0.005–0.02 mg/kg IV or IM), butorphanol (0.2–0.4 mg/kg IV or IM) or morphine (0.1–0.2 mg/kg IV or 0.2–0.4 mg/kg IM). In cats, buprenorphine is a safer analgesic than morphine. Besides, if not given slowly, morphine may induce histamine release (Fossum, 2019). The goal of a benzodiazepine combined with an opioid is to decrease patient's stress, catecholamine release and myocardial irritability (Veres-Nyéki, 2016; Fossum, 2019).

In turn, the use of ketamine, which sensitizes the heart to catecholamine-induced arrhythmias (Padgett, 2002; Ferguson, 2018; Fossum, 2019); α2-adrenergic agonists; anticholinergics, like atropine that may induce arrhythmias (Padgett, 2002); and phenothiazines is not recommended (Fossum, 2019). However, some authors refer that by adding a small dose of acepromazine (ACP) to the premedication cocktail, autonomic tone in hyperthyroid cases may be reduced and the heart protected against catecholamine-induced arrhythmias (Padgett, 2002; Veres-Nyéki, 2016). Other authors suggest two other drug combinations for premedication: a low dose of α2-adrenoceptor agonist with an opioid, highlighting that it could be beneficial to decrease HR and consequently myocardial oxygen demand, albeit preoxygenation before induction would be crucial; and alfaxalone (3 mg/kg SQ) plus butorphanol (0.2 mg/kg SQ), that has been shown to provide cardiovascular stability in hyperthyroid cats, despite inducing tremors during recovery (Veres-Nyéki, 2016).

Induction must be as stress-free as possible. Therefore, mask induction is usually contraindicated (Fossum, 2019). Instead, intravenous induction with propofol (2–6 mg/kg), alfaxalone (2–3 mg/kg) or etomidate (0.5–1.5 mg/kg) is advised (Veres-Nyéki, 2016; Fossum, 2019). Since intubation of a cat with FHT may be more difficult, due to compression of the trachea by the goiter, a small amount of lidocaine given through a tuberculin syringe can be administered. Moreover, this local anaesthetic will help reducing laryngeal spasm and the elevated HR and BP associated with intubation (Veres-Nyéki, 2016; Fossum, 2019).

Maintenance may be carried out with isoflurane or sevoflurane with oxygen through an endotracheal tube (Fossum, 2019). Considering that thyrotoxic cats demand higher oxygen amounts, in order to avoid hypoxia, it is essential to ensure adequate oxygenation throughout the perioperative period (Veres-Nyéki, 2016; Fossum, 2019). Moreover, patient hydration cannot be neglected. In order to support the circulating volume and renal function in patients with reduced or normal cardiac function a fluid rate of 5 mL/kg/h or 10 mL/kg/h is, respectively, indicated (Fossum, 2019). Sometimes, to counterbalance hyperthyroid animals' glucose demand, solutions containing 2.5–5% dextrose can be helpful (Veres-Nyéki, 2016). In addition, just like in any other surgical procedures, these patients must be connected to a multi parameter monitor and any arrhythmias, BP and HR changes should be treated accordingly (Padgett, 2002; Veres-Nyéki,

2016; Fossum, 2019).

6.1.2.3. Preparation of the surgical field

Since the gland will be approached through a ventral midline incision, caudal to the larynx (Padgett, 2002; Birchard, 2006), the entire ventral cervical area to the level of the thoracic inlet should be aseptically prepared (Padgett, 2002; Fossum, 2019). Thyroidectomy is best performed with the cat in dorsal recumbency with the neck somewhat hyperextended and the forelimbs pulled caudally (Padgett, 2002; Birchard, 2006).

6.1.2.4. Types of surgery

Overall thyroidectomy can be total (i.e., bilateral) or subtotal (i.e., unilateral) (Yu, Lacorcia & Johnstone, 2022). The main difference between the techniques is whether thyroid capsule is resected and, consequently, the way parathyroid function is preserved (Padgett, 2002; Birchard, 2006). Regardless, “the underlying principles of meticulous dissection, careful attention to preserving vascularity, and avoiding other vital structures in the area are crucial” (Padgett, 2002). Therefore, overall, the most effective option will be the one that allows preserving at least one external parathyroid gland and removing the thyroid gland as much as possible, including its capsule, to avoid recurrence (Flanders, 1999).

Sometimes, the choice for one type of surgery over the others may be a matter of surgeon’s qualifications or even preference (Flanders, 1999) and the anatomy of the affected glands.

A. Extracapsular thyroidectomy

The extracapsular technique is characterized by the complete removal of the encapsulated dysfunctional thyroid lobe(s), without interfering with its parenchyma (Birchard, 2006). Hence, the parathyroid glands are also removed (Flanders, 1999). Because there is no preservation of the parathyroids’ function, this procedure is related to a high incidence of postoperative health problems. Therefore its use is not recommended (Padgett, 2002).

B. Modified extracapsular thyroidectomy

The modified extracapsular technique also involves the removal of the encapsulated thyroid lobe(s). However, in contrast with the previous procedure, the external parathyroid glands’ preservation is attempted by carefully dissecting them off of the thyroid capsule (Padgett, 2002; Flanders, 1999; Fossum, 2019; Geddes & Aguiar, 2022).

After the caudal thyroid vein has been ligated or cauterized, the thyroid capsule is cauterized approximately two millimetres from and around the cranial parathyroid gland with the respective blood vessel. From there, the outlined area is cut with iris scissors and the thyroid gland sharp and bluntly dissected from surrounding tissues (Figure 12) (Padgett, 2002; Fossum, 2019). Care must be taken to not disturb the cranial thyroid artery and the branches that supply the external parathyroid glandular tissue (Fossum, 2019).

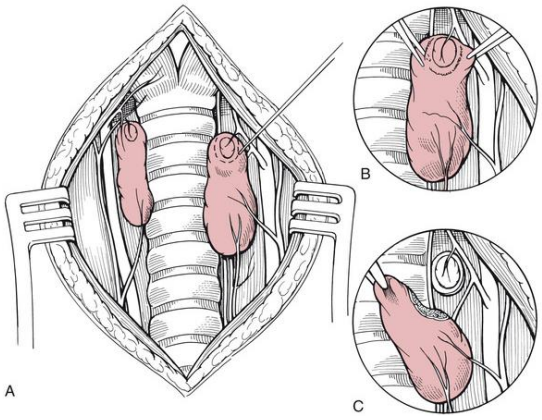


Figure 12 *– Modified extracapsular thyroidectomy. A: Using fine-tipped bipolar cautery forceps, cauterize the thyroid capsule approximately 2 mm from the external parathyroid gland. B: With small, fine scissors, cut the gland at the cauterized area and remove from the parathyroid gland. C: Carefully dissect all of the thyroid gland from the surrounding tissue and parathyroid gland. From (Fossum, 2019)*

C. Intracapsular thyroidectomy

In opposition to the previous techniques, the intracapsular thyroidectomy is characterized by the removal of the thyroid parenchyma while leaving its capsule in place. This ensures that the external parathyroid gland and respective blood supply remain preserved (Flanders, 1999; Padgett, 2002; Fossum, 2019).

To perform this technique, the incision is created in an avascular area of the capsule, caudoventrally, and extended cranially with iris scissors. Blunt dissection is then performed, with a saline-soaked cotton-tipped applicator (Figure 13), with the help of a bipolar cautery to ensure haemostasis, in order to separate the thyrotoxic parenchyma from its capsule (Flanders, 1999; Padgett, 2002; Fossum, 2019).

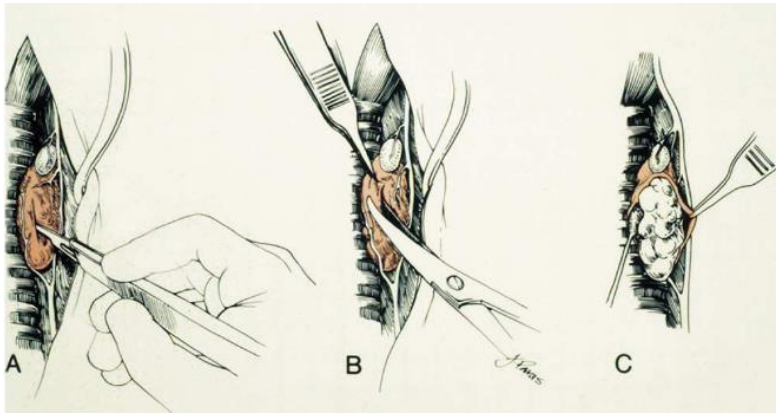


Figure 13 *- Intracapsular thyroidectomy. A: The incision is created in an avascular area of the capsule, caudoventrally. B: The incision is then extended with fine scissors. C: Blunt dissection is performed, with a saline-soaked cotton-tipped applicator, in order to separate the thyroid gland parenchyma from its capsule. Adapted from (Birchard, 2006)*

D. Modified Intracapsular thyroidectomy

To perform a modified intracapsular thyroidectomy a single last step is added to the traditional intracapsular procedure: after thyroid parenchyma has been removed, the majority of the capsule left behind is excised, leaving intact the small part in close contact with the external parathyroid gland and its blood supply (Padgett, 2002; Fossum, 2019).

E. Staged bilateral removal technique

In case total thyroidectomy is required, aiming to reduce the prevalence of postoperative complications, a staged removal of the gland can be an alternative surgical approach. This means that the thyroid lobes are removed, through one of the methods described above, ideally with two to four weeks apart, allowing potential parathyroid gland damage to resolve between thyroidectomies (Flanders, 1999; Padgett, 2002; Birchard, 2006; Fossum, 2019; Peterson, 2020). Although, after the first procedure, resolution of the clinical signs can be often experienced, the second intervention must be performed within six months. Otherwise, the remaining thyroid lobe might grow enough to induce a new thyrotoxic state (Flanders, 1999).

Obviously, anesthetising the animal twice, and the risk associated with it, especially in older cats with comorbidities, is the major disadvantage of this approach (Flanders, 1999; Padgett, 2002; Fossum, 2019; Peterson, 2020). Nonetheless, the interventions are usually very brief and less hospital time post-surgery is needed for these cases (Flanders, 1999).

F. Parathyroid autotransplantation

Regardless of the procedure, when the external parathyroids are unwittingly excised or their vascularization becomes compromised, parathyroid autotransplantation should be performed (Padgett, 2002; Fossum, 2019; Nelson & Couto, 2019), in order to avoid postoperative complications that otherwise iatrogenic hypoparathyroidism would lead to.

This technique involves mincing the parathyroid gland into approximately one-millimetre cubes (Padgett, 2002; Nelson & Couto, 2019) and then transfer it into a bluntly dissected muscle belly of the sternohoideus muscles (Flanders, 1999; ; Padgett, 2002; Fossum, 2019; Nelson & Couto, 2019). Within two weeks after the transplant, the gland is expected to be entirely revascularized (Flanders, 1999) and completely functional by the fourth week (Nelson & Couto, 2019).

6.1.2.5. Postoperative care

Once the cat recovers from anaesthesia, continued monitoring should follow just like in every other patient. Particularly, in these cases, respiratory obstruction and dysphagia are two emergencies that can be a consequence from the swelling around the surgical site and/or from possible iatrogenic tracheal damage (i.e., tracheomalacia) and consequent tracheal collapse. These situations require prompt reintubation (Veres-Nyéki, 2016).

During the recovery period, although thyroidectomy is not associated with high levels of pain postoperatively, patients submitted to the procedure are better prescribed an analgesic (i.e., buprenorphine: 0.005–0.02 mg/kg IV or IM q4–8h or 0.01–0.02 mg/kg OTM q6–12h) in order to be kept stress and pain free (Fossum, 2019).

6.1.2.6. Possible postoperative complications

Thyroidectomy comes with an extensive list of potential, albeit rare, complications, which must be discussed with owners so that they can make an informed and conscious decision (Peterson, 2020).

A. Hypoparathyroidism and hypocalcaemia

Regarding the importance of the parathyroid glands in the calcium regulation, iatrogenic hypoparathyroidism may lead to hypocalcaemia, that left untreated can be life-threatening (Peterson, 2006; Daniel & Neelis, 2014; Fossum, 2019). In fact, this is the biggest concern and the most frequent complication of performing a bilateral thyroidectomy (Padgett, 2002; Fossum, 2019; Nelson & Couto, 2019, 2019).

Depending on the degree of surgical trauma inflicted, hypoparathyroidism and hypocalcaemia may be transient or permanent (Fossum, 2019; Nelson & Couto, 2019). Transient hypoparathyroidism may last days, weeks or months; usually while there is local oedema and swelling of the gland, associated to the surgical manipulation or slight disruption of its blood supply (Flanders, 1999; Peterson, 2006; Carney *et al.*, 2016; Fossum, 2019; Nelson & Couto, 2019). In turn, persistent low serum calcium concentrations are usually related to iatrogenic parathyroidectomy or the creation of irreparable lesions to the gland and/or to the vessels responsible for its irrigation (Flanders, 1999; Fossum, 2019). Some factors like the chosen method, surgeon's experience, the size of the thyroid lobes and the (in)ability to actually visualize the external parathyroid gland during the procedure, may help judging whether hypocalcaemia after the procedure may occur (Carney *et al.*, 2016; Fossum, 2019; Nelson & Couto, 2019). Regarding the chosen method, despite the variability associated to the surgeon, extracapsular thyroidectomy has been consistently the procedure most associated with postoperative hypocalcaemia, followed by modified extracapsular and modified intracapsular techniques, whose percentages are quite variable (Padgett, 2002; Yu, Lacorcia & Johnstone, 2022). In opposition to what was initially suggested (Padgett, 2002), staged bilateral interventions have not shown to be associated with a significant reduction of post-surgical hypocalcaemia (Yu, Lacorcia & Johnstone, 2022). Regardless of such factors, the persistence of hypoparathyroidism and hypocalcaemia is overall unpredictable (Nelson & Couto, 2019). Hence, serum calcium levels should be measured at least for 48 to 72 hours postoperatively (Birchard, 2006; Fossum, 2019) and then once daily (SID) for five to seven days when total removal was performed. Since one functional parathyroid gland is sufficient to maintain calcium homeostasis in cats (Flanders, 1999; Nelson & Couto, 2019), hypocalcaemia is extremely rare after subtotal thyroidectomies (Fossum, 2019). Therefore, postoperative serum calcium monitoring in these cases is not as essential as in cats that undergo bilateral intervention (Flanders, 1999).

Since the decrease in serum calcium concentration is directly proportional to the increase of neuromuscular activity (Nelson & Couto, 2019), a variety of clinical signs can be found depending on how low the calcium is. While early signs of hypocalcaemia are mild and nonspecific, including anorexia, lethargy, facial rubbing, irritability, nervousness, stiff and stilted gait and growling; more severe signs, like ear and face twitching, seizure-like muscular tetany, ataxia and weakness usually appear later (Padgett, 2002; Birchard, 2006; Greco, 2012; Nelson & Couto, 2019, 2019). As hypocalcaemia worsens, associated with muscular weakness, bradycardia and panting can also be identified (Greco, 2012).

The decision to treat the patient is based on the severity of the clinical signs (Padgett, 2002). Usually mild and transient hypocalcaemia may only require oral supplementation (Padgett, 2002) or no treatment at all (Carney *et al.*, 2016). In fact, a decline in the blood calcium concentration is not an absolute indication to begin therapy because the remaining parathyroid glands may respond before clinical signs or severe hypocalcaemia develop. On the other hand, in the presence of clinical signs and serum total or ionized calcium (iCa) concentration <8 mg/dL or <0.8 mmol/L, respectively, a therapeutic plan must be put in action (Nelson & Couto, 2019).

Overall treatment requires administration of vitamin D and calcium supplements and is generally done in two phases: acute and maintenance therapy (Nelson & Couto, 2019). To manage the acute signs, firstly, 0.5 to 1.5 mL/kg of 10% calcium gluconate (CaG) should be slowly administered intravenously to effect (over 10-20 minutes) (Fossum, 2019; Nelson & Couto, 2019). Please note that CaG in any phase should be substituted by calcium chloride, due to its caustic effects, if not given intravenously, and because the cat can be overdosed too easily (Birchard, 2006; Fossum, 2019; Nelson & Couto, 2019). Then, once the clinical signs are controlled (Nelson & Couto, 2019) and if no problem with the HR develops (i.e., bradycardia) (Fossum, 2019), 10 mL of the CaG are added to 250 mL of lactated ringer's solution or diluted in saline and administered as a continuous intravenous infusion or subcutaneously (1:3-1:4; otherwise can cause an abscess) at multiple sites every six to eight hours, respectively (Fossum, 2019; Nelson & Couto, 2019). During this phase, it is crucial to measure serum calcium concentrations every eight to twelve hours, so that calcium administration can be adjusted accordingly (Nelson & Couto, 2019). The goal of the whole treatment is to maintain serum calcium levels between 8 and 10 mg/dL (Nelson & Couto, 2019, 2019), since such values avoid the undesired evolution to hypercalciuria (risk of calculi formation) or to severe hypercalcemia and hyperphosphatemia (risk of nephrocalcinosis and kidney failure) (Nelson & Couto, 2019).

Once the animal starts eating and the calcium levels are above the lower limit of that range, the second phase of the treatment can be established with daily calcium and vitamin D oral administrations, accompanied by weekly calcium monitoring (Fossum, 2019; Nelson & Couto, 2019). To supplement calcium orally there are different preparations with different concentration, like calcium lactate and CaG, but briefly speaking cats should be given 0.5–1.0 g of calcium/cat/day (Fossum, 2019). Vitamin D supplementation can be ensured with either dihydrotachysterol (initial dose of 0.02–0.03 mg/kg/d for three to five days) or calcitriol (initial dose of 0.02–0.03 µg/kg/d for two to four days) (Fossum, 2019; Nelson & Couto, 2019). The choice of one over the other is not really agreed. On one hand, some authors say that dihydrotachysterol has the fastest onset of action (Fossum, 2019), but on the other hand calcitriol is highlighted by others as the one that actually acts faster and is preferable for treating hypoparathyroidism (Nelson & Couto, 2019). Nevertheless, since the aim of this phase is to prevent recurrence of hypocalcemic concentrations and not inducing hypercalcemia, as soon as the calcium levels stabilize, attempts may be made to gradually taper the dose of both oral medications to the lowest dose able to ensure the balance of the calcium levels in circulation (Nelson & Couto, 2019). The

tapering process should extend over a period of three to four months and then stopped when no signs of hypocalcaemia are detected (Nelson & Couto, 2019). However, some cats may require lifelong vitamin D therapy (Nelson & Couto, 2019). In turn, the same is not very common for oral calcium supplementation (Padgett, 2002), since, after proper therapy, dietary calcium is usually enough to guarantee the animal's calcium requirements (Fossum, 2019; Nelson & Couto, 2019). After therapy has been stopped or adjusted, to meet the animal's ongoing needs and to make sure there is no recurrence of the complication, cats should be evaluated every three to four months (Nelson & Couto, 2019).

Post-operative prophylactic calcium and vitamin D supplementation has been suggested to reduce the prevalence of hypocalcaemia (Greco, 2012; Nelson & Couto, 2019). However, that idea has been rebutted (Yu, Lacorcia & Johnstone, 2022).

When everything goes as planned, the prognosis is excellent. However, in the event of postoperative hypocalcaemia, when cats no longer need parenteral support and can go home with oral medication, the prognosis also depends on owner's compliance. Finally, the more frequent the rechecks, the better the chance of preventing extremes in the calcium levels. Therefore, the better will be the chance of a normal life expectancy (Nelson & Couto, 2019). Obviously, if the problem recurs, therapy must be reinstituted (Nelson & Couto, 2019).

B. Persistent or recurrent hyperthyroidism

When thyroidectomy is the chosen treatment modality, there is always the chance that HT may persist or recur a few months to years after a successful surgical intervention, even in cats that undergo bilateral removal, although less common (Padgett, 2002; Peterson, 2006; Daniel & Neelis, 2014; Carney *et al.*, 2016; Fossum, 2019; Nelson & Couto, 2019). Therefore, so that these complications do not go unnoticed, postoperative measurements of TT4 should be performed within four to six weeks and then, once the cat seems healthy and stable, every four to six months. Obviously, in animals that in the meantime start showing clinical signs of recurrence, that period between evaluations has to be shortened (Nelson & Couto, 2019; Geddes & Aguiar, 2022).

A variety of reasons can explain this event. Two of them are the presence of ectopic hyperplastic thyroid tissue (Padgett, 2002; Peterson, 2006; Daniel & Neelis, 2014; Fossum, 2019; Nelson & Couto, 2019; Yu, Lacorcia & Johnstone, 2022) or ventrally descendent thyroid lobes, which were not correctly identified preoperatively (Peterson, 2006; Daniel & Neelis, 2014). Besides, there is always the possibility that bilateral involvement of the thyroid may have been misdiagnosed as unilateral disease (Peterson, 2006; Daniel & Neelis, 2014; Fossum, 2019; Nelson & Couto, 2019). In addition, recurrence may be associated to hyperfunctional tissue left at the surgical site due to the surgeon's performance (Padgett, 2002; Carney *et al.*, 2016; Yu, Lacorcia & Johnstone, 2022) and/or the technique chosen. For instance, the intracapsular method is usually related to a higher prevalence of FHT recurrence (Padgett, 2002). Alternatively, metastatic thyroid carcinoma should also be considered (Padgett, 2002; Nelson & Couto, 2019). Finally, since it is common for the remaining contralateral lobe to suffer adenomatous changes

some time after a successful unilateral thyroidectomy (Peterson, 2014; Carney *et al.*, 2016) it might be worth thinking about this possibility as well.

Due to all these possible causes, subjecting these cats to a more advanced means of diagnose before retreatment, like scintigraphy, may be really helpful (Birchard, 2006; Fossum, 2019).

C. Hypothyroidism

After the thyroidectomy, hypothyroidism may develop. Fortunately, in the majority of the patients, it resolves before clinical signs become apparent (Peterson, 2006; Carney *et al.*, 2016; Nelson & Couto, 2019; Yu, Lacorcia & Johnstone, 2022). However, in some cases, this postoperative complication is not transient, which means patients end up showing mild and nonspecific signs of low serum T4 concentration (i.e., lethargy, loss of appetite, weight gain, seborrhoea sicca, and a dull, dry unkempt haircoat) (Geddes & Aguiar, 2022; Yu, Lacorcia & Johnstone, 2022).

The treatment for IH requires thyroid hormone supplementation with levothyroxine (75–100 µg/cat PO BID), which, since it is not usually needed ongoing, is then gradually tapered and interrupted after two to three months (Nelson & Couto, 2019). However, the presence or absence of clinical signs, not the TT4 results solely, should dictate whose cats must initiate this protocol (Nelson & Couto, 2019). So, cats whose clinical signs of hypothyroidism remain undetectable, do not require treatment (Padgett, 2002; Geddes & Aguiar, 2022). All the others, with hypothyroidism for more than three months post-surgery and rapid decline of the renal function or even those without signs of azotaemia but whose TT4 levels have been persistently low for six months, should receive thyroid supplementation (Geddes & Aguiar, 2022).

To monitor these cases and be able to adapt the given doses, a blood sample to evaluate TT4 should be taken four to six hours after the morning dose of levothyroxine and then every six to twelve months (Geddes & Aguiar, 2022).

D. Horner's syndrome

The appearance of miosis, enophthalmos, ptosis and prolapsed nictitans (i.e., Horner's syndrome) after the surgery is suggestive that the sympathetic trunk was damaged during retraction of the cervical musculature, to access the thyroid (Padgett, 2002; Carney *et al.*, 2016; Fossum, 2019; Nelson & Couto, 2019; Yu, Lacorcia & Johnstone, 2022).

E. Laryngeal nerve paralysis

Considering the proximity between the left thyroid gland and the recurrent laryngeal nerve, postoperatively laryngeal paralysis or voice change may be a sign of iatrogenic nerve damage. Such situation is generally related to careless thyroid dissection from the paratracheal fascia (Padgett, 2002; Carney *et al.*, 2016; Fossum, 2019; Nelson & Couto, 2019; Yu, Lacorcia & Johnstone, 2022).

6.1.2.7. Expected outcome

Thyroidectomy is associated with both high short- and long-term success in more than 90% of

the intervened hyperthyroid cats (Carney *et al.*, 2016; Peterson, 2020). Due to the short half-life of cats' thyroid hormones, euthyroidism is expected to be achieved in the 24-48 hours following the surgical intervention (Peterson, 2014; Carney *et al.*, 2016; Geddes & Aguiar, 2022).

6.2. Reversible treatment

Treatment with antithyroid drugs or a low-iodine diet not only allow thyroid tumours to continue to grow, because they are not destroyed nor removed, but also require ongoing daily use, to limit thyroid hormone production, and frequent monitoring (Boland *et al.*, 2014; Nelson & Couto, 2019; Peterson, 2020; Yu, Lacorcia & Johnstone, 2022).

Hence, when opting for these types of treatment, owners must be informed and aware that the thyroid tumour will really remain with its potential to gradually keep growing and become malignant (Boland *et al.*, 2014; Peterson, 2014; Carney *et al.*, 2016; Fossum, 2019; Peterson, 2020; Yu, Lacorcia & Johnstone, 2022). Moreover, they must understand that, until HT is treated with definitive methods, the progression of the disease will not slow down. Clinical presentation may become severe and/or intrathoracic masses may develop as well (Peterson, 2020; Peterson *et al.*, 2020).

As an alternative to definitive treatment, palliative methods are best reserved for cats expected to have a shorter lifespan, due to either advanced age or the existence of moderate to severe concurrent NTI, which means they are less likely to live long enough to develop a carcinoma (Trepanier, 2007; Peterson, 2014, 2020). Nonetheless, such reversible options may also be employed to restore the euthyroid state or at least try to control T4 levels, in order to stabilise the patient prior to ^{131}I therapy and thyroidectomy or even while the owner is still deciding on the best treatment option (Peterson, 2014; Carney *et al.*, 2016; Nelson & Couto, 2019, 2019; Peterson, 2020; Yu, Lacorcia & Johnstone, 2022).

6.2.1. Antithyroid medication

Therapy with antithyroid medication (i.e., thioureylenes) is the best choice when definitive treatment has been excluded (Peterson, 2020), as it is widely available, relatively safe and effective (Nelson & Couto, 2019). However, this may not be appropriate for cats that are difficult or impossible to medicate and/or for those whose owners most likely will not strictly follow the treatment protocol (Padgett, 2002; Peterson, 2006; Geddes & Aguiar, 2022).

Currently, two antithyroid drugs are indicated for treating hyperthyroid cats: MMI and carbimazole (Carney *et al.*, 2016; Geddes & Aguiar, 2022; Yu, Lacorcia & Johnstone, 2022). A third one, propylthiouracil (PTU), has been suggested as an alternative drug to manage FHT (Trepanier, 2007; Ferguson, 2018; Fossum, 2019; Nelson & Couto, 2019), but most authors do not recommend its use in cats (Ferguson, 2018; Fossum, 2019).

Thioureylenes control FHT by inhibiting TP action and blocking the synthesis of new thyroid hormones (Padgett, 2002; Birchard, 2006; Trepanier, 2007; Daniel & Neelis, 2014; Carney *et al.*, 2016; Ferguson, 2018; Nelson & Couto, 2019; Peterson, 2020; Yu, Lacorcia & Johnstone, 2022). Hence, neither the NIS activity (Daniel & Neelis, 2014) nor the release of the already formed and

stored T4 and T3 into the bloodstream are directly affected by medication (Trepanier, 2007; Ferguson, 2018; Nelson & Couto, 2019). Additionally, PTU also has the capacity to stop the thyroxine's deiodination in peripheral tissues like liver and kidney (Ferguson, 2018). As therapy lowers serum T4 concentrations, TSH and uptake by the normal follicular cells will in turn increase (Daniel & Neelis, 2014).

Overall, therapy with thioureylenes should start with a more conservative dose (Aldridge *et al.*, 2015) and then titrated to effect until serum TT4 concentration has ideally reached the lower half of the RI (Geddes & Aguiar, 2022). Because of the recurrent need to adjust the dosage, these patients usually need to be constantly monitored (Padgett, 2002).

6.2.1.1. Methimazole

MMI is the drug of choice to medically manage thyrotoxic cats (Trepanier, 2007; Ferguson, 2018; Nelson & Couto, 2019).

Although medical protocols to manage FHT cases differ slightly among authors, the aim is always the same: minimize potential adverse reactions to MMI. So, keeping that in mind, according to the most recent source found, veterinarians are advised to start the treatment with a minimal dose rate for one week, such as 1.25–2.5 mg PO SID, and then titrate it upward 2.5-5 mg every 12-24h (Bugbee *et al.*, 2023), until serum T4 falls within the lower half of the RI (Ferguson, 2018; Nelson & Couto, 2019). The dose should only continue to be increased if every two weeks the animal is checked and if the following is confirmed: TT4 levels remain in the upper half of RI or higher, there is no suspicion of new NTI developing on PE, side effects are absent, and laboratory parameters (i.e., hemogram, platelet count, sCr) suffer no alarming changes (Nelson & Couto, 2019). If, during one of the check-ups, TT4 is below the lower limit of the RI, the dose rate should be reduced by 1.25-2.5mg/cat/day (Carney *et al.*, 2016). Although MMI can be administered once (Ferguson, 2018; Bugbee *et al.*, 2023), twice daily (Trepanier, 2007; Carney *et al.*, 2016; Veres-Nyéki, 2016; Nelson & Couto, 2019; Yu, Lacorcia & Johnstone, 2022), or even every eight hours (Trepanier, 2007; Veres-Nyéki, 2016; Ferguson, 2018) albeit rarely necessary, the second option seems to be most effective, because T4 values are controlled in a shorter period of time (Trepanier, 2007) and it is associated with less severe side effects (Carney *et al.*, 2016). On the other hand, once the animal is stable, although not ideal, a once-daily maintenance therapy might be as effective and even help with owner compliance (Carney *et al.*, 2016; Ferguson, 2018).

Cats can be treated with two different oral formulations of MMI: tablets and liquid solution (for instance Thyronorm® 5 mg/mLoral solution for cats; active substance thiamazole). This last option is usually preferred by the owners, because it is easier to administer and patients usually tolerate it better than tablets.

Besides the oral formulations, MMI is equally available compounded in a pluronic lecithin organogel (PLO) for transdermal application (Trepanier, 2007; Daniel & Neelis, 2014; Carney *et al.*, 2016; Ferguson, 2018; Fossum, 2019; Nelson & Couto, 2019; Yu, Lacorcia & Johnstone,

2022). PLO behave as a permeation enhancer, by disrupting the stratum corneum, so that drug absorption into the skin is promoted. Following the same or slightly higher dose protocol (Carney *et al.*, 2016; Nelson & Couto, 2019), owners are instructed to rub the cream into the inner surface of the pinnae (Carney *et al.*, 2016; Nelson & Couto, 2019; Yu, Lacorcia & Johnstone, 2022). It is important to alternate ears with each dose and to wipe away any residual MMI 30 to 60 minutes after application, to avoid build up crusted material, which may interfere with the subsequent dose. The medication is prescribed in tuberculin syringes so that the correct dosage can be applied with the fingertip. Owners should always wear gloves for each application (Carney *et al.*, 2016; Nelson & Couto, 2019). This topical preparation is particularly advantageous for cats that resist administration of oral MMI (Daniel & Neelis, 2014; Carney *et al.*, 2016; Ferguson, 2018; Fossum, 2019) or those with owners who find tablets hard to administer (Fossum, 2019).

6.2.1.2. Carbimazole

Carbimazole is a MMI pro-drug, in other words, once administered and absorbed it is rapidly converted into MMI (Trepanier, 2007; Bucknell, 2000; Fossum, 2019; Nelson & Couto, 2019; Yu, Lacorcia & Johnstone, 2022). Therefore, it is an alternative option when MMI is not available (Nelson & Couto, 2019).

However, since carbimazole is a larger molecule than MMI (i.e., 10 mg of carbimazole is equimolar to 6 mg of MMI), to achieve the same effect as the pharmacologically active drug compound, almost twice the dose of the pro-drug is needed (Bucknell, 2000; Ferguson, 2018). Therefore, although the range dosage is the same as for MMI (Ferguson, 2018; Nelson & Couto, 2019), an initial dose of 5 mg/cat PO BID of carbimazole is necessary to adequately counterbalance thyroid dysfunction (Veres-Nyéki, 2016; Yu, Lacorcia & Johnstone, 2022).

6.2.1.3. Possible complications during treatment

The major disadvantage of treating hyperthyroid cats with thioureylenes is the likelihood of side effects. A range of adverse reactions with a variable frequency have been described (Carney *et al.*, 2016).

Around 10-20% of the cats may develop GI signs, partially attributed to direct gastric irritation from the drug, exhibiting as anorexia, vomiting and lethargy (Trepanier, 2007; Ferguson, 2018; Fossum, 2019; Nelson & Couto, 2019; Bugbee *et al.*, 2023). GI upset is generally more common in the first month of treatment (Trepanier, 2007; Ferguson, 2018) and can either be transient, usually resolving despite continued therapy (Ferguson, 2018; Nelson & Couto, 2019). If it is persisting, changing the formulation or drug could solve the problem, since the transdermal MMI is associated with significantly fewer GI adverse reactions in comparison to oral preparations (Trepanier, 2007; Carney *et al.*, 2016; Ferguson, 2018; Fossum, 2019; Nelson & Couto, 2019; Bugbee *et al.*, 2023). Otherwise, treatment may have to be discontinued (Ferguson, 2018).

Around 50% of cats treated for more than six months test positively for antinuclear antibodies (ANA), especially those on a daily high doses (≥15 mg/day) over a long-term period (Ferguson, 2018). Although ANA antibody production is generally associated with lupus-like syndrome (i.e.,

dermatitis, polyarthritis, glomerulonephritis, haemolytic anaemia, or fever), no signs of such NTI are usually observed. Therefore, the importance of some cats testing positive for ANA, while being on a therapy plan with MMI, remains unknown (Ferguson, 2018; Nelson & Couto, 2019). In fact, as soon as the dosage is decreased to the minimum required amount, the ANA levels reduce and become negative (Ferguson, 2018).

Even though most of the adverse drug reactions typically occur within the first and second month of therapy and can be dealt without stopping the treatment (Carney *et al.*, 2016; *Surgery of the Endocrine System*, 2018; Nelson & Couto, 2019), others, more characteristic of longer periods of MMI administration (Carney *et al.*, 2016), usually require cessation and selection of a different treatment modality (Carney *et al.*, 2016; Ferguson, 2018; Nelson & Couto, 2019). Their mitigation by using the transdermal preparation is not even worth to attempt because no difference in the incidence of such side effects were found between transdermal and oral routes (Trepanier, 2007; Ferguson, 2018). This is the case for the side effects mentioned below.

Up to three percent of patients develop self-induced excoriations of the face and neck, which may result in scabbed lesions characteristically in the cranial aspect of the pinnae (Ferguson, 2018; Trepanier, 2007). Generalized erythema and pruritus may develop as well (Ferguson, 2018; Trepanier, 2007). When associated to the place where transdermal MMI was applied, generally pinnae, a therapy change for oral MMI should be attempted in order to reduce those signs (Carney *et al.*, 2016; Nelson & Couto, 2019). The skin lesions may be responsive to administration of systemic glucocorticoids, but discontinuation of MMI is usually necessary (Trepanier, 2007; Ferguson, 2018).

A wide variety of bone marrow dyscrasias, may develop in hyperthyroid cats subjected to MMI. Mild abnormalities, such as eosinophilia, lymphocytosis and temporary leukopenia are expected to be found in less than 10% of the cases (Ferguson, 2018; Nelson & Couto, 2019). Animals with such MMI-induced blood changes usually recover within a week of drug discontinuation (Trepanier, 2007). More alarming, albeit rare, haematological abnormalities may include thrombocytopenia, leukopenia and IMHA (Ferguson, 2018; Fossum, 2019; Nelson & Couto, 2019). Once thrombocytopenia is detected, the longer it takes to stop treatment, the higher the likelihood of haemorrhage to occur will be, for instance as epistaxis and oral bleeding. Note that in case of haemorrhage without thrombocytopenia other comorbidities should be considered (Trepanier, 2007).

Hepatic toxicity is another worrisome side effect of the antithyroid drug therapy, but is rare, occurring in less than two percent of cats (Padgett, 2002; Trepanier, 2007; Carney *et al.*, 2016; Ferguson, 2018; Fossum, 2019; Nelson & Couto, 2019). Anorexia, vomiting and lethargy accompanied with jaundice and markedly raised ALT, AST, ALP and total bilirubin are typical signs of hepatotoxicity. Although clinical signs may resolve within few days after cessation of MMI, resolution of icterus and liver enzyme elevations may take several weeks (Trepanier, 2007; Ferguson, 2018; Nelson & Couto, 2019). Reintroduction of MMI will lead to recurrent hepatopathy. Hence, attempting to continue antithyroid medical therapy is contraindicated (Trepanier, 2007;

Ferguson, 2018;).

In addition and also rare, myasthenia gravis may be an adverse reaction to MMI (Trepanier, 2007; Nelson & Couto, 2019). Finally, it is noteworthy to highlight that kidney damage is not a side effect of MMI therapy (Carney *et al.*, 2016).

The side effects of carbimazole are similar to those observed in patients receiving MMI, however they appear less frequently (Nelson & Couto, 2019). It is thought that such decrease, particularly of GI upset, might be related to the actual mechanism of this pro-dug, which reduces direct contact of MMI on GI mucosa (Ferguson, 2018). Unfortunately, due to the lack of data comparing the adverse reactions rate of both drugs and regarding that one is converted in the other, it may not be ideal to start carbimazole in cats that responded adversely to MMI (Trepanier, 2007).

Likewise, PTU can be associated with cases of anorexia, vomiting, lethargy and the development of ANA. However, it can additionally lead to IMHA and ITP, which are the most worrisome side effects. For this reason, PTU has fallen into disfavour and is no longer recommended for routine use in cats with FHT (Ferguson, 2018; Fossum, 2019).

Because some of the described side effects are common, it is important to regularly monitor hyperthyroid cats under medical management with antithyroid drugs. The latest recommendations suggest that TT4 levels should be monitored every two to four weeks until the lowest effective dose is determined (Bugbee *et al.*, 2023). Simultaneously, CBC, platelet count and kidney function should be checked (Bucknell, 2000; Nelson & Couto, 2019; Geddes & Aguiar, 2022). After that period, once stable, at least every six months (Bugbee *et al.*, 2023), cats should visit the clinic so that all those tests can keep being performed, but in this phase instead of just evaluating kidney function, a complete serum biochemistry panel is preferable (Nelson & Couto, 2019; Geddes & Aguiar, 2022). The timing of blood sampling after MMI administration does not seem to affect the usefulness of the results (Fossum, 2019; Bugbee *et al.*, 2023). Such periodic reassessments help to keep an eye on TT4 values, so that dosage can be adjusted accordingly over time (Bugbee *et al.*, 2023).

Animals treated with MMI are less prone to develop IH due to autoregulatory mechanisms in the peripheral tissues associated with the drug itself, in which serum T3 levels are maintained within the RI even when TT4 concentration is quite decreased (Ferguson, 2018). Even so, it is important to avoid overdosing the animals and also monitor them to avoid misdiagnosing IH (Bugbee *et al.*, 2023).

6.2.1.4. Expected outcome

Treatment with MMI has been shown to be successful in more than 90% of hyperthyroid cats (Trepanier, 2007; Yu, Lacorcia & Johnstone, 2022), although some authors only report a success rate of 75% (Peterson, 2020). Remission has also been achieved in cats under routine administration of carbimazole (Fossum, 2019). On average, the euthyroid status is regained within two to four weeks of treatment (Trepanier, 2007; Carney *et al.*, 2016; Ferguson, 2018; Nelson &

Couto, 2019; Geddes & Aguiar, 2022). This period usually coincides with the moment when thyroid hormones storage becomes depleted (Ferguson, 2018).

Transdermal MMI is associated with a slower (Ferguson, 2018; Nelson & Couto, 2019) and a lower efficacy of control (Trepanier, 2007; Ferguson, 2018; Fossum, 2019; Nelson & Couto, 2019), when compared to oral MMI. Multiple factors, like a more variable bioavailability, lack of regulation of compounding pharmacies and lack of consistency between products created can contribute to such decrease of effectiveness, but overall long-term treatment can still lead to reduction of serum T4 levels (Trepanier, 2007; Ferguson, 2018; Nelson & Couto, 2019).

While in the past the median MMI dose required was 10 mg/cat/day; nowadays, with earlier diagnosis and treatment (Aldridge *et al.*, 2015), the majority of FHT cases seem to control T4 values with 5 to 7.5 mg/day (Nelson & Couto, 2019). In fact, cats receiving high maintenance doses (for instance 10mg/day) may indicate poor owner compliance (Carney *et al.*, 2016) or the presence of an undiagnosed carcinoma (Nelson & Couto, 2019).

Finally, because antithyroid medication is not curative nor has anti-tumour properties, as the goiter becomes larger, the tendency is for ascending doses of MMI or carbimazole to be dispensed as an attempt to chronically manage the patient's euthyroidism status (Padgett, 2002; Trepanier, 2007; Carney *et al.*, 2016; Ferguson, 2018; Peterson, 2020; Geddes & Aguiar, 2022; Bugbee *et al.*, 2023). Sooner or later, some patients will not tolerate the dosage of medication required to maintain euthyroidism or will even become completely resistant to thioureylenes (Carney *et al.*, 2016; Yu, Lacorcia & Johnstone, 2022). At this point, other treatment methods will have to be considered (Carney *et al.*, 2016).

Regarding median survival times, overall uncomplicated hyperthyroid cats treated with MMI alone, tend to live approximately more two years (Chapman, 2011; Fossum, 2019; Nelson & Couto, 2019).

6.2.2. Dietary therapy

Of all the four treatment modalities available, dietary therapy has the lowest rate of success. Hence, it should be considered as the last resort (Peterson, 2020). Usually, the candidates for nutritional management include: cats unable to be treated by definitive methods, either due to concurrent severe NTI or the owner's preference; or cats unable to be treated with antithyroid medication because of adverse reactions, poor owner compliance or the cat's low tolerance to be medicated (Nelson & Couto, 2019; Peterson, 2020; Yu, Lacorcia & Johnstone, 2022).

Up to the current date, there is only a veterinary iodine-restricted diet commercially available for cats: Hill's Y/D, by Hill's Pet Nutrition (Daniel & Neelis, 2014; Carney *et al.*, 2016; Nelson & Couto, 2019; Geddes & Aguiar, 2022; Yu, Lacorcia & Johnstone, 2022; Bugbee *et al.*, 2023). It is known that the decreased dietary iodine will lead to a decrease in iodine uptake by the thyroid gland and, consequently, limit the excessive production of thyroid hormones (Daniel & Neelis, 2014; Laflamme & Gunn-Moore, 2014; Davies, 2016; Nelson & Couto, 2019; Peterson, 2020). Therefore, there is no direct effect in the autonomous thyroid tumour and the disease is not cured.

Hence, high thyroid hormone concentration are not effectively supressed in all cats with FHT (Peterson, 2020).

Other limitations are associated with a lack of palatability (Carney *et al.*, 2016; Grossi *et al.*, 2019; Yu, Lacorcia & Johnstone, 2022). Initially, that might not be a limitation, inasmuch the polyphagia caused by HT makes cats accept the diet well. However, as T4 levels start to decrease, they start getting better and tend to reject it (Grossi *et al.*, 2019). Due to such rejection, or even in cases of poor compliance, owners sometimes alternate the iodine-restricted diet with a non-restricted one, which affects the efficacy of the therapy. On one hand, dietary iodine fluctuations are thought to contribute to the onset of HT (Yu, Lacorcia & Johnstone, 2022). On the other hand, these animals must really not have access to any other food apart from the restricted one (Yu, Lacorcia & Johnstone, 2022; Bugbee *et al.*, 2023), so that results can be achieved. This includes not eating human food; other pet's food, which can be a challenge in multi-cat households (Carney *et al.*, 2016; Davies, 2016; Peterson, 2020); and not hunting (Nelson & Couto, 2019; Bugbee *et al.*, 2023). Therefore, animals subjected to this treatment must be kept rigorously indoors, as well (Nelson & Couto, 2019; Geddes & Aguiar, 2022). In addition, tap water, some medications and supplements may interfere with the treatment, as they represent sources of iodine. Thus, whenever necessary and if possible, they should be replaced accordingly (Carney *et al.*, 2016; Nelson & Couto, 2019; Geddes & Aguiar, 2022).

In resume, all these factors can, in fact, contribute to a poor long-term effectiveness of this treatment modality. Thus, particularly in cats that live with other animals, that cannot live without going outside and/or require additional nutritional or pharmacological management, therapy with Hill's Y/D diet must be carefully considered (Nelson & Couto, 2019; Peterson, 2020).

6.2.2.1. Monitoring during treatment

The first TT4 recheck values should be conducted at two, four and eight weeks after the prescribed diet has been initiated. Then, once T4 levels are controlled within the RI, every four to six months those rechecks must be complemented with PE, bloods, a chemistry panel and urinalysis (Carney *et al.*, 2016; Nelson & Couto, 2019). Every time the diet dosage is changed, a subsequent test should be performed in the following two to four weeks (Carney *et al.*, 2016).

6.2.2.2. Complications

Although dietary iodine restriction is considered a risk factor for the development of FHT (Laflamme & Gunn-Moore, 2014), until recently no long-term effects related to it have been described in hyperthyroid cats (Daniel & Neelis, 2014; Nelson & Couto, 2019; Geddes & Aguiar, 2022; Yu, Lacorcia & Johnstone, 2022).

This unknown risk should also be taken into consideration when, as an attempt to present a solution for multi-cat households, where it is difficult to provide separate diets, owners are suggested to feed all the cats (i.e., healthy and hyperthyroid cats) with Hill's Y/D diet. This is actually a topic where authors' opinion diverge: some consider feeding non-hyperthyroid animals with low iodine diets contraindicated (Laflamme & Gunn-Moore, 2014; Davies, 2016), others see

that as acceptable if an iodine supplement is added to their diet (Nelson & Couto, 2019) while others believe that is not harmful at all (Bugbee *et al.*, 2023).

Regardless, the reality is that investigation to learn about the possible complications related to ongoing iodine-deficient diet is warranted (Daniel & Neelis, 2014; Nelson & Couto, 2019; Geddes & Aguiar, 2022; Yu, Lacorcia & Johnstone, 2022), especially considering that I_2 seems to play a variety of other roles in the body, for example acting as an antioxidant, promoting apoptosis, supporting immune function and having antineoplastic properties (Laflamme & Gunn-Moore, 2014).

6.2.2.3. Compatibility with other methods of treatment

A cat fed with a Hill's Y/D diet may be subjected to a surgical thyroidectomy (Carney *et al.*, 2016). However, the combination of iodine-restricted diet therapy with administration of antithyroid medication or radioiodine therapy is not recommended. The restricted diet should only be introduced after the medication has been tapered and stopped for a period of one to two weeks (Nelson & Couto, 2019). Regarding radioactive treatment, the ideal withdrawal time from the diet remains unknown (Carney *et al.*, 2016).

6.2.2.4. Expected outcome

Depending on the degree of thyrotoxicosis (Carney *et al.*, 2016; Geddes & Aguiar, 2022; Bugbee *et al.*, 2023) and on the factors previously mentioned, the outcome is variable between patients. One month of dietary management is sufficient to achieve euthyroidism in some cats (Daniel & Neelis, 2014; Carney *et al.*, 2016; Nelson & Couto, 2019), for others the double that time is necessary (Daniel & Neelis, 2014; Nelson & Couto, 2019; Yu, Lacorcia & Johnstone, 2022), in severely hyperthyroid cats, it may take up to six months (Daniel & Neelis, 2014; Carney *et al.*, 2016; Geddes & Aguiar, 2022) and others may take a year (Daniel & Neelis, 2014), while some never have their values normalized with this treatment method (Carney *et al.*, 2016; Geddes & Aguiar, 2022). Overall, 75%–83% of cats with FHT go into remission after eight weeks of exclusive feeding (Yu, Lacorcia & Johnstone, 2022) and around 90% after three months (Davies, 2016).

Although dietary therapy has been effective for many patients (Davies, 2016; Grossi *et al.*, 2019; Nelson & Couto, 2019; Yu, Lacorcia & Johnstone, 2022; Bugbee *et al.*, 2023), TT4 concentrations do not usually achieve the lower half of the range interval and clinical signs might not necessarily improve significantly (Yu, Lacorcia & Johnstone, 2022). This may explain the low success rate (i.e., 50%) of dietary management in controlling HT reported by (Peterson, 2020).

6.3. Homeopathic therapy

Homeopathic therapy has been proposed as an effective alternative to definitive or reversible methods of treatment. This approach was supported by (Chapman, 2011), who believes this untraditional therapies are beneficial because they avoid side effects of pharmacological management or surgery, are more affordable than radioiodine and allow cats, whose owners decline conventional methods, to be treated.

However, despite the authors who claim that homeopathic therapy is able to normalise

thyrotoxic clinical signs and thyroid hormone levels, it remains controversial and lacking in evidence. In fact, clinicians are advised to always direct pet owners to pursue traditional treatments for this disease (Bugbee *et al.*, 2023).

7. Prevention

Because the underlying causes of FHT are still not fully understood, definitive recommendations of how to prevent such common disease are yet to be established (Peterson, 2012; McLean, Lobetti & Schoeman, 2014). Nonetheless, based on the information already available on the subject, prophylactic measures to minimize the risk of cats developing HT have been suggested (Peterson, 2012).

Starting with the diet, cat food products containing soy should be avoided, because not only it is not physiologically required by cats, but it is also a recognized goitrogen. Feeding the animal with foods containing balanced amounts of I_2 is equally recommended. Generally, 1 µg/kg body weight or about 100 µg/cat/day is the I_2 daily amount required to prevent thyroid disorders (Ferguson, 2018).

Likewise, it is important to ensure a proper balance of other vitamins and minerals like vitamin A, vitamin D and selenium. In addition, restricting the quantity of fish-flavoured ingested foods could be reasonable since some fishes are high in I_2content. Water can also be analysed and if necessary purified or filtrated. Unless the home water source is known to be contaminated, it is preferable to always use filtered tap water instead of commercially bottled water (Peterson, 2012).

Efforts should also be made to avoid cat's exposure to BPA. Food sachets are a good alternative to pop-top canned food because they do not contain an epoxy coating. However, if canned food is intended to be fed, it could be wise to inquire whether BPA is part of the can's lining. In case that information is not accessible, opting for smaller cans, which are less likely to contain the bisphenol, may be preferable. Moreover, heat may lead BPA to leach from plastic containers into food. So, the cat's food should be only heated in ceramic or glass recipients. The plastic bowls should be avoided to serve water as well (Peterson, 2012).

In terms of controlling the indoor environment, to minimize cat's contamination with PBDEs, the following measures are recommended: vacuuming the house frequently specially with a device with a HEPA filter incorporated; this filter can also be found in air cleaners, which may help reduce particle-bound contaminants in the house; bathing the animal at least once a month or wiping the cat daily with a wet cloth or towel; regular brushing to remove old hair, dander and chemical particles; when buying new furniture and electronics enquiring the manufacturer about the type of fire retardant within it and avoiding buying those that indeed have PBDEs (Peterson, 2012). Making sure that foam items are intact and covered with a protective fabric is also ideal (Peterson, 2012).

In addition, environmental herbicides, pesticides or insecticides should be avoided in the cat's environment and topical flea control products used only when strictly necessary. Biodegradable cat litters are preferable than those containing chemicals like deodorizers and odour neutralizers

(Peterson, 2012).

Finally, to quote (Peterson, 2012), “even if these measures do not prevent the development of hyperthyroidism, they are unlikely to be detrimental and may even improve the cat’s health”.

8. Concomitant disorders and how they affect the diagnosis and treatment of feline hyperthyroidism

It is not unusual for hyperthyroid cats to present with one or more concurrent NTI (Carney *et al.*, 2016; Peterson, 2020; Bugbee *et al.*, 2023), which may either be a direct consequence of the thyrotoxicosis or a reflexion of the advanced age of the overwhelming majority of these cats. Either way, their existence may interfere with the successful identification of HT and even make it more difficult for the thyrotoxic state to be controlled (Peterson, 2020). Despite that, because FHT is a life-threatening disorder if left untreated, those cats should still be treated for HT with equal management of the comorbidities in order to optimize the patients’ well-being (Carney *et al.*, 2016; Bugbee *et al.*, 2023).

Some of the most common comorbidities associated with FHT, include: CKD, cardiac disease, DM, GI disease and neoplastic abnormalities, to name a few (Padgett, 2002; Nelson & Couto, 2019; Peterson, 2020; Bugbee *et al.*, 2023). If at least one of them is indeed confirmed, owners must be aware that their cat’s clinical signs may not resolve with the achievement of euthyroidism alone (Peterson, 2020).

8.1. Chronic kidney disease

Being both FHT and CKD common disorders in senior and geriatric cats, often occurring concurrently and sharing a number of historical findings and clinical signs, they repeatedly present as each other’s differential diagnoses (Peterson & Eirmann, 2014; Fossum, 2019; Nelson & Couto, 2019; Geddes & Aguiar, 2022; Yu, Lacorcia & Johnstone, 2022). Between 15 and 51% of cats with HT were found to have CKD (Geddes & Aguiar, 2022).

However, diagnosing co-existing CKD and FHT can be challenging. CKD can mask FHT by lowering serum thyroid hormone levels into the RI (Fossum, 2019; Geddes & Aguiar, 2022), representing what is called the occult HT, the NTI syndrome (Geddes & Aguiar, 2022) or the euthyroid sick syndrome (Fossum, 2019). At the same time, multiple mechanisms associated with HT can mask kidney disease.

The characteristic hypermetabolic state of HT affects the renal function by assorted mechanisms, including activation of the renin–angiotensin–aldosterone system, stimulation of the sympathetic nervous system and decline of the peripheral vascular resistance, which ultimately leads to an abnormally high renal blood flow (RBF) and glomerular filtration rate (GFR) (Birchard, 2006; Syme, 2007; Peterson & Eirmann, 2014; Carney *et al.*, 2016; Vaske, Schermerhorn & Grauer, 2016; Petroff & Greco, 2020; Geddes & Aguiar, 2022; Matos *et al.*, 2022; Yu, Lacorcia & Johnstone, 2022).

On one hand, this increase in RBF and consequently GFR, possibly accompanied by proteinuria, which is common in FHT (Syme, 2007; Vaske, Schermerhorn & Grauer, 2016), can

directly exacerbate kidney damage (Reynolds & Lefebvre, 2013; Peterson & Eirmann, 2014; Carney *et al.*, 2016; Nelson & Couto, 2019). The role of high levels of T4 in circulation and its involvement with the progression of kidney disease was supported through a study conducted by (Peterson & Eirmann, 2014), where the prevalence of CKD was higher in hyperthyroid cats within the same age range.

On the other hand, the increment of GRF may, simultaneously, counterbalance the low GFR and azotaemia from CKD and mask it. Also, the increased endogenous protein catabolism and muscle wasting from the thyrotoxic state can further help lowering sCr concentrations, despite the presence of mild to moderate renal disease (Syme, 2007; Trepanier, 2007; Peterson & Eirmann, 2014; Aldridge *et al.*, 2015; Vaske, Schermerhorn & Grauer, 2016, 2016; Fossum, 2019; Peterson, 2020; Geddes & Aguiar, 2022; Matos *et al.*, 2022; Yu, Lacorcia & Johnstone, 2022). Unfortunately, even the renal biomarker symmetric dimethylarginine (SDMA), that is supposed to have excellent specificity for renal dysfunction (Syme, 2019), is not helpful in animals with uncontrolled HT, due to being equally influenced by RBF and GFR (Yu, Lacorcia & Johnstone, 2022). Even though the traditional renal markers may not translate into trustworthy results in the presence of FHT (Yu, Lacorcia & Johnstone, 2022), BUN, sCr and SDMA borderline high or USG less than 1.035, definitely under 1.020, are suggestive of masked CKD (Peterson, 2020). Identification of small kidneys during PE can also be an indicator of such comorbidity (Nelson & Couto, 2019).

When TT4 values stabilise within the RI, both RBF and GFR also tend to normalise (Birchard, 2006; Syme, 2007; Peterson & Eirmann, 2014; Aldridge *et al.*, 2015; Fossum, 2019; Nelson & Couto, 2019; Peterson, 2020; Yu, Lacorcia & Johnstone, 2022). However, in cats with concurrent CKD, especially in cases of moderate dysfunction, those parameters are expected to fall to the low-normal or subnormal levels (Peterson & Eirmann, 2014; Peterson, 2020). Consequently, BUN and sCr concentrations typically increase as the amount of glomerular filtrate formed by the kidney, per minute, falls (Syme, 2007). Although this kidney parameters rise fairly consistently after treatment, regardless of therapy modality (Peterson, 2006; Syme, 2007; Carney *et al.*, 2016), most of the increases occur within the RI (Syme, 2007). Only approximately 25% of successfully treated cats (Peterson, 2006, 2020) actually become azotemic within three to six months of euthyroidism (Xifra, Serrano & Peterson, 2022). Fortunately, only a few of these animals develop severe azotaemia (i.e., International Renal Interest Society [IRIS] stage 3-4), with a poorer long-term prognosis. The majority become mild to moderately ill (i.e., IRIS stage 1 or 2) and are able to remain stable for a long time (Nelson & Couto, 2019; Peterson, 2020). Unfortunately, no single parameter has been shown to consistently predict which cats will develop post-treatment azotaemia, despite SDMA, BUN, sCr, BP, USG and proteinuria have been considered (Syme, 2007; Reynolds & Lefebvre, 2013; Vaske, Schermerhorn & Grauer, 2016; Fossum, 2019; Nelson & Couto, 2019; Geddes & Aguiar, 2022; Bugbee *et al.*, 2023). Nevertheless, such worsening of serum kidney function tests or an apparent development of renal dysfunction after therapy is expected to occur (Padgett, 2002; Birchard, 2006; Peterson & Eirmann, 2014; Carney *et al.*,

2016; Fossum, 2019; Nelson & Couto, 2019). If that is the case, a potential consequence of the successful establishment of euthyroidism, is the exposure of pre-existing subclinical CKD, rather than a side effect of the therapy itself (Peterson, 2006; Syme, 2007; Carney *et al.*, 2016; Peterson 2020; Yu, Lacorcia & Johnstone, 2022). In point of fact, direct kidney damage or renal failure are not described to be side effects of any of the treatment options available to treat cats with HT (Carney *et al.*, 2016).

Reduced GFR and azotaemia can also occur as a consequence of IH (Birchard, 2006; Nelson & Couto, 2019; Yu, Lacorcia & Johnstone, 2022). In fact, evaluating both TT4 and TSH in cats that become azotemic post-treatment might help differentiate between the unmasking of pre-existing CKD or the onset of IH (Yu, Lacorcia & Johnstone, 2022). In case of the latter, it is important to start therapy with thyroid hormone supplementation (Vaske, Schermerhorn & Grauer, 2016; Nelson & Couto, 2019; Peterson, 2020), because persistent IH may worsen existing azotaemia and enhance the progression of CKD (Vaske, Schermerhorn e Grauer, 2016; Morré *et al.*, 2018; Fossum, 2019; Peterson, 2020; Peterson e Rishniw, 2021; Chow e White, 2022; Xifra, Serrano e Peterson, 2022).

Given the difficulties associated with diagnosing CKD in hyperthyroid cats, multiple authors suggest a trial with reversible treatment modalities, prior implementing the actual therapy plan. With this trial, clinicians attempt to test renal function, determine whether the patient tolerates successful treatment without leading to unacceptable renal decompensation and also assess the suitability of the cat for definitive treatment (Padgett, 2002; Trepanier, 2007; Carney *et al.*, 2016; Nelson & Couto, 2019; Peterson, 2020; Geddes & Aguiar, 2022; Yu, Lacorcia & Johnstone, 2022). Medical management with MMI is the preferred approach to achieve temporary euthyroidism, rather than dietary management, as it can be titratable to effect as much as possible in order to control FHT, while avoiding further kidney deterioration (Padgett, 2002; Birchard, 2006; Trepanier, 2007; Carney *et al.*, 2016; Fossum, 2019; Peterson, 2020; Geddes & Aguiar, 2022; Yu, Lacorcia & Johnstone, 2022). As any other antithyroid drug therapy plan, the trial must start with the lowest recommended dose (Syme, 2007; Geddes & Aguiar, 2022) and then titrated up as needed. If azotaemia becomes apparent or worsens significantly, for instance to IRIS stage 3 or higher, a protocol with a more appropriate dose of antithyroid drug, and possibly with medication to help treating CKD, should be instituted (Trepanier, 2007; Nelson & Couto, 2019). In these cases, if irreversible treatment is pursued, after the procedure, careful monitoring and aggressive kidney support may be required until the preserved normal suppressed thyroid tissue regains its secretory function (Carney *et al.*, 2016). If renal parameters remain unchanged or improve as serum T4 concentration decreases, underlying CKD can be excluded and ^{131}I or thyroidectomy can be recommended (Carney *et al.*, 2016; Nelson & Couto, 2019; Peterson, 2020), but with the caveat that this test does not always correctly predict or exclude CKD and that protocols of only one to two months can never ensure the patient will not become azotemic after definitive treatment (Peterson, 2020). In fact, to better assess renal function, at least three to six months of euthyroidism are necessary (Peterson, 2020). A more recent approach defends that instituting a

MMI trial may not be necessary before definitive treatment in cats with mild renal changes (i.e., IRIS stage 1) (Bugbee *et al.*, 2023). Only patients moderately to severely azotemic would benefit from such precaution (Yu, Lacorcia & Johnstone, 2022).

Treating FHT is essential regardless of renal dysfunction, both in animals that present with pre-existing azotaemia and in those that develop azotaemia after serum thyroid hormone concentration starts dropping (Carney *et al.*, 2016; Yu, Lacorcia & Johnstone, 2022). Cats should never be deliberately left mildly hyperthyroid as an attempt to maintain kidney parameters within the RI (Syme, 2007; Carney *et al.*, 2016; Geddes & Aguiar, 2022). Having a sense of the systemic effects resulting from the hypermetabolic state, characteristic of FHT, when patients are kept thyrotoxic, multiple body organ systems will remain vulnerable to ongoing damage, including the kidney whose injuries will exacerbate proportionally to the GFR increment under the false sense of security based on artificially lowered sCr concentrations (Syme, 2007; Carney *et al.*, 2016; Geddes & Aguiar, 2022; Yu, Lacorcia & Johnstone, 2022). Therefore, leaving a hyperthyroid cat untreated will not protect the kidney from getting further damaged but will be counterproductive. Alternatively, maintaining TT4 levels in the upper half of the RI, might help control kidney dysfunction while euthyroidism is ensured (Carney *et al.*, 2016). At the same time, managing CKD in a thyrotoxic cat should be no different than in a euthyroid cat (Geddes & Aguiar, 2022), which means an adequate diet and management of proteinuria and/or hypertension should be instituted, following the IRIS guidelines, whenever necessary (Carney *et al.*, 2016). Because feeding a phosphate-restricted diet is recommended to control CKD (Peterson & Eirmann, 2014; Quimby & Ross, 2022), a renal diet should take precedence over the use of an Hill's Y/D diet (Geddes & Aguiar, 2022). Therefore, managing TT4 values with an iodine-restricted diet does not seem to be the best option for hyperthyroid azotemic cats.

Overall, regardless of therapy protocol, hyperthyroid cats with kidney dysfunction are expected to have a shorter survival time than hyperthyroid cats without concurrent CKD (Fossum, 2019; Nelson & Couto, 2019). Likewise, in hyperthyroid cats that were non-azotemic at the time of treatment, the unmasking of azotaemia following effective therapy does not seem to adversely impact on their survival (Syme, 2007; Vaske, Schermerhorn & Grauer, 2016; Chow & White, 2022; Yu, Lacorcia & Johnstone, 2022). However, the same is not true for thyrotoxic cats with pre-existent azotaemia. Hyperthyroid cats, azotemic at the time of treatment are expected to have shortened survival compared with those that develop signs of CKD only after initiation of therapy (Syme, 2007; Aldridge *et al.*, 2015; Vaske, Schermerhorn & Grauer, 2016; Chow & White, 2022; Yu, Lacorcia & Johnstone, 2022). Likewise, hypothyroid-induced azotaemia also has a negative impact on patient's QoL (Peterson, 2020) and survival time (Aldridge *et al.*, 2015; Vaske, Schermerhorn & Grauer, 2016; Morré *et al.*, 2018; Peterson, 2020; Peterson & Rishniw, 2021; Chow & White, 2022; Geddes & Aguiar, 2022; Matos *et al.*, 2022; Xifra, Serrano & Peterson, 2022). For that reason, it is important to avoid protocols more likely to induce post-treatment hypothyroidism (Carney *et al.*, 2016; Nelson & Couto, 2019; Peterson, 2020; Xifra, Serrano & Peterson, 2022) and, if IH still occurs, replacement therapy should improve most cats' survival

times (Fossum, 2019; Peterson, 2020).

Although there is not a defined kidney monitoring protocol, the overall specialists' opinion highlight the importance of monthly kidney evaluation within the first months of therapy (Ferguson, 2018; Nelson & Couto, 2019) and then at least at three and six months after the establishment of euthyroidism (Vaske, Schermerhorn & Grauer, 2016; Geddes & Aguiar, 2022). After that, clinicians can keep measuring kidney parameters up to or beyond one year (Yu, Lacorcia & Johnstone, 2022), depending on case progression.

8.2. Cardiovascular disease

As previously mentioned, thyroid hormone excess increases the cardiovascular system's sensitivity to catecholamines. Hence, it is not uncommon to find cardiovascular abnormalities in hyperthyroid animals (Peterson, 1984; Birchard, 2006; Fossum, 2019; Petroff & Greco, 2020). However, long-standing thyrotoxicosis may equally enhance the production of myocardial contractile proteins (Miller, 2022), leading to HCM (Peterson, 1984; Padgett, 2002; Daniel & Neelis, 2014; Nelson & Couto, 2019; Petroff & Greco, 2020; Miller, 2022).

Considering that thyrotoxic and primary cardiac hypertrophy share a range of clinical signs, it is important to make that distinction (Peterson, 1984). Fortunately, thyrotoxic heart disease has been described to be reversible once euthyroidism is achieved (Peterson, 1984; Daniel & Neelis, 2014; Nelson & Couto, 2019; Miller, 2022). Therefore, once FHT has been corrected, the assessment of the cardiovascular system is more accurate (Syme, 2007; Carney *et al.*, 2016; Peterson, 2020). According to (Peterson, 2020), a six-month period or longer between the establishment of euthyroidism and cardiac evaluation is ideal. The author also highlights that, in fact, cases are rare that require further therapy beyond treatment of HT itself (Peterson, 2020). Nevertheless, if patients keep showing signs of HCM further investigation is warranted (Carney *et al.*, 2016).

When HT remains uncontrolled and HCM worsens, CHF might follow (Peterson, 1984; Daniel & Neelis, 2014; Nelson & Couto, 2019; Peterson, 2020). In fact, around 20% of the hyperthyroid cats with thyrotoxic heart disease may develop CHF (Fossum, 2019). In such cases, findings of tachypnoea or dyspnoea during initial assessment of the hyperthyroid patient, should raise the suspicion that more diagnostic tests should be performed (Syme, 2007; McLean *et al.*, 2017; Geddes & Aguiar, 2022). Regarding that the development of CHF in the majority of hyperthyroid cats is a consequence of a severe thyrotoxic state, usually these patients are not suitable candidates for definitive hyperthyroid treatment and may even be no longer controlled with MMI (Peterson, 2020). Even if thyroid hormone levels are still manageable, they will most certainly require further, and possibly simultaneous (Carney *et al.*, 2016), therapy with diuretics (Peterson, 2020). Fortunately, with earlier diagnosis, the incidence of CHF in FHT cases has become rare (Syme, 2007; Peterson, 2020).

Considering that such comorbidities may develop in hyperthyroid cats, thoracic radiography, echocardiography and electrocardiography are useful diagnostic tools and should be pursued in

case thyrotoxic or primary heart disease are suspected, in order to assess the extent of cardiac involvement (McLean *et al.*, 2017).

The effect of increased thyroid hormone levels on the sympathetic system may also result in hypertension in a high percentage of hyperthyroid cats (Geddes & Aguiar, 2022). Antihypertensive therapy should be instituted only when SBP is consistently higher than 180 mmHg (Nelson & Couto, 2019) or if retinal lesions are present (Nelson & Couto, 2019; Geddes & Aguiar, 2022). Otherwise, antihypertensive treatment should only be given if the patient remains hypertensive once euthyroidism is achieved. Hyperthyroid-induced hypertension tends to resolve with HT treatment alone, unless there are other underlying diseases behind the problem (Nelson & Couto, 2019) (for instance: CKD, DM, hyperaldosteronism and hyperadrenocorticism [Carney *et al.*, 2016]). In such situations, hypertension may persist, despite HT treatment (Nelson & Couto, 2019), and therapy with antihypertensive is definitely warranted (Trepanier, 2007; Carney *et al.*, 2016).

Some cats that were not hypertensive during the thyrotoxicosis state, may develop hypertension several months after restoration of euthyroidism, which in most cases coincides with the unmasking of CKD (Syme, 2007; Trepanier, 2007; Geddes & Aguiar, 2022). For that reason, even if initial BP readings were normal, patients should be rechecked for hypertension two to three months after establishment of thyroid hormone levels within the RI (Trepanier, 2007; Geddes & Aguiar, 2022).

8.3. Diabetes *mellitus*

As mentioned before, elevated blood glucose concentration may be commonly found in FHT cases and it is usually interpreted as a reflection of a stress response (Shiel & Mooney, 2007; Peterson & Eirmann, 2014). However, such hyperglycaemia can potentially be attributed to changes in the glucose and insulin mechanism promoted by the thyroid hormone excess. On one hand, thyrotoxicosis influences pancreas to secrete insulin (Shiel & Mooney, 2007; Hall, 2011). On the other hand, moderate to severe endogenous insulin resistance accompanied by glucose intolerance, due to delayed glucose clearance, is caused by increased T4 levels (Shiel & Mooney, 2007; Peterson & Eirmann, 2014). Therefore, untreated hyperthyroid cats may develop DM (Peterson & Eirmann, 2014). Unfortunately, is it not uncommon for hyperthyroid cats to not improve or even get worse despite successful establishment of euthyroidism, which leads some authors to believe thyrotoxicosis might induce long-term changes of glucose and insulin mechanisms (Peterson & Eirmann, 2014).

Interestingly, it has been recently postulated that Hill's Y/D, as a high carbohydrate content-diet, may potentially contribute to the development of glucose intolerance and insulin resistance in hyperthyroid patients (Yu, Lacorcia & Johnstone, 2022).

Besides, DM has been reported to develop in some patients, not diabetic at the time of diagnosis, in the months to years after treatment of HT, mostly due to weight gain or even obesity associated to normalization of thyroid hormone values (Peterson & Eirmann, 2014).

8.4. Gastrointestinal disease

As mentioned before, HT may be related to GI signs. However, the suspicion of the existence of concurrent GI tract disorder, such as IBD and alimentary lymphoma, must be considered should hyperthyroid cats present as primary clinical signs moderate to severe diarrhoea and/or their vomiting episodes do not resolve once euthyroidism is reached. If such disorders are suspected, more emphasis should be given to abdomen palpation, since it allows searching for intestinal tract and mesenteric lymphadenopathy, which could both be indicative of intestinal neoplasia. Further investigation through abdominal ultrasound, endoscopy and/or intestinal biopsy should be also taken into consideration (Nelson & Couto, 2019; Peterson, 2020) before irreversible treatment is carried on. Likewise, a trial with MMI could be beneficial given that if, after the short-term of medication, GI signs persist despite adequate control of the HT, then primary GI disease is more likely (Peterson, 2020).

8.5. Sarcopenia of ageing

Old cats tend to suffer from what is called sarcopenia of aging, characterized by a degenerative loss of skeletal muscle mass and strength accompanied by increased muscle fatigability. Especially in senior and geriatric hyperthyroid cats, the sarcopenia of aging contributes to the loss of weight, if the patients' energy requirements are not met. In fact, this process can occur even after thyroid hormones levels have been effectively normalized. Therefore, in order to try to prevent or slow the cumulative effect of both processes on these cats' body condition, feeding them with a higher protein, highly digestible, energy-dense diet is recommended (Peterson & Eirmann, 2014). Considering that Hill's Y/D is a protein-restricted diet, it might aggravate hyperthyroid patients' malnutrition, particularly in senior ones with associated sarcopenia (Yu, Lacorcia & Johnstone, 2022).

9. Thyroid storm, a possible complication of feline hyperthyroidism

Thyroid storm is a well-defined syndrome in human medicine, characterized by being a form of acute thyrotoxicosis responsible for significant cases of mortality in humans (Ward, 2007). However, in feline medicine there is a certain ambiguity around the subject and lack of investigation as well.

Considering the limited information found about thyroid storm in cats, this condition is triggered by the excessive catecholamine release that leads to excessive thyroid hormone production (Fossum, 2019). However, the rapidity and magnitude with which this increase occurs seem to be the determining factors for the syndrome to be triggered (Carney *et al.*, 2016; Ward, 2007), rather than the actual serum levels themselves (Ward, 2007).

The diagnosis of thyroid storm requires confirmation of the excessive amount of thyroid hormone in circulation, identification of certain clinical signs and recognition of a precipitating event (Ward, 2007). Regarding the first part of the diagnostic process, serum T4 levels and laboratory abnormalities are usually the same as those reported in uncomplicated FHT cases. Likewise, clinical signs of feline thyroid storm will be a manifestation of the acute intensification of

the clinical signs characteristic of FHT, which may include marked tachycardia, tachypnoea, hyperthermia, respiratory distress, cardiac arrhythmias, severe muscle weakness or even sudden death (Ward, 2007; Fossum, 2019). For the last part of the diagnosis, multiple potential precipitating factors for feline acute thyrotoxicosis have been listed, including: forceful thyroid gland palpation, iatrogenic damage to the gland during definitive treatment, sudden withdrawal of antithyroid medication, worsening of NTI (Ward, 2007; Carney *et al.*, 2016) and being subjected to a stressful event (Ward, 2007; Carney *et al.*, 2016; Veres-Nyéki, 2016).

Once the diagnosis is made, treatment with antithyroid medication should be quickly instituted in order to decrease the acute production of T4 and T3, neutralize the multisystemic effect of the hormones and ensure systemic support. In addition, elimination of the triggering factor is equally important (Ward, 2007).

Although rare, thyroid storm is thought to be a deadly complication of FHT (Carney *et al.*, 2016). Hence, it is suggested that 24 hours before an event, that is expected to be stressful for the animal, β-adrenergic antagonist, for instance atenolol at 6.25 mg/cat SID, can be administered as a precaution in order to prevent the onset (Carney *et al.*, 2016).

Nonetheless, some of the statements made by (Carney *et al.*, 2016) and (Ward, 2007) received a lot of criticism from (Peterson, 2016). (Peterson, 2016) starts by agreeing with (Ward, 2007) on the fact that thyroid storm was yet to be considered a well-defined syndrome in feline medicine (Ward, 2007; Peterson, 2016). Actually, despite recognising the existence of severe and chronic hyperthyroid cats whose clinical signs have worsened due to stress or acute cessation of chronic antithyroid treatment, (Peterson, 2016) raised his doubts about those cases being truly representative of thyroid storm. Furthermore, (Peterson, 2016) questioned the role of radioiodine treatment as a potential precipitant factor of thyroid storm as mentioned by both (Carney *et al.*, 2016) and (Ward, 2007), concluding that based on his clinical experience, over 36 years of working with ^{131}I, and the data collected from 1179 hyperthyroid cats treated with radioiodine over four years, by the time, he did not believe “that cats develop what can or should be termed thyroid storm” and that even if they did, there were no reports of such syndrome being induced by ^{131}I therapy in feline medicine. Therefore, considering the lack of feline thyroid storm cases, (Peterson, 2016) considered the information available could lead to overdiagnosis of the syndrome, which would be concerning regarding that unnecessary aggressive therapy for suspected thyroid storm is not without possible adverse effects. Besides, since thyroid storm lacked recognition in feline medicine the prophylactic treatment recommended by (Carney *et al.*, 2016) would be too premature.

Unfortunately, to date, no further information nor more recent data about the true incidence and mortality of thyroid storm in feline medicine was found.

IV. Clinical case - Patient treated with thyroidectomy: ERIC

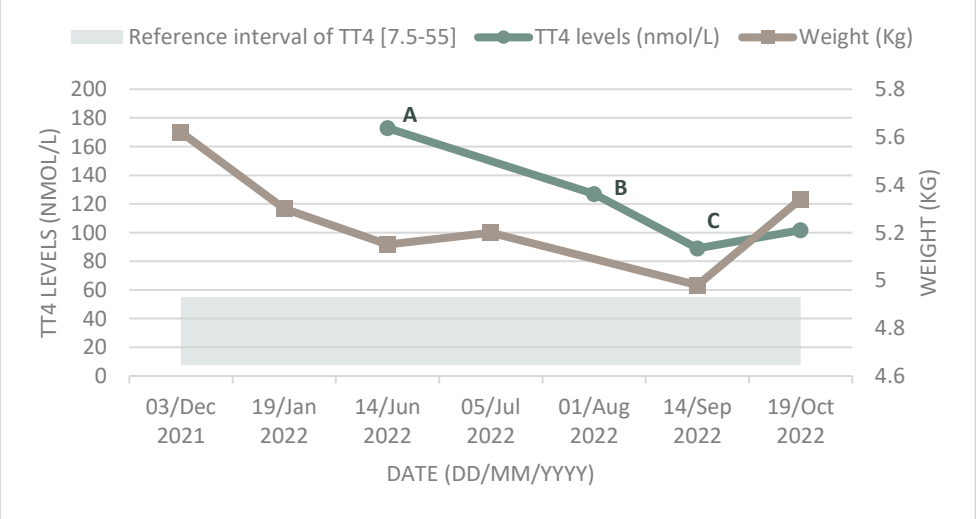
1. Patient information

Eric, a 12-year-old male neutered domestic shorthair cat, was presented to PVS on the 14th of June 2022 with polyphagia, weight loss and "for not being himself" for the past three to four months. At the time he weighed 5.15 kg and had a body condition score of 5/9.

2. Initial case work-up and treatment

According to Eric's owners, he had always been greedy towards his food, but the past few months the food obsession was getting more serious, as such he was eating easily twelve sachets a day. Besides, despite his vigorous appetite, a loss of weight was starting to be noticeable. The owners also reported that Eric, that usually was very active outdoors, was eerily more sedentary. Otherwise, he had recently been wormed and no PU/PD, vomiting, diarrhoea nor haematochezia had been noticed. For this consult, because of his history of being stressed or even aggressive during consults, Eric had been treated with gabapentin (one 50 mg tablet the night before and one 50 mg tablet two hours before the appointment).

On presentation, Eric was bright, alert, responsive (BAR) and vocal, despite being a little sedentary on examination. Regarding his ears, eyes and nose there was nothing abnormal discovered (NAD). Eric weighted 5.15 kg, which represented a loss of 150 g since his last appointment five months before (he had been involved in a cat fight and needed medical assistance) (Graphic 2). His mucous membranes (MM) were pink, with capillary refill time (CRT) less than two seconds. PE revealed a palpable goiter particularly on the right side, with a slight increase of the left thyroid lobe as well. HR was 180 bpm and thoracic auscultation revealed a heart murmur compatible with a grade three out of six. Respiratory system was difficult to assess due to constant purring. Abdominal palpation revealed no evidences of organomegaly. Rectal temperature was not taken.



***Graphic 2** - Evolution of TT4 levels and Eric's weight during antithyroid therapy. (A) Eric started being treated with Thyronorm® Oral Solution for Cats® 2.5mg PO BID; (B) The dose protocol was readjusted to 5mg in the morning and*

2.5mg in the afternoon; (C) Thyronorm® dose was increased to 5mg BID

Considering such clinical presentation, FHT, CKD, DM, liver disease, IBD and exocrine pancreatic insufficiency (EPI) were equated. With the owners' permission, during the consult a blood sample was obtained to measure blood glucose with a glucometer, which was 5.3 mmol/L, and to run an in-house feline comprehensive panel (FeC) (Table 32), where BUN (18.60 mmol/L), ALT (161.00 u/L) and TT4 (172.9 nmol/L) were shown to be increased, particularly TT4 that was markedly elevated (see Graphic 2). Otherwise, bloods were unremarkable. These laboratory findings in association with Eric's clinical presentation, confirmed the diagnosis of HT.

***Table 32** - Laboratory abnormalities found on the 14th of June while Eric was on antithyroid therapy*

Date	**14th of June**				
Required panel	**FeC**				
Evaluated parameter	**RI**	**Result**	**Evaluated parameter**	**RI**	**Result**
sCr (umol/L)	<180	NAD	Bile acid (umol/L)	<15	NAD
BUN (mmol/L)	**3-15**	**18.60**	FSpL	>5.4= pancreatitis	NAD
ALT (u/L)	**<100**	**161.00**	**TT4 (nmol/L)**	**19-65**	**172.9**
ALP (u/L)	<300	NAD	ck (u/L)	<225	NAD
Total protein (g/L)	60-80	NAD	Cholesterol (mmol/L)	<5.5	NAD
Albumin (g/L)	25-40	NAD	Total bilirubin (umol/L)	<7.0	NAD
Globulin (g/L)	25-50	NAD	Hemogram		NAD
Glucose (mmol/L)	4-6	NAD	Electrolytes		NAD

Because the owners had already had a cat with HT before, they were aware of the condition and the treatment options available. Despite being keen to eventually pursue surgery, their choice was to start Eric's treatment with antithyroid medication. Hence, Eric was sent home on oral liquid solution of MMI 2.5mg PO BID (see Graphic 2), being the owners aware of its possible side effects.

3. Follow-up and treatment adjustments

At the re-examination three weeks later, owners reported that Eric had become really unwell within a week of treatment. He stopped eating, had vomited a few times and had visibly lost more weight, which led the owners to voluntarily stop treatment, that was only restarted once Eric regained his appetite. This means, by this time, he had only been continuously medicated for the previous eight to ten days. On PE goiter was unsurprisingly still present, he had slightly put on some weight (5.2 kg) (see Graphic 2), HR was 160 bpm with a heart murmur still audible and SBP was 165 mmHg (measured using a Doppler). Abdominal palpation revealed no palpable abdominal masses, the presence of a large bladder and symmetrical and normodimensioned kidneys. Because of the intermittent administration of MMI, the protocol was not changed.

By the seventh week of antithyroid therapy, TT4 levels were still very elevated (126.9 nmol/L), despite the slight decrease. Therefore, the dose protocol was readjusted to 5 mg in the morning and 2.5 mg in the afternoon (see Graphic 2) for four to six weeks, with the agreement that if side effects to MMI returned, Eric would be subjected to thyroidectomy.

Six weeks later, despite resolution of polyphagia, his weight had fallen (4.98 kg), which was most likely due to yet uncontrolled TT4. Hence, a blood sample was sent to an external laboratory

for a senior wellness feline panel (SEFEU) (Table 33). The abnormalities found included: increased phosphate (2.46 mmol/L), increased BUN (16.1 mmol/L), increased ALP (85 u/L), increased ALT (129 u/L), increased TT4 (89.0 nmol/L) and decreased blood glucose (2.4 mmol/L - defined by the laboratory as an artefact). Although TT4 had decreased, the results were still within the thyrotoxic diagnostic range, which required increasing the dose to 5 mg BID (Graphic 2).

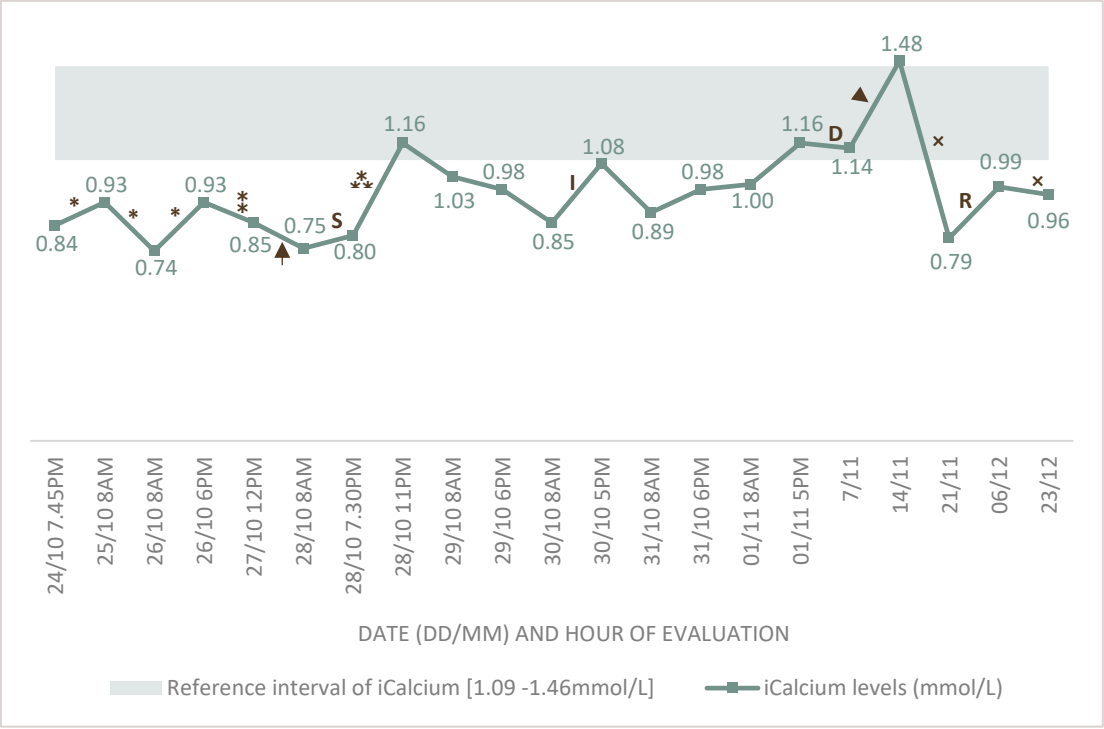
Finally, after more than four months of medical management, considering the lack of success in controlling thyrotoxicosis (TT4 had increased to 101.8 nmol/L) and the permanently raised parameters (i.e., phosphate, BUN and ALT) on laboratory thin cat A panel (FEL4) (Table 33), despite weight gain (5.34 kg) (see Graphic 2), Eric's owners made the informed decision to submit him to thyroidectomy.

Table 33 *- Laboratory abnormalities found on the 14th of September and 19th of October while Eric was on antithyroid therapy*

Date		14th of September	19th of October
Required panel		SEFEU	FEL4
Evaluated parameter	RI	Result	Result
sCr (umol/L)	45-170	NAD	NAD
BUN (mmol/L)	**6.1-12.5**	**16.1**	**14.6**
ALT (u/L)	**18-77**	**129**	**198**
ALP (u/L)	**11-67**	**85**	NAD
Total protein (g/L)	56-81	NAD	NAD
Albumin (g/L)	26-42	NAD	NAD
Globulin (g/L)	15-57	NAD	NAD
Glucose (mmol/L)	**3.8-7.6**	**2.4**	**1.4**
Sodium (mmol/L)	140-157	NAD	Not measured
Potassium (mmol/L)	3.40-5.60	NAD	Not measured
Phosphate (mmol/L)	**0.70-2.10**	**2.46**	**3.05**
TT4 (nmol/L)	**7.5-55**	**89.0**	**101.8**
Total bilirubin (umol/L)	0-10	NAD	NAD
Hemogram		NAD	Not measured

4. Thyroidectomy, follow-up and treatment adjustment

On the 24th of October 2022, Eric was surgically prepared for a bilateral modified intracapsular thyroidectomy. He was sedated with 0.05 mL (0.02 mg/kg) of ACP and 0.33 mL (0.018 mg/kg) of buprenorphine both IV, induced with up to 3 mL (0.6 mg/kg) of propofol IV and maintained with sevoflurane and oxygen via endotracheal tube during the whole procedure. For pain management post-surgery, an injection of 0.5 mL (0.3 mg/kg) of meloxicam was given subcutaneously. The anaesthesia was uneventful and Eric's anaesthetic recovery was equally unremarkable. The surgeon was aware of the possible complications following total thyroidectomy, despite attempting to preserve the external parathyroid on both sides, and so Eric was kept hospitalised for monitoring. By the evening, despite being asymptomatic, electrolytes evaluation revealed that iCa levels were below the RI (0.84 mmol/L; RI 1.09-1.46). Therefore, Eric (5.0 kg) was given 10 mL (2 mL/kg) SQ of 10% CaG diluted in sterile water for injection (WFI) (Graphic 3). During the night, he had been stable and eating all the food offered.



Graphic 3 *- Evolution of Eric's iCa levels after total thyroidectomy and action taken according to those values. (*) Administration of 10 mL of 10% CaG diluted in WFI or saline given SQ; (⁂)0.03 mL PO from a 0.25 µg capsule of calcitriol was given to Eric; (arrow) Eric was prescribed one capsule (0.25 µg) of calcitriol PO SID for seven days; (S) Eric was discharge in the morning with calcitriol to go home, had a seizure at home early in the afternoon and was readmitted at the hospital; (⁂) Eric received a bolus and was continuously infused with CaG; he started protocol with calcitriol and CaGP PO BID; (I) Eric received more 12.5 mL of CaG diluted and set on a drip, and started therapy with amoxicillin and clavulanic acid; (D) The patient went home with calcitriol, CaGP and amoxicillin and clavulanic acid ; (arrow head) Calcium supplementation was stopped and calcitriol reduced to one capsule SID; (x) Treatment with calcitriol was stopped completely; (R) Treatment with calcitriol was restarted but one capsule every other day*

The next morning, iCa levels had improved slightly but were still low (0.93 mmol/L; RI 1.09-1.46). Hence, he received a second dose of the same amount of CaG (Graphic 3). Because iCa were unstable and he would be staying mostly outdoors if he was discharged, Eric's owners agreed with keeping him hospitalized for two days so that he could be closely monitored.

At the morning of the second day postoperatively, iCa had yet not normalized and was even lower (0.74mmol/L; RI 1.09-1.46). Fortunately, after re-administration of CaG, this time diluted in saline, by the afternoon iCa values had gone up (0.93 mmol/L; RI 1.09-1.46) again, despite remaining below the RI (Graphic 3). Since both electrolytes' re-evaluations were unsatisfactory, by the evening, 0.03 mL of calcitriol, drawn from a 0.25 µg capsule to a syringe, was added to Eric's dinner.

The next day, 27th of October, by midday iCa values were once again lower than previously (Graphic 3). Therefore, Eric was prescribed one 0.25 µg capsule of calcitriol PO SID for seven days.

On the 28th of October 2022 during the morning, despite remaining hypocalcemic (iCa of 0.75 mmol/L), the patient was discharged with instructions to follow the calcitriol protocol at home for the remaining days (Graphic 3).

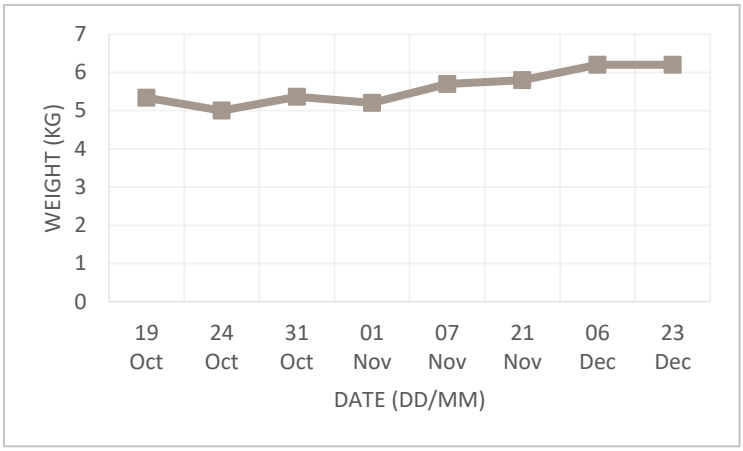
During the hospitalization period, regardless of low iCa levels, Eric was BAR, vocal, eating

very well all the food offered, even when the medication started to be added to it, and was passing urine and faeces normally, without ever showing clinical signs of hypocalcaemia. However, in the afternoon of 28th of October 2022, at home, Eric had a seizure, which led him to be re-hospitalised. According to the owners, since the single episode, Eric was normal and eating a lot. PE revealed a rectal temperature of 38.5ºC, a regular HR of 130 bpm and a respiratory rate (RR) of 65 breaths/min. In addition, Eric was able to strongly support his weight, but he was presenting some, albeit very fine, eyelid and ear twitching. Upon verification of iCa, which was 0.8 mmol/L (RI 1.09-1.46), 7 mL of 10% CaG were slowly administered intravenously to Eric. Then, 2.5 mL/kg (i.e., 12.5 mL) of CaG were diluted in a 100 mL bag of saline and continuously infused at a 12 mL/hr rate, over eight hours. Because Eric never lost his appetite, one 0.25 µg capsule of calcitriol PO BID and 15 g (i.e., 3 g/kg) PO BID of calcium gluconate powder (CaGP) was prescribed, until directed otherwise. By midnight iCa values had finally normalized within the RI (1.16 mmol/L; RI 1.09-1.46) (Graphic 3). During that night, until 3am of the following day, Eric continued to show signs of ear twitching while being awake. However, these were absent while he was sleeping. Otherwise, HR, RR, MM and temperature were all normal and he was eating voraciously. At 8am, Eric's iCa were still within the RI (1.03 mmol/L; RI 1.09-1.46), but by the evening they were already lower (0.98 mmol/L; RI 1.09-1.46). During that night no twitching was registered.

On the morning of the second day of re-hospitalization, 30th of October, Eric was once again hypocalcemic (0.85 mmol/L; RI 1.09-1.46). Therefore, a continuous infusion of 12.5 mL of CaG diluted in saline were administered one more time. With this, by 5pm iCa had gone up to 1.08 mmol/L. On that day, infection just cranial to the end of the surgical site was detected, that was initially treated with one dose of 0.23 mL (8.75 mg/kg) of amoxicillin and clavulanic acid administered subcutaneously and continued for six days with amoxicillin and clavulanic acid 1.5 50 mg tablets (12.5 mg/kg) PO BID.

Until Eric was discharged on the 1st of November, in the afternoon, iCa was measured every 12 hours. As illustrated in Graphic 3, he was only discharged after having two consequent iCa above 1 mmol/L. By then his weight had gone up to 5.2 kg. He went home with the same treatment protocol (i.e., with calcitriol, CaGP and amoxicillin and clavulanic acid).

On the 7th of November, Eric was presented to the practice for a recheck consult. According to the owners, he had been well, was kept indoors and had not shown any obvious signs of seizure. It was also reported that Eric's appetite was reduced and that he was not eating his food with the medication on it. Therefore, the calcitriol capsules were being forced with a pill popper, which he seemed to tolerate. Otherwise, he had finished the CaGP for two days. At presentation, the patient was BAR, chest auscultation revealed a regular HR (120 bpm) with no audible murmur and RR of 40 breaths/min. The infection was resolved. Moreover, since the last visited he had gained 500 g (Graphic 4). Upon re-evaluation of the iCa, which was normal (1.14 mmol/L; RI 1.09-1.46), the treatment protocol was changed to one capsule of calcitriol PO SID for seven days and calcium supplementation was not reinstituted (Graphic 3).



Graphic 4 *– Evolution of Eric's weight after thyroidectomy*

One week later, the highest value of iCa post-surgery was recorded, which was even above the RI. Hence, treatment with calcitriol was stopped.

On the 21st of November, hypocalcaemia was revealed on Eric's electrolytes (Graphic 3), which was consistent with the presence of ear twitching reported by the owners. Therefore, calcitriol was reinstituted, but with one capsule every other day, instead. Otherwise, Eric was doing great at home and had even gained more 100 g.

Eric revisited PVS after three weeks. Since the last consult, he was comfortable at home, perhaps a bit lazier, and was eating around two to four sachets a day. This time, iCa was measured using a different method. The result was within the RI (0.99 mmol/L; RI 0.9-1.3) (Graphic 3). Considering he had reached 6.2 kg in just two weeks (Graphic 4), owners were advised to restrict food down to two to three sachets daily.

Finally, after two months of constant monitoring, Eric's last visit to PVS happened on the 23rd of December 2022 (Graphic 3). By that time, he had been off calcitriol for the previous three weeks, his weight (6.2 kg) had stabilized and iCa was 0.96 mmol/L (RI 1.09 -1.46). Owners showed no concerns apart from the fact that Eric was showing signs of polydipsia. Because of that, they were to collect a urine sample for a urinalysis, but that never happened.

Once back to Portugal, the author was informed that Eric had never been rechecked since last seen in December and that he was doing well.

5. Discussion

Regarding that the diagnosis of FHT is achieved by the presence of at least one clinical sign typical of the disease and the laboratory confirmation of an elevated TT4 (Shiel & Mooney, 2007; Quimby *et al.*, 2021; Yu, Lacorcia & Johnstone, 2022), Eric's diagnosis was straightforward.

On one hand, Eric had more than one clinical sign of FHT classic presentation. As in more than 80% of hyperthyroid cats (McLean *et al.*, 2017), Eric was presented with weight loss. In fact, since the 3rd of December 2021 until he was diagnosed on the 14th of June 2022, he had lost 470 g (see Graphic 2). Moreover, he had clear signs of polyphagia and a palpable goiter was detected. The signs of stress and aggressiveness during the consult could also be a manifestation of the

disease (Peterson, 1984; Nelson & Couto, 2019), as well as the audible murmur. Otherwise, in contrast to most hyperthyroid cats, Eric was never tachycardic. No other classic signs of FHT (i.e., PU/PD, vomiting or diarrhoea) were reported, which is uncommon in these patients. However, the cat was mostly outdoors. Hence, such signs could have been missed. From the owners' report, apart from advanced age, no other factor was potentially related to the onset of the clinical signs.

On the other hand, TT4 was markedly elevated (see Table 32 – 14th of June). Therefore, evaluating fT4 would have add no value to the diagnosis, because it would have been most certainly elevated as well (Peterson, 2006; Shiel & Mooney, 2007; Nelson & Couto, 2019).

The biochemistry panel FeC (see Table 32 – 14th of June) also helped to exclude other potential DD. Despite ALT being elevated, this was interpreted as a consequence of the excess of thyroid hormone in circulation rather than due to liver disease, especially because no other liver parameters were increased and no signs of liver disease were detected. Elevated BUN was most probably a result of muscle catabolism associated with elevated TT4, as well. Blood glucose levels were unremarkable with the glucometer evaluation and the laboratory analysis, so DM was excluded. Although sCr was normal, CKD could not be completely excluded as an underlying disease, considering that FHT can mask CKD. However, CKD was not responsible for Eric's overall clinical presentation. With the immediate confirmation of FHT, EPI and IBD were considered less likely to be behind Eric's clinical presentation. Therefore, no further diagnosis was pursued regarding these DD.

On the second recheck Eric's SBP was assessed. Considering that cats with SBP between 160-179 mmHg are considered hypertensive (Brown & Roura, 2022), Eric's SBP (165 mmHg) was indicative of hypertension. Further ocular signs of hypertension were not investigated. Bearing in mind that 25-87% of hyperthyroid patients develop hypertension (Trepanier, 2007; Geddes & Aguiar, 2022) that tends to resolve after successful treatment for HT (Nelson & Couto, 2019) and that SBP was not higher than 180 mmHg (Nelson & Couto, 2019), no further antihypertensive therapy was added to the treatment protocol.

Despite being presented with all four treatment options, Eric's owners took the informed decision to start his therapy with medical management. This decision, was also influenced by the owners' experience with a previous cat.

Within the first week of treatment with Thyronorm® Oral Solution for Cats 2.5 mg PO BID, Eric developed GI signs (i.e., anorexia and vomiting) which led the owners to voluntarily stop treatment. Despite being expected with antithyroid medication (Trepanier, 2007; Ferguson, 2018; Fossum, 2019; Nelson & Couto, 2019; Bugbee *et al.*, 2023), this could have also been related to the initial non-conservative dosage protocol; possibly, if he had started with a dose of 1.25–2.5 mg PO SID or divided BID, those side effects would have been minimized (Bugbee *et al.*, 2023). Fortunately, those signs were transient. Therefore, administration of MMI did not have to be discontinued. For the following months, Eric's protocol was increased twice: first to 5 mg in the morning and 2.5 mg in the afternoon and then to 5 mg BID. Despite the increasing doses, TT4 never fell within the lower half of the RI, even on a dose of 10 mg/day, which could have been

indicative of the presence of an undiagnosed carcinoma (Nelson & Couto, 2019) or poor owner compliance (Carney *et al.*, 2016). However, none of the possibilities were addressed, because in the meantime it was decided that Eric would be submitted to a thyroidectomy.

Preoperative ultrasound examination of the mass or scintigraphy could have been helpful to characterized the morphology of the thyroid (Daniel & Neelis, 2014; Fossum, 2019; Nelson & Couto, 2019; Geddes & Aguiar, 2022; Yu, Lacorcia & Johnstone, 2022). However, regarding that both thyroid lobes were considered altered on PE, those would have represented an additional and unnecessary expense for Eric's owners. In turn, because on PE an audible murmur was also detected, performing an echocardiography would have been important to characterize cardiac disease and the risk it would have represented for the surgery. Moreover, considering, Eric's resistance to MMI, chest radiography could also have been useful to rule out metastasis of an undiagnosed carcinoma. To ensure Eric was relatively stable for surgery, only a blood test was performed (see Table 33 – 19th of October).

Although Eric was premedicated with ACP, which is contraindicated by (Fossum, 2019), both the surgery and the anaesthesia were uneventful. Postoperative complications, like Horner's syndrome and laryngeal paralysis, were not seen either. In turn, Eric developed hypocalcaemia. Fortunately, the surgeon was aware of the association between bilateral thyroidectomy and the development of postoperative hypocalcaemia and Eric was already hospitalized when that occurred.

Depending on the severity of the clinical signs, some patients with iCa below the RI may only need oral supplementation and others may not require treatment at all (Padgett, 2002; Carney *et al.*, 2016). However, when animals develop clinical signs of hypocalcaemia and iCa below 0.8 mmol/L, treatment is definitely required (Nelson & Couto, 2019). In an acute phase, hypocalcaemia is treated with a bolus of 10% CaG slowly given IV to effect and, once the clinical signs are controlled, with 10 mL of CaG diluted in saline administered as a continuous intravenous infusion every six hours or subcutaneously at multiple sites every eight hours (Fossum, 2019; Nelson & Couto, 2019). During this phase calcium levels should be evaluated every eight to twelve hours, so that the therapy can be adjusted accordingly (Nelson & Couto, 2019). Then, if the patient is eating and iCa is still above the RI, vitamin D supplementation orally should be added to the protocol (Fossum, 2019; Nelson & Couto, 2019). The goal of the treatment is to maintain iCa between 0.8 and 1 mmol/L. Therefore, it should be stopped once those values are reached (Nelson & Couto, 2019, 2019). Overall, this was the basis of Eric's treatment. However, there may be some discrepancies between this protocol and the one put in action that may have contributed for unstable iCa values during hospitalization.

During the first period of hospitalization (i.e., from 24/10 to 28/10 – Graphic 3), Eric never had to receive a bolus of 10% CaG IV, because he remained asymptomatic and stable. Instead, he received diluted CaG SQ three times and then started calcitriol. The treatment was started because iCa was below the laboratory RI (1.09-1.46 mmol/L). However, from the three first iCa evaluations, only the third one was actually below 0.8 mmol/L. Therefore, one could argue that

the first two postoperative administrations may have been two premature since before each, iCa was above that value. Regarding the first administration, since iCa measurement was very close to 0.8 mmol/L (i.e., 0.84 mmol/L), if Eric had been left untreated during the night, the value on the 25th October at 8am would most probably be lower than it was. So, overall, the first administration of CaG may have been justifiable, especially because of the increasing effect that it had on calcium. Regarding the second administration, since Eric was eating very well, the question is raised whether starting supplementing him with both calcium (0.5–1.0 g of calcium/cat/day [Fossum, 2019]) and vitamin D (initial dose of 0.02–0.03 μg/kg/d for two to four days [Fossum, 2019; Nelson & Couto, 2019]) orally, would have been enough to maintain iCa between 0.8 and 1 mmol/L. Instead, this was only attempted on the evening of 26th of October and only with calcitriol. Regardless of the speculations about the course of treatment, a regular monitoring of iCa values every eight hours could have been useful to detect earlier low calcium levels and allow treatment adjustments earlier. However, that was difficult to follow strictly (see Graphic 3), due to aspects regarding the work flow of the practice.

On the 28th of October, Eric went home, despite iCa being under 0.8 mmol/L (i.e., 0.75 mmol/L, see graphic 3), which was questionable. This discharge happened on the grounds that he had been asymptomatic for four days, would be receiving vitamin D supplementation at home and he would be kept indoors so that his owners could close monitor him. However, Eric then developed clinical signs of hypocalcaemia (i.e., seizure and twitching). One may question if Eric should have never left the hospital with such low value and potentially should have been treated with diluted CaG as before. On the other hand, this might have happened due to poor owner compliance.

Once he was readmitted, the best course of action was taken. Eric received CaG both as a bolus slowly given IV, because he presented with ear and eyelid twitching, and as a continuous infusion also IV. Since he was eating, oral supplementation of both calcitriol and CaGP was also immediately instituted. Ideally, after the acute phase of treatment, iCa should have been rechecked and only then, if necessary, Eric should have started the second phase. However, his iCa level was only rechecked once and before the infusion was even concluded. This can be explained by the fact that Eric arrived during the evening and CaG was going to be infused over eight hours. Therefore, by the time it ended (i.e., around 3.30 am) the nurse would be alone and taking bloods from Eric would have been difficult without help. Fortunately, this protocol stabilized iCa within the RI. Actually, during that period of hospitalization, with Eric on calcitriol and CaGP BID, the level of iCa followed an upward trend and intravenous CaG was only administered once. This time, Eric was only allowed to go home after two consecutive iCa equal or above 1 mmol/L. From there, Eric was first seen every week until the end of November and then every two weeks until the end of the year. During this period, one may argue that as soon iCa stabilized between 0.8 and 1 mmol/L, oral medication should have been gradually tapered down until Eric no longer needed supplementation (Nelson & Couto, 2019), instead of being abruptly ended, to avoid relapses, like the one on the 21st of November.

Regarding hypocalcaemia, Eric's prognosis was excellent, considering that it proved to be

transient and the patient did not require long-term supplementation. Hence, at least one of the parathyroids seem to have been preserved. From there, in case of recurrence, iCa should be rechecked every three to four months (Nelson & Couto, 2019). However, calcium was last evaluated on the 23rd of December 2022.

Overall, Eric's prognosis in relation to the treatment of HT is good, considering that the clinical signs of weight loss, polyphagia, audible heart murmur and nervousness resolved after the thyroidectomy. At least short-term the surgery seemed to be successful. However, TT4 levels were never reassessed during the postoperative period. Ideally, TT4 should have been evaluated within four to six months postoperatively (Geddes & Aguiar, 2022; Nelson & Couto, 2019). Nonetheless, because in patients that undergo bilateral thyroidectomy, HT is less likely to persist and considering hospitalization costs due to hypocalcaemia, that was not performed. In turn, TT4 evaluation could have been useful to rule out hypothyroidism when on the 7th of November, Eric was reported to be more lethargic and with poor appetite, despite weight gain (i.e., signs of hypothyroidism [Peterson, 2006; Yu, Lacorcia & Johnstone, 2022]).

Likewise, kidney parameters should have been assessed monthly during the first months after surgery (Ferguson, 2018; Nelson & Couto, 2019), in order to exclude the unmasking of CDK. However, this did not happen. Moreover, liver parameters and SBP should have been re-evaluated after surgery to make sure they normalized and no further investigation for liver and cardiac disease was necessary.

To assess about long-term effectiveness of HT treatment, Eric should at least be evaluated every six months (Vaske, Schermerhorn & Grauer, 2016; Nelson & Couto, 2019; Geddes & Aguiar, 2022). However, by the end of August 2023 (i.e., 10 months after the surgery) Eric had not revisited the practice for a re-evaluation, since his last visit on the 23rd of December 2022. Besides, it would have been beneficial to send the removed thyroid for histopathology to rule out thyroid carcinoma (Padgett, 2002; Nelson & Couto, 2019) and better determine Eric's prognosis, but that involved additional costs that his owners could not afford.

V. Conclusion

The six-month traineeship at PVS, was without a doubt, one of the most fulfilling experiences of the author's life, both personally and professionally. Personally, because the author was able to successfully complete what she set out to do, overcame the obstacles of going abroad for six months and was always very loved by the team who received her. Professionally, because by being constantly immersed in the hospital environment for such a long period, the author was able to deepen the theorical knowledge acquired during university, to improve her clinical reasoning and also to develop surgical skills.

Writing this report about FHT was also important for the author, who became more aware of the disease's incidence, particularly in senior cats. Moreover, it allowed her to better understand the diagnostic process that should be followed, especially in non-straightforward cases. Learning about the treatment options available, their pros and cons and which patients are more suitable

for which treatment, was also an advantage of choosing this theme. At least, regarding FHT, the author will be able to advise the owners and treat the patients in a more informed and confident way.

To conclude, the curricular traineeship in the context of the Master's degree in Veterinary Medicine from the University of Évora, is crucial for the development of the students into professional and competent veterinarians.

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