

# CANINE HYPOTHYROIDISM



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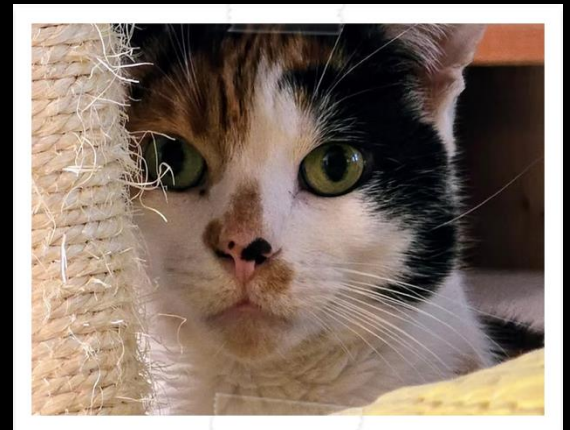
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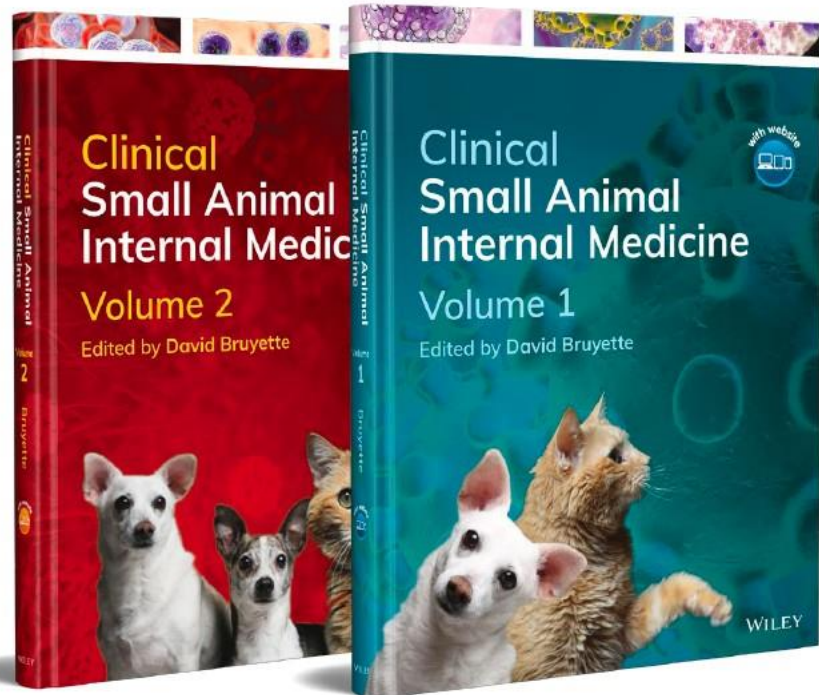
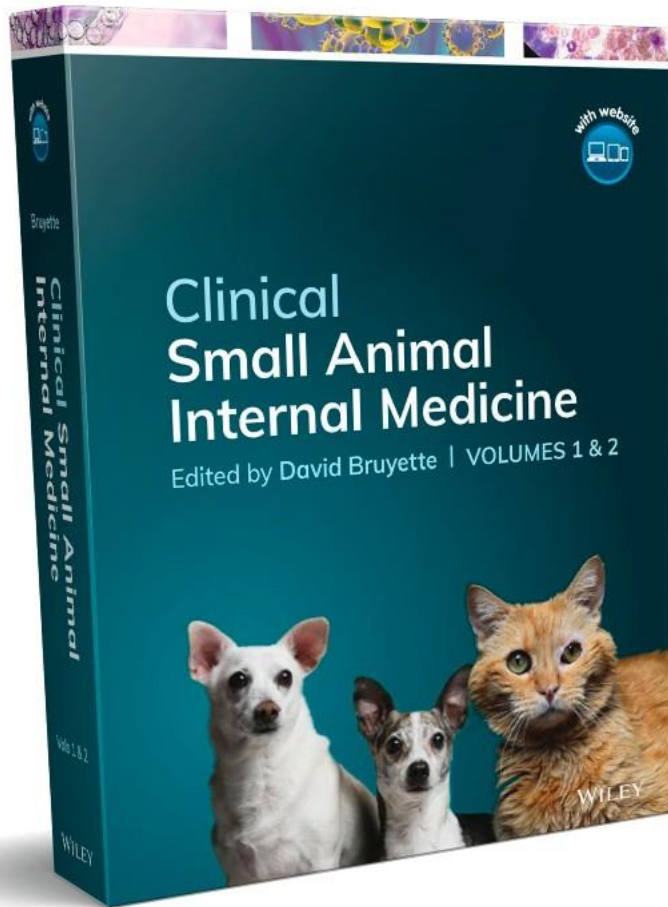
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# *Canine Hypothyroidism*

Incidence: Overly Diagnosed

Diagnosis: TT4 + fT4ED

Treatment: Once daily; 0.1 mg/10 #

Monitoring: Clinical signs; fT4ED

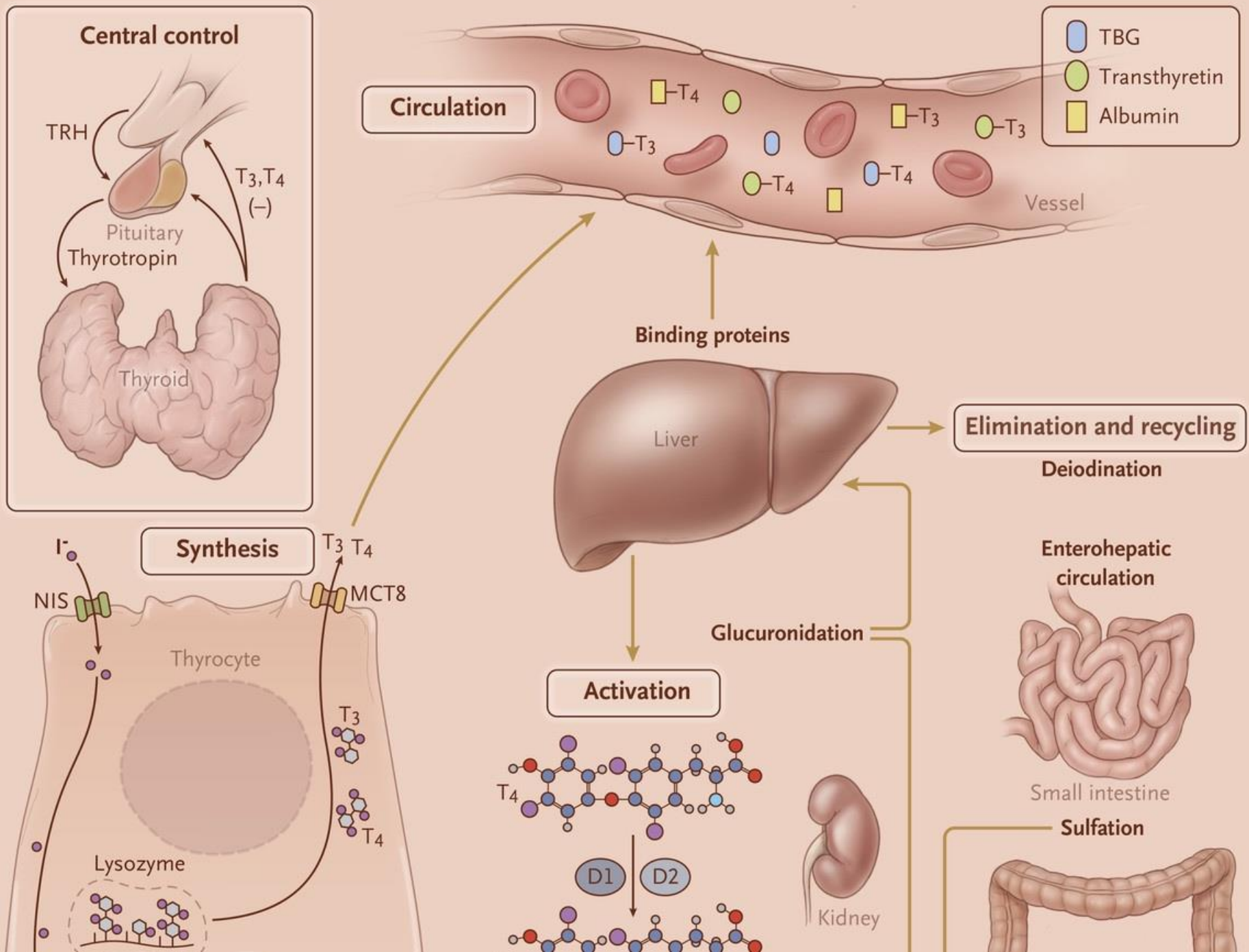
# CANINE HYPOTHYROIDISM

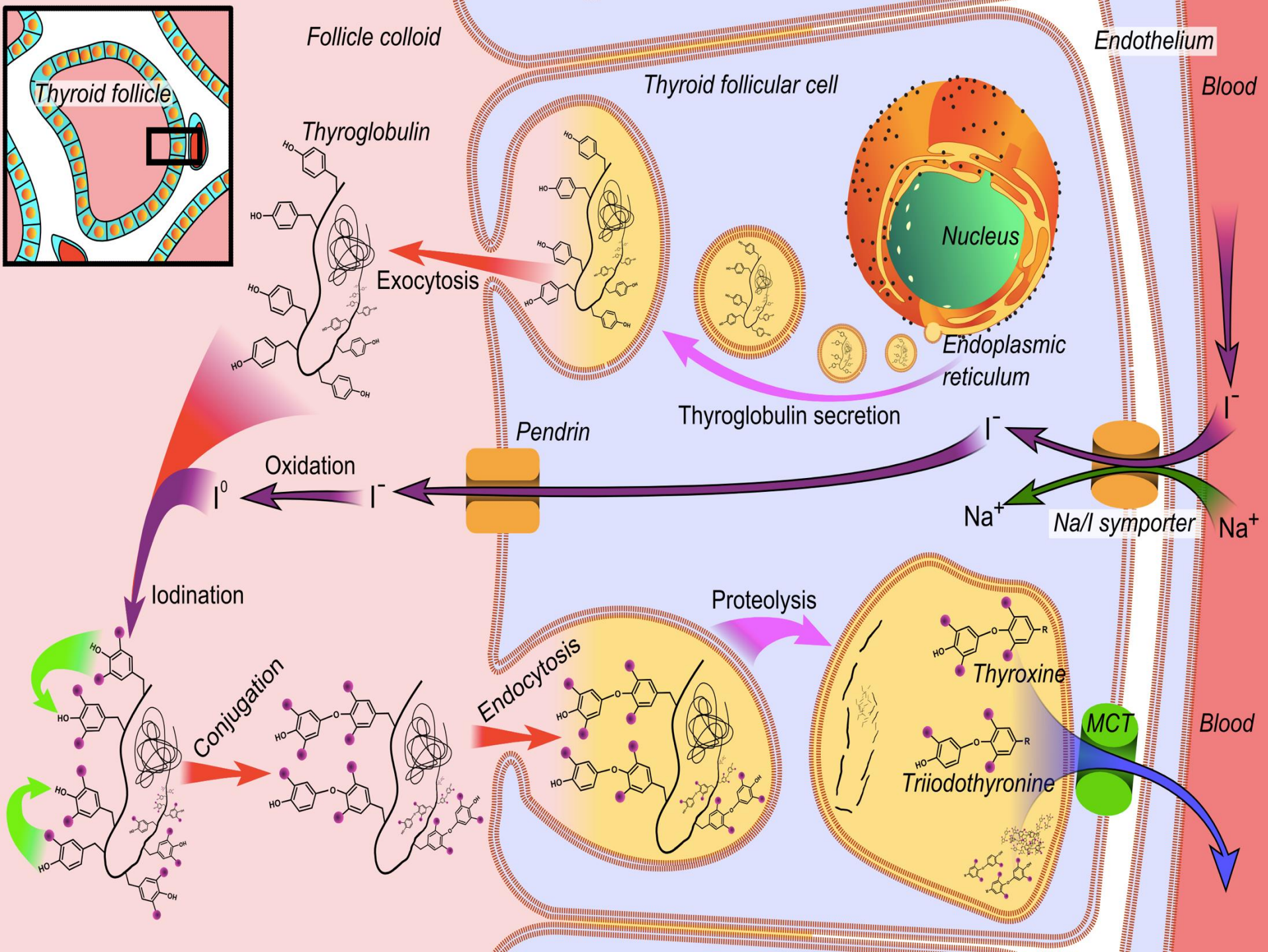
Review of normal thyroid physiology

Etiology of canine hypothyroidism

Role of thyroid function testing

Specific thyroid function tests





# CANINE HYPOTHYROIDISM

## Canine Thyroid Hormone Binding

T4 is bound to:

TBG	60 %
TBPA	17%
Albumin	12%
HDL <sub>2</sub>	11%

# CANINE HYPOTHYROIDISM

## Canine thyroid hormone binding

Dogs only have 15% of human TBG

Lower affinity for binding proteins

TT4 lower

fT4 higher

Plasma half-life of TT4 is 10-16 hours in dogs and 7 days in man

# CANINE HYPOTHYROIDISM

## Etiology of Canine Hypothyroidism

Lymphocytic thyroiditis

Idiopathic atrophy

Congenital

Neoplasia

Secondary (TSH deficiency)

Tertiary (TRH deficiency)

# CANINE HYPOTHYROIDISM

## Etiology of Canine Hypothyroidism

### Lymphocytic thyroiditis

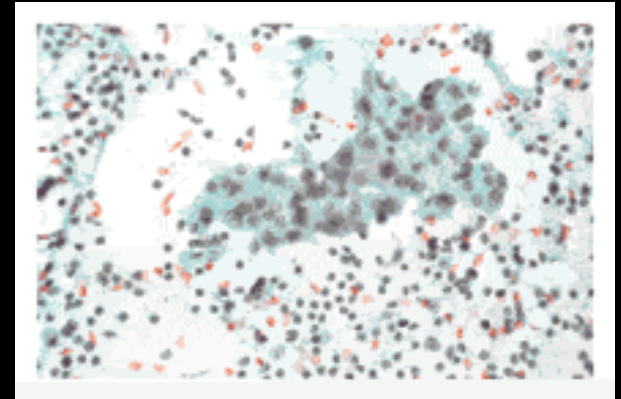
50 % of cases

Auto-immune disease

Presence of anti-thyroglobulin  
AB' s

Presence of anti-microsomal  
AB' s

T3 and T4 autoantibodies



## Changes in thyroid hormone concentrations over time in dogs with autoimmune thyroiditis

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### OBJECTIVE

The objective of this study was to follow long-term changes in the concentration of thyroid hormones in dogs with subclinical thyroiditis.

### SAMPLES

Samples were obtained from 125 dogs with subclinical thyroiditis. The study population included 70 female and 55 male dogs. The mean testing interval was 3.9 years from initial testing (SD, 2.3 years; range, 1 to 9 years).

### METHODS

Dogs with subclinical thyroiditis were identified retrospectively using results from the Orthopedic Foundation for Animals Canine Thyroid Profile performed by the Endocrinology Section of the Michigan State University Veterinary Diagnostic Lab. Owners were invited to submit follow-up serum samples with their veterinarian along with a medical history form, including subsequent treatments.

### RESULTS

At the time of retesting, 30% of the dogs had progressed to hypothyroidism and/or were treated with thyroxine. Fifty percent maintained positive or equivocal thyroglobulin autoantibody (TgAA) results while remaining euthyroid. Fourteen percent of the dogs became TgAA negative and remained euthyroid. In 6% of the cases tested, proper medical histories were not available, and a final classification could not be determined.

### CLINICAL RELEVANCE

These results indicate that most dogs with elevated thyroglobulin autoantibodies either exhibit persistent autoimmune thyroiditis with continued risk of hypothyroidism or progress to hypothyroidism when monitored for more than 1 year. Thyroid function in dogs with subclinical thyroiditis should be monitored every 12 months or if there is change in the clinical presentation.

**Keywords:** dog, autoimmune, hypothyroidism, thyroglobulin, thyroiditis

Thyroglobulin is a major product of the thyroid gland and is also the molecular site of synthesis for thyroid hormones from tyrosine and iodine through the actions of thyroperoxidase.<sup>1,2</sup> In addition to this functional role, thyroglobulin is a common antigen in autoimmune thyroiditis (AIT) in dogs.<sup>3,4</sup> AIT is the major cause of hypothyroidism in dogs and a common autoimmune disorder in humans, known as Hashimoto's thyroiditis.<sup>3,5,6</sup>

Thyroglobulin autoantibody (TgAA), in conjunction with free and total thyroxine (FT4 and TT4, respectively) and thyroid-stimulating hormone (TSH), can be used to diagnose AIT and hypothyroidism. When an animal exhibits elevated TgAA but otherwise normal results, the animal is diagnosed with subclinical thyroiditis. Elevated TSH and TgAA levels, in combination with low FT4 or TT4 level, results in a diagnosis of primary hypothyroidism. The risk of hypothyroidism associated with a positive TgAA result in dogs with otherwise normal concentrations of thyroid hormones and TSH (subclinical thyroiditis) is not well defined. Several studies have shown an

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These results indicate that most dogs with elevated thyroglobulin autoantibodies either exhibit persistent autoimmune thyroiditis with continued risk of hypothyroidism or progress to hypothyroidism when monitored for more than 1 year. presentation.

# CANINE HYPOTHYROIDISM

## Etiology of Canine Hypothyroidism

### Idiopathic atrophy

45 -50 % of cases

Lack of inflammatory infiltrate

Role of anti-thyroid AB' s ?

As with thyroiditis, hypothyroidism develops slowly over time

# CANINE HYPOTHYROIDISM

## Etiology of Canine Hypothyroidism

### Thyroid neoplasia

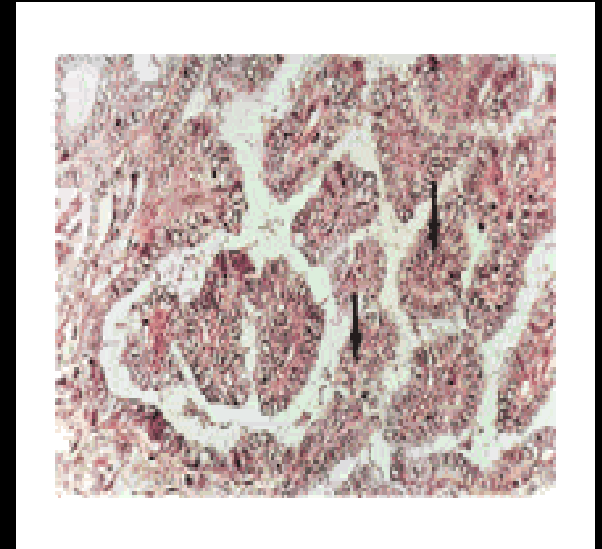
Most are euthyroid

In a retrospective study of 92  
thyroid tumors:

7 % hyperthyroid

40 % hypothyroid

Based on TT4 levels alone



# CANINE HYPOTHYROIDISM

## Etiology of Canine Hypothyroidism

### Congenital Hypothyroidism

Very rare (<1%)

Most are primary

Defective iodine intake

Dyshormonogenesis

Central disease suspected in giant schnauzers

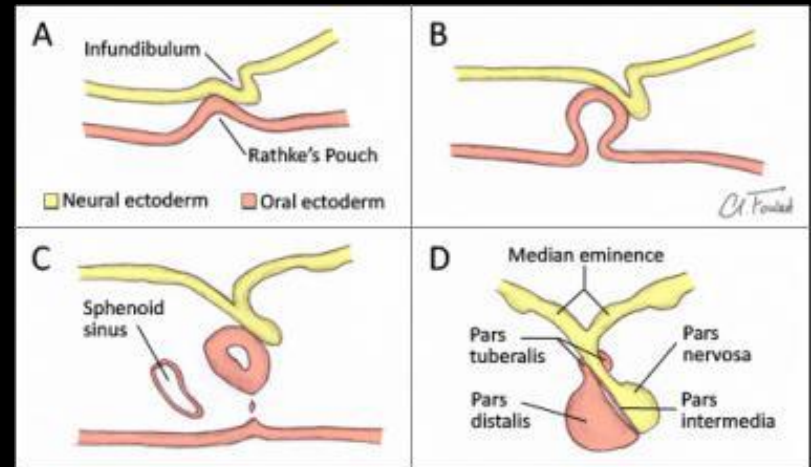
Genetic defect in fox terriers

# CANINE HYPOTHYROIDISM

## Secondary Hypothyroidism

Rare (<5%)

Expanding pituitary tumor  
Cystic Rathke's pouch  
Isolated TSH deficiency



# CANINE HYPOTHYROIDISM

## Tertiary Hypothyroidism

TRH deficiency

Trauma

Neoplasia/infiltrative disease

Biochemical defect

Occurrence in dogs

# CANINE HYPOTHYROIDISM

## Epidemiology of Canine Hypothyroidism

True incidence is unknown

Referral hospital data

Severity of illness

Pure breed dogs

Unusual cases

Diagnostic criteria

## Assessment of the likelihood of hypothyroidism in dogs diagnosed with and treated for hypothyroidism at primary care practices: 102 cases (2016-2021)

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### Abstract

**Background:** There is a possibility that an incorrect diagnosis of hypothyroidism could be made in euthyroid dogs, and the prevalence of hypothyroidism in the dog population remains unknown.

**Objectives:** To retrospectively assess the percentage of dogs diagnosed with, and treated for, hypothyroidism at first opinion practice which are likely to be hypothyroid and require levothyroxine supplementation.

**Animals:** One hundred two client-owned dogs were included in this study.

**Materials and Methods:** The computerized databases of 7 first opinion practices were searched to identify dogs treated with levothyroxine supplementation. Three European College of Veterinary Internal Medicine—Companion Animals (ECVIM-CA) diplomates independently assigned 1 of 4 clinical assessments to each case as follows: confirmed or likely hypothyroid, hypothyroidism suspected but not confirmed, hypothyroidism considered unlikely, and no reason to suspect hypothyroidism. They commented as to whether or not they thought levothyroxine supplementation was appropriate.

**Results:** The clinical assessments of “confirmed or likely hypothyroid”; “Hypothyroidism suspected but not confirmed”; “Hypothyroidism considered unlikely”; and “No reason to suspect hypothyroidism” was assigned respectively by Clinician 1 to 38.2%, 5.9%, 3.9%, and 52% of cases, by Clinician 2 to 48%, 22.6%, 22.6%, 6.9% of cases, and by Clinician 3 to 55.9%, 11.8%, 13.7% and 18.6%. Clinician 1, Clinician 2, and Clinician 3 considered levothyroxine supplementation not indicated in 58.8%, 52.9%, and 45.1% of cases, respectively.

These results support the concern that hypothyroidism might be overly and incorrectly diagnosed in first opinion practice, and that thyroid function testing should be performed only in those dogs with a high pretest probability of the disease.

# CANINE HYPOTHYROIDISM

## Epidemiology of Canine Hypothyroidism

### Age at diagnosis

46 % were 1 – 3 years of age

29% were 4 – 6 years of age

Breeds at risk develop the disease at an earlier age

# CANINE HYPOTHYROIDISM

## Epidemiology of Canine Hypothyroidism

Gender Predisposition (63,184 dogs)

2.5: 1 ratio female to male

Higher risk in spayed vs intact females

# CANINE HYPOTHYROIDISM

## Breed Predispositions

Golden Retrievers

Doberman pinchers

Dachshunds

Shetland sheepdogs

Irish setters

Airedales

Cocker spaniels

# CANINE HYPOTHYROIDISM

## Clinical Signs of Hypothyroidism

Dermatologic

Reproductive

Reprod Domest Anim 2:211-3, 2009.

Thyroid function and infertility in the dog: a survey in five breeds.

Hematologic

Cardiovascular

Neurologic

# CANINE HYPOTHYROIDISM

## Clinical Signs of Hypothyroidism

### Behavioral

**Conclusions and Clinical Importance:** The results of this study indicate increased activity of hypothyroid dogs after 6 weeks of thyroid hormone supplementation. None of the hypothyroid dogs in this cohort showed a significant change in any of the evaluated behavioral signs and neurohormonal status after 6 months of thyroid hormone supplementation.

Behavior in dogs with spontaneous hypothyroidism during treatment with levothyroxine JVIM 2018

# CANINE HYPOTHYROIDISM

## Role of Thyroid Function Testing

Confirm a clinical suspicion

Establish cellular thyroid status

Distinguish hypothyroid from “sick euthyroid”

Predict and monitor response to therapy

# CANINE HYPOTHYROIDISM

## Role of Thyroid Function Testing

### Total T4

Diagnostic if normal ( $> 1.5$  ug/dl)

Low values can be seen with:

Non-thyroidal illness

Time of day

Medications

# CANINE HYPOTHYROIDISM

## Role of Thyroid Function Testing

Total T4

Time of day

50-60 % of normal dogs have concentrations below the reference range at some time during the day

# CANINE HYPOTHYROIDISM

## Role of Thyroid Function Testing

### Total T4

#### Effect of age

TT4 two to 5 times higher in first 3 months

Age dependent decline in resting and post TSH

TT4

Decline in TSH response to TRH in aged dogs

# CANINE HYPOTHYROIDISM

## Role of Thyroid Function Testing

Total T4

Breed related normal range

Greyhounds, sight hounds, basenji' s

TT4 about 50% of normal

fT4 also lower

# CANINE HYPOTHYROIDISM

## Role of Thyroid Function Testing

Assessment of criteria used by veterinary practitioners to diagnose hypothyroidism in sighthounds and investigation of serum thyroid hormone concentrations in healthy Salukis. J Am Vet Med Assoc. 2010 Feb 1;236(3):302-8.

76.1 % diagnosed with hypothyroidism based on low TT4

7.5 % diagnosed with hypothyroidism with normal results

83.6 % incorrectly diagnosed

# CANINE HYPOTHYROIDISM

In summary, there is breed-specific variability in serum T4 (total and free) and TSH concentrations in the breeds studied, and the use of breed-specific RIs is warranted. However, laboratory values will always be subject to variability because of the potential for preanalytical, analytical, and postanalytical error. Therefore, the accurate assessment of canine thyroid health will continue to require the essential integration of laboratory data with the full context of the clinical presentation.

Breed-specific reference intervals for assessing thyroid function in seven dog breeds. *Journal of Veterinary Diagnostic Investigation* 2015, Vol. 27(6) 716–727

# CANINE HYPOTHYROIDISM

## Role of Thyroid Function Testing

### Total T4

#### Non-thyroidal illness

- Euthyroid sick syndrome

  - Low T3 syndrome

  - Low T4 state of medical illness

  - Predictor of mortality in man and cats

# CANINE HYPOTHYROIDISM

## Role of Thyroid Function Testing

### Total T4

#### Non-thyroidal illness

Hyperadrenocorticism

Diabetes mellitus

Hypoadrenocorticism

Chronic renal failure

Hepatic disease

Intensive care

# CANINE HYPOTHYROIDISM

## TT4 and Medications

### Lowering TT4

Steroids (↓ in TT4, ↓ or = fT4ED, = or (↓) TSH)

Phenobarbital (= or ↓TT4 and fT4ED, = or ↑ TSH)

Sulfonamides (↓TT4 and fT4ED, ↑ TSH)

Rimadyl (↓TT4, = or (↓) fT4ED, ↓ TSH)

Clomipramine (↓TT4 and fT4ED)

# Influence of medications on thyroid function in dogs: An update

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## Abstract

Erroneous thyroid function test results can occur because of drugs that alter thyroid hormone physiology in one or more aspects, including synthesis, secretion, distribution, and metabolism. Research since publication of the last review in the *Journal of Veterinary Internal Medicine (JVIM)* 20 years ago has evaluated the effects of amiodarone, zonisamide, inhalant anesthetics, clomipramine, trilostane, and toceranib on thyroid function tests in the dog. In addition, recent work on the effects of glucocorticoids, sulfonamides, phenobarbital, and nonsteroidal anti-inflammatory drugs will be reviewed. Awareness of these effects is necessary to avoid misdiagnosis of hypothyroidism and unnecessary treatment.

## KEYWORDS

amiodarone, aspirin, clomipramine, glucocorticoids, phenobarbital, sulfonamides

## 1 | INTRODUCTION

The diagnosis of hypothyroidism is confirmed by thyroid function tests in a dog with compatible clinical and clinicopathologic abnormalities. Serum total thyroxine (TT4) or free thyroxine (FT4) hormone concentration or both below and serum thyroid-stimulating hormone (TSH) concentration above their respective reference intervals indicate a diagnosis of primary hypothyroidism. However, no single thyroid function test is completely reliable, and approximately 25% of dogs with primary hypothyroidism have normal serum TSH concentrations.<sup>1-4</sup> Furthermore, age,<sup>5,6</sup> reproductive status,<sup>7</sup> breed,<sup>8-10</sup> body condition,<sup>11,12</sup> exercise or training,<sup>13,14</sup> nonthyroidal illness,<sup>1,2,15,16</sup> and drugs<sup>17</sup> impact thyroid function test results.

Drugs affect thyroid hormone physiology in several possible ways, including synthesis, secretion, distribution, and metabolism. The administration of many drugs results in mild changes in thyroid function, whereas hypothyroidism can be induced during treatment with others.

Although the effects of some drugs on thyroid function tests in dogs are well documented, the introduction of new drugs and additional research on older drugs have resulted in new findings that have relevance to clinical practice since the last review of this topic in the *JVIM*.<sup>17</sup> Understanding the impact that various drugs have on thyroid function tests accomplishes 2 clinically applicable objectives: (1) prevents the inappropriate diagnosis of hypothyroidism and subsequent prescription of unnecessary thyroid hormone treatment, and (2) establishes when accurate thyroid hormone testing can be conducted after drug discontinuation. This review will provide an update on the effects of drugs that alter thyroid function tests in dogs, including those found in the previous review article<sup>17</sup> and those studied during the intervening 20 years.

## 2 | PHYSIOLOGY OF THE HYPOTHALAMIC-PITUITARY-THYROID AXIS

### 2.1 | Hypothalamic-pituitary-thyroid axis overview

Serum thyroid hormone concentrations are determined by the interaction of the hypothalamus, anterior pituitary gland, and thyroid gland,

Abbreviations: FT3, free T3; FT4, free thyroxine; HPT, hypothalamic-pituitary-thyroid; NSAIDs, nonsteroidal anti-inflammatory drugs; rT3, reverse T3; T3, 3,5,3'-triiodothyronine; T4, thyroxine; TCAs, tricyclic antidepressants; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; TT3, total T3; TT4, total thyroxine.

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Research since publication of the last review in the *Journal of Veterinary Internal Medicine (JVIM)* 20 years ago has evaluated the effects of amiodarone, zonisamide, inhalant anesthetics, clomipramine, trilostane, and toceranib on thyroid function tests in the dog.

**Table 1. Classification of Drug Effects on the Thyroid.\***

**Interference with endogenous thyroid function**

Disruption of hypothalamic–pituitary control

Decreased thyroid hormone production or release

Increased thyroid hormone production

Enhanced thyroid autoimmunity

Destructive thyroiditis

Changes in thyroid hormone–binding proteins

Inhibition of thyroid hormone activation (T<sub>4</sub>-to-T<sub>3</sub> conversion)

Displacement of thyroid hormone from binding proteins

Increased thyroid hormone metabolism or elimination

**Interference with thyroid hormone therapy**

Decreased pill dissolution

Decreased thyroid hormone absorption

Decreased free thyroid hormone levels

Increased thyroid hormone metabolism or elimination

**Interference with thyroid laboratory testing in euthyroid persons**

Falsely elevated thyroid hormone levels

Falsely low thyroid hormone levels

Falsely low serum thyrotropin levels

Falsely elevated thyrotropin-receptor antibody levels

\* T<sub>3</sub> denotes triiodothyronine, and T<sub>4</sub> thyroxine. For a detailed list of drugs interacting with the thyroid, see Tables S1 and S2 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

**Table 2. Drugs That Cause Spurious Thyroid Test Results in Euthyroid Persons.**

Drug	Drug Class	Test Results			Condition Mimicked
		Thyrotropin	Free T <sub>4</sub>	T <sub>3</sub>	
Amiodarone	Class III antiarrhythmic agent	High end of normal range	High	Low end of normal range	Thyrotropin-secreting pituitary adenoma, thyroid hormone resistance
Biotin	Micronutrient	Low	High	High	Primary hyperthyroidism
Carbamazepine and oxcarbazepine	Antiepileptic agent	Normal	Low	Low end of normal range	Central hypothyroidism
Enoxaparin	Anticoagulant	Normal	High	High	Thyrotropin-secreting pituitary adenoma, thyroid hormone resistance
Heparin	Anticoagulant	Normal	High	High	Thyrotropin-secreting pituitary adenoma, thyroid hormone resistance
Phenytoin	Antiepileptic agent	Normal	Low	Low end of normal range	Central hypothyroidism
Salsalate	Nonsteroidal anti-inflammatory drug	Normal	Low end of normal range	Low end of normal range	Central hypothyroidism

# Total thyroxine, triiodothyronine, and thyrotropin concentrations during acute nonthyroidal illness and recovery in dogs

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#### Abstract

**Background:** Acute illness can result in changes in serum total thyroxine (tT4), total triiodothyronine (tT3), and thyrotropin (TSH) concentrations in euthyroid dogs defined as nonthyroidal illness syndrome, but longitudinal evaluation of these hormones during the recovery phase is lacking.

**Objectives:** To longitudinally evaluate serum tT4, tT3, and TSH concentrations during the acute phase and recovery from acute illness in dogs.

**Animals:** Nineteen euthyroid client-owned dogs hospitalized for acute illness at a veterinary teaching hospital.

**Methods:** Prospective longitudinal study. Serum tT4, tT3, and TSH concentrations were measured at the admission (T0), at last day of hospitalization (T1), and during the recovery phase at 3, 7, 14, and 21 days after the discharge (T2, T3, T4, and T5), respectively.

**Results:** tT4 and tT3 were below the reference interval (RI) at T0 in 3 (16%) and 18 (95%) dogs, respectively; tT4 normalized in all dogs early in the recovery phase, while low tT3 persisted at the end of the study in 16 (83%) dogs. Median TSH concentrations were increased at T5 compared with T1 (0.19 ng/mL [range 0.03-0.65] vs 0.11 ng/mL [range (0.05-0.26)], mean difference = 0.09 ng/mL;  $P = .03$ ). Five (26%) dogs had TSH above the RI at least at 1 time point during the recovery phase. None of the dogs had concurrent low tT4 and high TSH during the study.

**Conclusions and Clinical Relevance:** In euthyroid dogs acute illness can interfere with evaluation of thyroid function up to 21 days during the recovery phase. Thyroid testing should be avoided or postponed in these dogs.

Abbreviations: ANOVA, analysis of variance; APPL score, acute patient physiologic and laboratory evaluation score; CLIA, chemiluminescent enzyme immunoassays; IRIS, International Renal Interest Society; NTIS, nonthyroidal illness syndrome; rTSH, recombinant human TSH; T3, triiodothyronine; tT3, total triiodothyronine; T4, thyroxine; tT4, total thyroxine; TSH, thyroid-stimulating hormone; TSHst, TSH stimulation test.

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In euthyroid dogs acute illness can interfere with evaluation of thyroid function up to 21 days during the recovery phase. Thyroid testing should be avoided or postponed in these dogs.

# CANINE HYPOTHYROIDISM

TT4 (low TT4)

Sensitivity 89 – 100 %

Specificity 75 – 82 %

Accuracy 85 %

# CANINE HYPOTHYROIDISM

Free Thyroid Hormone Measurement

Free Hormone Hypothesis (Mendel)

Linear correlation of fT4 and metabolic rate

Inversely correlated with the log of TSH

# CANINE HYPOTHYROIDISM

Free Thyroid Hormone Measurement

Direct Dialysis (EqD)

Nichols Institute  
Antech Diagnostics

# CANINE HYPOTHYROIDISM

fT4ED (low fT4ED)

Sensitivity 98 %

Specificity 94%

Accuracy 95 %

# CANINE HYPOTHYROIDISM

## Canine cTSH Assays

History

Experimental models

TRH testing

Supplementation

Real world

25% of confirmed hypothyroid dogs have normal cTSH

# CANINE HYPOTHYROIDISM

## Canine cTSH Assays (high cTSH)

Sensitivity 76 – 87 %

Specificity 82 – 93 %

Accuracy 84 %

# CANINE HYPOTHYROIDISM

## •Low fT4ED/High cTSH

## Low fT4ED

•Sensitivity 74 – 80%

80 – 98 %

•Specificity\* 97 – 98%

93 – 94 %

•Accuracy 86 %

95 %\*

# CANINE HYPOTHYROIDISM

Can We Evaluate Thyroid Function  
in Sick Dogs ??

In the sick dogs, serum TT4 and fT4 concentrations are less than reference range values in (80% ) and (32%) dogs, respectively

*J Am Vet Med Assoc* 2001;219:765–769

*J Am Vet Med Assoc* 2003;222:1079–1085

*J Vet Emerg Crit Care* 2014; May-Jun;24(3):264-71.

# CANINE HYPOTHYROIDISM

## Replacement Therapy

Dose: 20 ug/kg (0.1 mg/10#)

Once daily dosing

Clinical evaluation of a novel liquid formulation of L-thyroxine for once daily treatment of dogs with hypothyroidism. J Vet Intern Med. Jan-Feb;23(1):43-9, 2009.

Pharmacokinetics of total thyroxine after repeated oral administration of levothyroxine solution and its clinical efficacy in hypothyroid dogs. J Vet Intern Med. Jul-Aug;28(4):1229-34, 2014.

Name brand vs generic

# CANINE HYPOTHYROIDISM

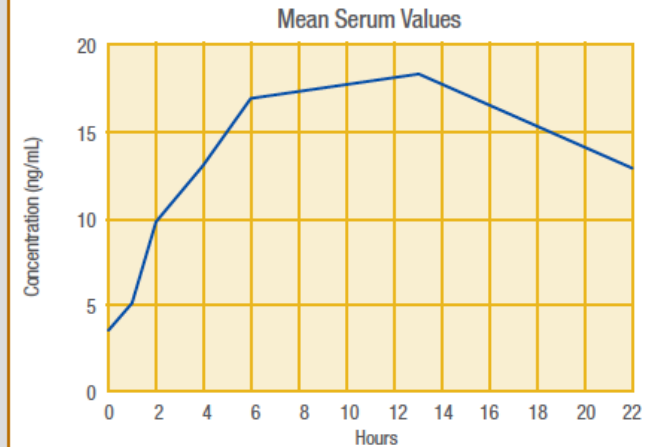
Only approved formulation is:

Thyro-Tabs Canine made by  
Lloyd Inc.



Efficacy proven in  
clinical studies

## CANINE T4 BIOAVAILABILITY STUDY



Blood serum thyroxine (T4) concentration in four thyroidectomized dogs given a single Thyro-Tabs® dose of 20 µg per kilogram body weight.

# CANINE HYPOTHYROIDISM

## Monitoring Therapy

Why

Pre vs Post Pill

Monitor cTSH, TT4, fT4ED