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## EFFECT OF DIET ON DEVELOPMENT OF FELINE HYPERTHYROIDISM

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### INTRODUCTION

Hyperthyroidism was first reported in cats in 1979, and has since become the most common endocrinopathy in cats. The pathogenesis of feline hyperthyroidism is still a mystery even though the morphology of affected thyroid glands has been well characterized. Many different factors may play a role in the pathogenesis of feline hyperthyroidism, including heredity, genetics, environment, and diet. These different factors may influence thyroid hormone production at any step in thyroid gland metabolism.

### REVIEW OF THYROID HORMONE SYNTHESIS

Thyroid hormone synthesis involves a number of coordinated steps.<sup>1</sup> First, the thyroid gland actively traps most of the ingested dietary iodine, and approximately 90% of the iodine found in the body is concentrated within the thyroid glands. Next, tyrosyl residues of thyroglobulin are iodinated forming monoiodotyrosine and diiodotyrosine within thyroglobulin. These monoiodotyrosines and diiodotyrosines are coupled to form triiodothyronine (T3) and thyroxine (T4). Proteolysis of thyroglobulins releases free iodotyrosines and iodothyronines, with secretion of iodothyronines into the blood. Deiodination of iodotyrosines occurs within the thyroid gland so that the liberated iodide can be reused. Finally there is deiodination of T4 to produce the biologically active hormone T3.

### DEVELOPMENT OF THYROID NODULES

Feline hyperthyroidism has a strong pathologic resemblance to toxic nodular goiter in humans. Toxic nodular goiter is characterized by thyroid cells that grow and produce T4 and T3 autonomously in the absence of thyroid stimulating hormone (TSH). A toxic nodular goiter evolves gradually, starting with a small hyperfunctioning adenoma. Since the adenoma is small and only slightly more active than the surrounding thyroid gland, it contributes little to thyroid hormone secretion. As the adenoma grows more hormones are released, TSH secretion decreases, resulting in decreased secretion by the remaining normal thyroid tissue. With further growth, thyroid secretion becomes supernormal, TSH concentration remains low, and the adenoma displays autonomous function (toxic nodular goiter or thyrotoxicosis). The progression of a small adenoma to toxic nodular goiter is a slow process in humans. A study in Germany has shown that nearly 50% of deceased cats exhibited nodular adenomas in their thyroid glands in the absence of hyperthyroidism.<sup>2</sup> Thus it is likely that adenomas are present long before the development of hyperthyroidism, suggesting a slow progression of a nontoxic goiter to toxic nodular goiter in cats as has been observed in humans.

### POTENTIAL ENVIRONMENTAL/NUTRITIONAL CAUSES OF FELINE HYPERTHYROIDISM

There have been several studies that have tried to identify environmental or nutritional links to the incidence of feline hyperthyroidism. In a study of 56 cats with hyperthyroidism, the development of hyperthyroidism was significantly

associated with exposure to flea powders and sprays, fertilizers, herbicides, an indoor lifestyle, and the consumption of canned cat food.<sup>3</sup> In a subsequent study of 379 hyperthyroid cats and 351 control cats, cats consuming predominantly canned cat foods were at twice the risk for developing hyperthyroidism.<sup>4</sup> The use of cat litter and topical parasite preparations was also associated with an increased risk of hyperthyroidism. Several breeds of cats (Siamese and Himalayan) showed a decrease risk of hyperthyroidism in this study, suggesting a potential genetic role in hyperthyroidism. The regular use of beef or poultry as a dietary supplement was also associated with a decreased risk for hyperthyroidism. Factors not associated with hyperthyroidism included exposure to smoke, sex or neutering status, number of cats in the household, frequency of vaccination, other dietary supplements (hairball products, urinary acidifiers, etc.), brand of cat litter, fertilizer, environmental insecticides, or dry cat food consumption. In a study of 100 hyperthyroid and 163 nonhyperthyroid cats, cats that had a preference for fish or liver and giblets flavors of canned cat foods had a significantly increased risk of hyperthyroidism.<sup>5</sup> All these studies have shown a link between canned cat food and the development of hyperthyroidism, but what hyperthyroid-causing factors that may be present in canned cat foods remains to be determined. A few possibilities include iodine content, or other ingredients/chemicals that may act as goitrogens.

### IODINE

A deficiency of iodine has been recognized as a cause of nodular goiter in humans.<sup>1</sup> In iodine-deficient areas of Europe, the frequency of toxic adenoma was inversely related to iodine intake, and the incidence decreased by 73% after the iodine content of salt was increased.

Iodine deficiency may result in thyroid hyperplasia in the cat.<sup>6</sup> However, there are no detailed studies in cats to suggest what daily iodine intake is consistent with normal thyroid function. Fecal iodine excretion is independent of iodine intake, but urinary excretion is significantly correlated to iodine intake. It appears that an intake of 20 µg iodine/kg BW/day may be sufficient for iodine balance. Using this quantity of iodine as a minimum daily requirement for iodine, a diet must supply approximately 38 µg iodine/100 kcal metabolizable energy (ME). Unfortunately the bioavailability of iodine in cat foods is unknown.

Prior to the fall of 2003, the National Research Council (NRC) iodine requirement for cats was 350 µg/kg diet on a dry matter basis. This level of iodine in the diet only supplies approximately 7.0 µg iodine/100 kcal, which is considerably less than the 38 µg iodine/100 kcal ME needed to meet endogenous losses.

Cat foods can vary considerably in iodine content. Of 13 cat foods, 4 did not meet calculated endogenous iodine losses even though all diets did meet the NRC requirement for iodine.<sup>7</sup> All of these diets met then current NRC requirements for iodine, but 4 did not meet calculated endogenous iodine losses. In a study of 19 dry and 19 wet cat foods in France, only 50% of foods met endogenous iodine losses. A study of 28 commercial cat foods (23 canned, 5 dry) in New Zealand also showed a wide variation in iodine content.<sup>8</sup> Only 2 canned foods and none of the dry foods had an iodine concentration greater than endogenous iodine loss; however, iodine content was higher overall in the dry foods. In Germany, 92 commercial cat foods

were analyzed (74 canned, 18 dry) for iodine content.<sup>2</sup> Again, the widest variation was seen in canned cat foods, with only 47% of the foods meeting endogenous iodine loss. Thus there is evidence that many cat foods may not contain sufficient iodine to meet daily endogenous losses.

Thyroid hormones in the cat acutely change in response to differing iodine content in the diet.<sup>9</sup> Cats do appear to adapt to varying iodine concentrations to maintain fairly constant thyroid hormone concentrations. When cats were fed varying iodine content diets for 5 months, there was no significant differences in free T4 levels.<sup>10</sup> Abrupt changes in iodine intake can result in hyperthyroidism in iodine-deficient humans, and variability in iodine intake may result in iodine-induced hyperthyroidism (Jodbasedow syndrome). Hyperthyroidism may potentially develop in the cat due to continually switching between diets that are high or low in iodine content which overwhelms adaptive mechanisms in the cat.

In the fall of 2003, the NRC iodine requirement was increased to 550 µg iodine/1000 kcal ME for adult cats. This requirement exceeds the 380 µg/1000 kcal ME minimum iodine content required to meet endogenous iodine loss, and these levels are considerably higher than the previous requirement of 350 µg iodine/kg diet. Iodine-induced hyperthyroidism has been reported in all iodine-supplementing programs, and is due to the sudden introduction of iodized salt in populations that have had a chronic iodine deficiency. Iodine-induced hyperthyroidism appears to be a transient problem in humans. In Switzerland, the incidence of hyperthyroidism increased 27% in iodine-deficient humans in the first year after increasing iodine intake. However, after a second year, the incidence of hyperthyroidism decreased. If many cats are currently iodine deficient, it will be interesting to observe whether a transient increase in the incidence of hyperthyroidism occurs as a result of increased dietary iodine as has been seen in human supplementation programs.

### IODOLACTONES

Iodolactones are metabolites of arachidonic acid and docosahexaenoic acid (DHA) and are present in the thyroid glands.<sup>1</sup> These compounds help inhibit thyroid cell proliferation, and can prevent goiter formation. Goitrogenesis may be related to a relative iodolactone deficiency, which may be important in the cat since arachidonic acid is an essential fatty acid in the cat. Variation in fatty acid ingestion may influence the iodolactones synthesized within the thyroid gland. The utilization of iodolactones or certain dietary fatty acids in the prevention or treatment of hyperthyroidism may be an area for future investigation.

### SELENIUM

Selenium is present in high concentration in normal thyroid glands. Selenium is important in enzymatic reactions, including those responsible for detoxification of toxic derivatives of oxygen and in the conversion of T4 to T3. Selenium deficiency may be important if iodine deficiency is also present. If less T4 is converted to T3 resulting in an increase in TSH, increased production of toxic derivatives of oxygen (H<sub>2</sub>O<sub>2</sub>) occurs within thyroid cells. The H<sub>2</sub>O<sub>2</sub> accumulates due to decreased detoxification causing thyroid cell destruction. There is no evidence in the cat that an excess of selenium is toxic.

### OTHER POTENTIAL GOITROGENS

A number of environmental agents may affect thyroid gland function. Environmental goitrogens are agents that cause thyroid enlargement, and may act directly on thyroid cells or may interfere with steps in thyroid hormone synthesis. Natural goitrogens in foods were first discovered in cabbage, but have also been identified in cassava, bamboo shoots, turnips, sweet potatoes, lima beans, onions, garlic, millet, sorghum, and soybeans.<sup>11</sup> Goitrogenic compounds may be metabolized by hepatic glucuronidation which is a limiting pathway in cats. This slow degradation of goitrogens may contribute to the development of hyperthyroidism. Protein calorie malnutrition enhances the effects of goitrogens, and thus overall nutrition may also be important in the development of hyperthyroidism.

Soy is used as a source of vegetable protein in a number of cat foods. Soy contains isoflavones (including daidzein, genistein, and glycitein) which are polyphenolic compounds with estrogenic properties. In a recent study, cats fed a soy-containing diet exhibited significantly higher concentrations of T4 and free T4.<sup>12</sup> The clinical implications of this study in the development of feline hyperthyroidism remains unclear.

Recently an association has been noted between the development of hyperthyroidism and the consumption of canned cat food from pop-top cans, suggesting that chemicals present in the can linings are responsible for hyperthyroidism.<sup>13</sup> However, there are many different types of can linings, and chemicals that could have potentially leached into the food from linings were not measured. In addition this study noted an increased risk of hyperthyroidism in those cats that consumed baby foods, which makes a goitrogen present in an ingredient source a more likely candidate. The association with can linings also does not explain the percentage of cats developing hyperthyroidism that do not consume canned cat foods.

An important potential source of goitrogens is water, and goitrogens have been observed in well water, chemically-treated water, and ground water in certain geographical areas. Canned cat foods contain greater than 75% water, and contaminants within that water source may be goitrogenic. Dry cat foods contain a much lower percentage of water in the finished product (typically around 10%), but a considerable amount of steam is used during extrusion which may concentrate goitrogenic contaminants.

### CONCLUSION

Many factors are most likely involved in the pathogenesis of feline hyperthyroidism. Consumption of canned cat food appears to be associated with development, and future studies should focus not only on ingredients, but also on the unique metabolic characteristics of the cat that allow hyperthyroidism to develop.

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