COMMENTARY

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Perspectives on the diagnosis of feline hyperthyroidism

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Nature and distrubtion

First reported in 1979(1), feline hyperthyroidism is a multisystemic disease resulting from excessive triiodothyronine (T3) and thyroxine (T4) secretion, most common in middle-aged to older cats (2). Prior to the first description of feline hyperthyroidism, feline thyroid adenomas were recognized at necropsy (3–5), but most adenomas did not result in thyroid gland enlargement and signs of hyperthyroidism. However, when these cases were reviewed retrospectively (6), clinical signs of hyperthydoidism may have been present but were not recognized (3,5). The frequency of diagnosis of feline hyperthyroidism has been suggested to be one in 300 cats (7). A report of incident cases in cats seven years and older using data from the Veterinary Medical Data Program suggested that the frequency of diagnosis of feline hyperthyroidism increased between 1979 and 1985 (6). Age-specific proportional hospital accession ratios varied widely amongst participating institutions, ranging from 5.7 to 141.3 per 1,000 accessions in 1985 and 1986 (6). It is felt that over time there has been a real increase in the incidence of this disease, not simply an increase due to diagnosticians' heightened awareness of hyperthyroidism (6,7).

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To investigate the frequency of hyperthyroxinemic and potentially hyperthyroid cats in Southern Ontario, we retrospectively studied test results from feline sera submitted to a radioimmunoassay service at the University of Guelph over the past five years. These included sera submitted through the Ontario Ministry of Agriculture and Food, the University of Guelph Veterinary Teaching Hospital, and private laboratories (Table 1). A radioimmunoassay (Tetra-Tab, Organon, Durham, N.C.) was used for all samples. This assay measures the antibody-bound radiolabelled T4 which has been separated from the unbound T4 by precipitation with ammonium sulfate. Hypothetically, if thyroxine autoantibody were present in the patient's serum, then the patient's serum thyroxine concentration would be falsely decreased when using this assay. The adult feline reference interval of 10 - 65 nmol/L, representing the minimum and maximum values, was determined from 40 clinically healthy cats subjected to physical, hematologic, and biochemical examinations. The number of feline serum T4 submissions increased then levelled out in 1988. A frequency distribution of these data (Figure 1) showed a very

TABLE 1
Feline serum T_4 accessions at the University of Guelph

Year	Feline Accessions for Serum T_4	Number (Percentage) of Cats with Serum T_4 > 65 nmol/L
1984	109	20 (18)
1985	119	24 (20)
1986	218	33 (15)
1987	431	78 (18)
1988	425	89 (21)

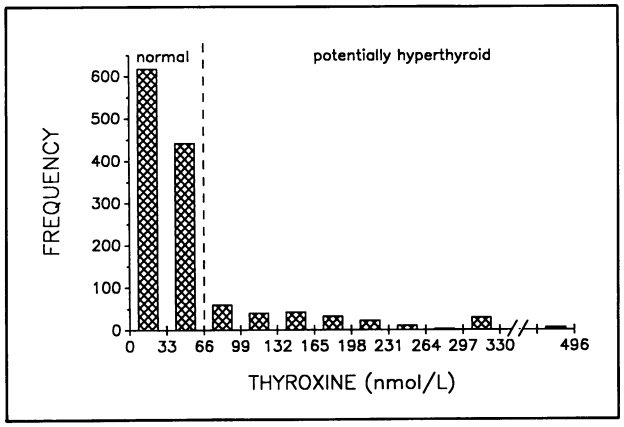

Figure 1. Frequency of feline serum T_4 concentrations determined at the clinical pathology laboratory at the University of Guelph. The histogram represents 1,302 data points. The reference interval is 10 to 65 nmol/L.

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broad range of abnormal test results (66 to over 400 nmol/L). The increase in the numbers of accessions is probably a result of practitioners' increased awareness of the disease, but the percentage of those sera with T4 concentrations greater than our upper reference limit remained about the same, that is about 20%. Therefore, the prevalence of potentially hyperthyroid cats has remained fairly constant among cats suspected of being hyperthyroid.

Feline hyperthyroidism is most commonly due to multinodular adenomatous hyperplasia associated with multiple, or less frequently single, hyperfunctioning thyroidal adenomas (2). In man, Graves' disease is the most common form of hyperthyroidism (2,8). It is an autoimmune disease in which circulating anti-TSH receptor antibodies, termed thyroid-stimulating immunoglobulins (TSIs), stimulate thyroid hormone secretion resulting in diffuse thyroid hyperplasia (9). A similar pathogenesis is not suspected in hyperthyroid cats since TSIs are undetectable (9,10). Toxic multinodular goiter and thyroid adenoma of people more closely resemble the feline disease (7,11). Hyperthyroid cats, and humans with thyroid disease, sometimes have increased serum concentrations of thyroid growth stimulating immunoglobulins (TGIs) which stimulate thyroid growth but do not cause increased thyroid hormone secretion (7). The role of TGIs in feline hyperthyroidism is unknown (7). Thyroid microsomal and nuclear autoantibodies were found in 34% and 14% of 29 hyperthyroid cats, respectively (10). The role of these autoantibodies in the development of hyperthyroidism remains to be determined. In dogs, hyperthyroidism appears to be associated almost exclusively with thyroid carcinoma, whereas thyroid carcinoma occurs in only 1 - 2% of hyperthyroid cats (12).

Environmental exposure to some chemical(s), genetic predisposition, and perhaps infectious agents may all play a role in the development of feline hyperthyroidism

The increase in the frequency of diagnosis of feline hyperthyroidism has stimulated study of risk factors and potential etiologies. Significant associations with feline hyperthyroidism have been found for regular treatment with flea sprays or powders, strict or predominant indoor confinement, feeding of canned foods, and exposure to herbicides, fertilizers, or pesticides (6). Non-Siamese cats were almost 10 times more likely to be affected than Siamese cats (6). There was a significantly greater risk for the development of hyperthyroidism among cats in multiple cat households in which hyperthyroidism had been previously diagnosed (6). A sex predisposition has not been reported (2). These data suggest that environmental exposure to some chemical(s), genetic predisposition, and perhaps infectious agents may all play a role in the development of feline hyperthyroidism.

Clinical signs and diagnostic tests

Triiodothyronine and thyroxine affect all body tissues through their regulatory effects on energy, carbohydrate, protein and lipid metabolism. The signs of hyperthyroidism reflect the systemic response to the inappropriate and excessive amounts of circulating thyroid hormones. Clinically, progressive weight loss, accompanied by polyphagia, hyperexcitability, nervousness, polydipsia, polyuria, and polypnea are noted (2,11-13). Occasional vomiting, with increased frequency and volume of stools, steatorrhea and soft stools may be present (2,11-13). Cardiovascular abnormalities such as tachycardia, systolic murmurs, gallop rhythms, arrhythmias and intensified arterial pulses are common in hyperthyroid cats (2,11,12). The haircoat is often unkempt, matted and greasy (2,7,11,12). Enlargement of the thyroid gland(s) is palpable in 85 to 90% of hyperthyroid cats (14). Of these enlargements, 70% are bilateral and 30% are unilateral (15). One report suggested that 10% of hyperthyroid cats have an apathetic or masked form of the disease, with signs of depression, weakness, weight loss, anorexia, and cardiac abnormalities (14).

Laboratory findings vary depending on the duration of the disease, concomitant unrelated illnesses, and the ability of the various body systems to respond to the increased thyroid hormone concentrations (2). The packed cell volume, hemoglobin, and erythrocyte count are increased in 15-20% of hyperthyroid cats (14). These changes are considered to be a direct effect of thyroid hormones on erythroid marrow through beta-adrenergic stimulation, as well as increased production of erythropoietin (2,14). Macrocytosis is found in up to 50% of hyperthyroid cats and is believed to result from an increased rate of red cell differentiation and a shortened maturation time (2). Mild anemia is found in a small number of hyperthyroid cats, possibly reflecting an uncharacterized nutritional deficiency (12) or concurrent renal disease. Leukocytosis, with mature neutrophilia, lymphopenia, and eosinopenia, is consistent with the stress of the thyrotoxicosis (2). Increases in serum activities of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and lactate dehydrogenase are found in 50 to 75% of hyperthyroid cats (12). The pathogenesis of the increased serum enzyme activities is uncertain, but may be due to a combination of direct hepatotoxicity caused by the excessive thyroid hormones, hepatic hypoxia, heart failure, infections and accelerated bone turnover (2,11). Increased serum phosphorus concentration was reported in 20% of hyperthyroid cats. The increase may be related to enhanced bone resorption and lower parathormone secretion, as well as muscle catabolism caused by excessive T3 and T4 (2).

Basal serum T3 and T4 concentrations are increased in most hyperthyroid cats (12). In one study of 131 cats diagnosed as hyperthyroid based on clinical signs, all of the serum T4 concentrations were greater than the upper reference limit, while T3 was increased in 97% (2). The serum T4 concentration is considered by some to be the most reliable laboratory determination in confirming a diagnosis of feline hyperthyroidism (2,11). Serum T3 concentrations may be within the

reference limits in a few mildly affected cats, and although the mechanism is unclear, it is likely that T3 concentrations increase over time as the disease progresses (12,16).

Most of the information on the clinical signs and laboratory abnormalities of feline hyperthyroidism had been determined from a limited number of sources, mainly case series of cats determined to have hyperthyroidism based on clinical signs with or without determinations of serum hormone concentrations. Therefore, the percentage of hyperthyroid cats with any particular abnormality do not necessarily reflect the true sensitivity of that abnormality for identifying hyperthyroidism. As well, the specific and predictive value are unknown. Sensitivity, specificity and predictive value of a clinical sign or test result can only be accurately determined by comparison with a "gold standard" which reflects the "true state of nature" with respect to a disease. Histologic examination of a thyroid biopsy may serve as the "gold standard" for feline hyperthyroidism, but may not be practicable. If hormonal analysis is used as the "gold standard", then one makes the assumptions that all unaffected cats have serum hormone concentrations within normal limits and all affected cats have increased hormone concentrations. Intuitively, we know that these assumptions are, in all likelihood, not correct in all instances.

Hormonal analysis is widely used because there are good theoretic and physiologic bases, it is non-invasive, practical, and of reasonable cost. Since various hormonal tests are most commonly used to support a diagnosis of feline hyperthyroidism these are reviewed. *Radioimmunoassay* (RIA) is now commonly used for measuring serum T3 and T4 concentrations. The principle of the assay is the competitive binding of specific antibody with radioactively labeled T3 and T4 and the unlabeled hormone in the patient's serum. In the serum T4 essay, inactivation of thyroxine binding protein releases the patient's serum T4 which allows interaction with a constant amount of labeled T4 and a specific anti-T4 antibody. Following an incubation period, the antibody-bound and unbound T4 portions are separated using chemical, physical or immunological methods. The radioactivity in the bound or the unbound portion is counted. A reference curve, prepared using standards containing known amounts of hormone, is used to estimate the patient's serum hormone concentration.

The *competitive protein binding assay* was used to determine T4 concentration prior to the availability of RIA techniques. It relied on similar principles using naturally occurring plasma proteins rather than specific antibodies, but was more complex and time-consuming (17). Other assays formerly used include protein-bound iodine, T4 iodine by column chromatography, and butanol extractable iodine (17). These assays are of historical interest only.

Other techniques for evaluation of thyroid gland function have been reported. In the *thyroid stimulating hormone* (TSH) *response test*, normal cats show an increase of at least two times the resting value four to six hours after the intravenous administration of TSH using a dosage of 1.0 U/kg. Most hyperthyroid cats show little or no increase in serum T4 concentration when TSH is administered (7,11). A *T3 suppression test* is done by measuring the resting serum T4 concentration and giving T3 at a dosage of 35 ug every eight hours for two days. On the third day one more dose of T3 is given and four hours later a blood sample is taken for determination of the serum T4 concentration. In normal cats there is a decrease of at least 50% with the resultant serum T4 concentration usually below 20 nmol/L, while in hyperthyroid cats there is little or no decrease (7). The TSH response and T3 suppression tests may be used when the clinical signs are consistent with hyperthyroidism, but the serum T4 concentration is either at the upper end of normal or only slightly increased. The T3 suppression test is preferred (7). In one study, cats with hyperthyroidism had serum free T4 concentrations of 40–300 pmol/L while normal cats had 10–20 pmol/L, suggesting some usefulness for the measurement of the free hormone (19). Radioiodine uptake is relatively insensitive and may be normal or even low depending on dietary iodine and treatment with iodine-containing drugs or radiographic contrast material (7). Thyroid scanning with either radioiodine or sodium pertechnetate has been described in the cat. The latter isotope is preferred (2,7,11,12). Thyroid scanning may show no difference in the thyroid profile between affected and normal cats, but may demonstrate the extent of thyroid gland involvement, including ectopic or malignant thyroidal tissue in the chest (7). Lack of reference limits, undetermined sensitivity and specificity, cost, and technical requirements may preclude the use of these tests in many situations. Because of their complexity, these tests are generally only available at research facilities and institutional practices.

Use of laboratory tests

An essential factor in confirming a diagnosis is the critical evaluation and selection of patients to be tested. Some veterinarians feel that all mature cats should be tested for hyperthyroidism despite the absence of signs — in effect using serum thyroxine determinations as a screening test. There are a number of factors that must be considered when using a test for screening purposes. These include the cost of testing all patients rather than selecting animals based on history and clinical findings; the prevalence of the disease in the population and the effect of this prevalence on the predictive value of the test; and the potential for false positive and false negative test results.

The cost of screening all cats for hyperthyroidism will depend on the assay used and the overall frequency of sample submissions within a practice. Screening all cats would be expensive and it could be argued that, in the absence of clinical signs, there is no reason to determine the absence of clinical signs, there is no reason to determine the serum T4 concentration. However, screening all cats would provide information on the prevalence of hyperthyroidism, and the associations between increased T4 concentrations and clinical signs could be assessed. The costs should be considered relative to the benefit of detecting additional cases that may have been missed when patients were selected for testing based on clinical findings.

If cats of all ages were tested rather than those selected on the basis of history and clinical findings, the prevalence of hyperthyroidism would be much lower. Assuming that the sensitivity and specificity remain unchanged, and that the specificity is less than 100%, the predictive value (i.e. the proportion of animals with the disease among those that test positive) of an increased serum T4 concentration would decrease. Under these circumstances, a higher proportion of animals subjected to further diagnostic tests would be false positives.

The frequency and causes for false positive and negative results should be considered. For the T4 assay, falsely increased concentrations may be caused by T4 autoantibodies, depending on type of radioimmunoassay used. These antibodies have been identified in people and dogs (18). Recently, thyroid autoantibodies have been demonstrated in almost 50% of cats under investigation for hyperthyroidism (10). The signifigance of these autoantibodies on the test systems for the detection of feline hyperthyroidism requires further study. Reference intervals, when determined using sufficient numbers, represent the range of test results for 95% of the normal population. Therefore 2.5% of normal cats can be expected to have serum T4 concentrations above the reference interval. Of particular concern with feline hyperthyroidism is the fact that most affected cats are middle to old-age while the reference interval has been determined using young adults. It is possible that the upper reference limit is inappropriately low for the cats at risk for the development of hyperthyroidism. False negative results are possible also in cats with early hyperthyroidism where T4 concentrations may be below the upper reference interval because of hormone fluctuations (16). These fluctuations have been investigated on an hourly and daily basis. The day-to-day fluctuations were found to be significantly greater than within-day variation (16,20). The reasons for this variability are unknown. When the clinical signs are suggestive of early hyperthyroidism, but the serum T4 concentration is not increased, confirmation may require several T4 determinations on separate days; waiting for 2–8 weeks to allow for progression of the disease and then repeating the serum T4 determinations (11); or using the TSH response and T3 suppression tests (7,11). It is known in other animals and people that extrathyroidal illnesses and certain drugs generally decrease serum T4 concentrations. It is postulated that this is true for the cat, and this could be another reason for a serum T4 concentration to be within the reference interval in a hyperthyroid cat (7). It has been suggested that if the serum T4 concentration is felt to be inaccurate due to laboratory error then it is best to repeat the determination of the serum T4 concentration either immediately on the same serum sample, or less preferably on a second serum sample. It should be kept in mind that retesting increases the likelihood of obtaining an abnormal test result in a normal animal or vice versa.

Conclusions

We question the concept of using serum T4 determinations as a screening test in all sick cats or all middle-age and older cats. Treating simply on the basis of an increased serum T4 concentration increases the potential for therapeutic mismanagement based on abnormal test results caused by physiological changes or laboratory error. It is not an easy decision to treat for hyperthyroidism since all treatments for hyperthyroidism can result in serious side-effects or toxic complications which may be lifelong. Laboratory data should be used to support a clinical impression and not vice versa. Given the current understanding of the disease, clinical signs of hyperthyroidism are quite sensitive (possibly greater than 90%) and apparently very specific. A combined test (that is, two tests applied in series so that only cats with both clinical signs of hyperthyroidism *and* increased serum T4 concentration are considered to have the disease) will have a very high predictive value of a positive test, and very few false positive diagnoses. When the two tests are used in series, there will be less chance for instituting inappropriate therapy, although fewer cats will be diagnosed as hyperthyroid.

The veterinarian should treat only those hyperthyroxinemic cats with history, clinical signs, and laboratory data supporting a diagnosis of hyperthyroidism

The veterinarian should treat only those hyperthyroxinemic cats with history, clinical signs, and laboratory data supporting a diagnosis of hyperthyroidism. Therapy based on a single serum T4 concentration above the reference interval without other supportive evidence is inappropriate. Asymptomatic, hyperthyroxinemic cats or hyperthyroxinemic cats with nonspecific or atypical signs, and symptomatic euthyroid cats should be investigated further before treatment is begun. Further diagnostic steps should include, in the following order, a repeat determination of serum T4 concentration, clinical and hormonal re-evaluation in several weeks or a month, a thorough search aimed at eliminating other etiologies possibly accounting for any atypical clinical signs, and then possible referral to an appropriate institutional or speciality veterinary practice where the hormonal status can be more fully examined. In contrast, middle-aged and old cats with severe extra-thyroidal disease (renal failure, diabetes mellitus, hepatic disease) and signs compatible with hyperthyroidism, but with serum T4 concentrations in the euthyroid range, should initially be treated for the extra-thyroidal illness. In truly hyperthyroid cats, the serum T4 concentration will increase beyond the upper reference limit once the extra-thyroidal illness is controlled (7).

Feline hyperthyroidism is a common disease; however, potential problems with the serum T4 concentration reference interval and the sensitivity and specificity of the serum T4 concentration for feline hyperthyroidism need to be resolved so that hyperthyroid cats are correctly identified and appropriate

patient care given. The recent study on risk factor assessment in felne hyperthyroidism (6) has suggested several areas in which work needs to be expanded and will hopefully lead to the discovery of the etiologies, pathogenesis, and ultimately preventive strategies.

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