

Canine hypothyroidism

Clinical signs, diagnosis and treatment



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Canine hypothyroidism: Introduction

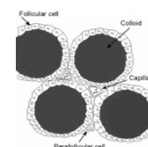
- One of the most frequent endocrinopathy
- Commonly misdiagnosed endocrinopathy
 - Hypothyroidism remains a disease difficult to diagnose accurately in many instances
- Myriad of clinical signs but none are specific
- No perfect diagnostic test available

Canine hypothyroidism: Plan of the presentation

- Brief review of pathophysiology of the thyroid gland
- Canine hypothyroidism
 - Clinical features
 - Diagnostic tests
 - Treatment and Monitoring

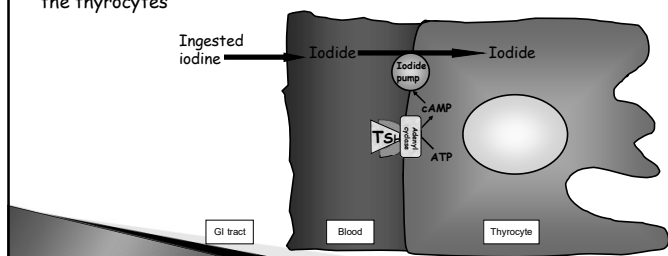
Synthesis and secretion of the thyroid gland

- The thyroid gland synthetize and secrete:
 - Thyroxine (T4)
 - Triiodothyronine (T3)
 - reverse T3 (rT3)
 - Calcitonin
 - Thyroglobulin



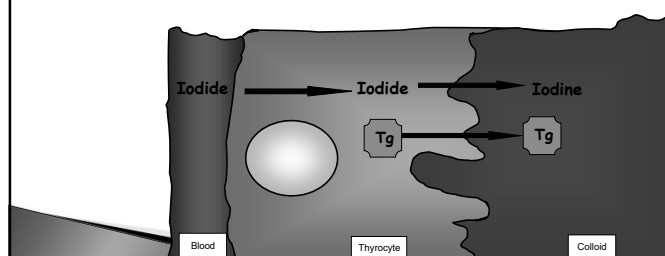
Synthesis of thyroid hormones

- Ingested iodine is converted in iodide in the GI tract and absorbed into the circulation and then iodide is trapped into the thyrocytes



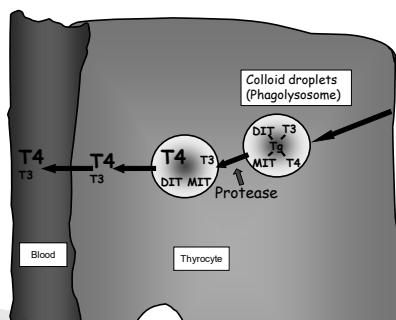
Synthesis of thyroid hormones

- Afterward, iodide is transported from the thyrocytes into the lumen of thyroid follicles (colloid) along with thyroglobulin



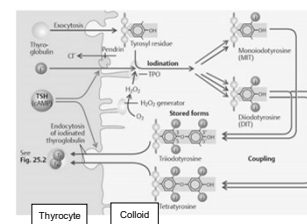
Secretion of thyroid hormones

- Proteolysis of thyroglobulin liberates large amounts of T₄, but small amounts of T₃ into the cytosol
- Free T₄ and T₃ are then released into the blood stream



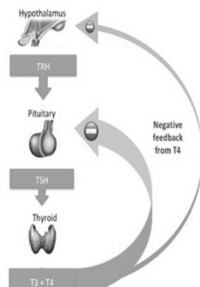
Synthesis of thyroid hormones

- After synthesis of TH, each thyroglobulin molecule contains up to 30 T₄ molecules and a few T₃ molecules
- TH are stored in this form in the follicles in a sufficient amount to supply body requirements for 2 to 3 months



Thyroid hormone action

- >99% of TH bind with plasma proteins which will slowly release them to target tissues
- In the healthy euthyroid dog, < 1% of TH are free
 - Only free TH enter cells to produce a biological effect
 - Only free TH have a negative feedback effect on pituitary and hypothalamus
- T₃ is the major metabolically active TH in the dog



Biological effects of thyroid hormones

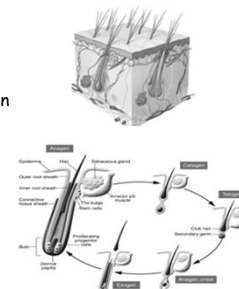
- Myriad of physiologic effects
 - Necessary for normal cell metabolism of virtually every tissues and organs
 - Essential for normal growth and development of the neurological and skeletal systems
 - Act on many different cellular processes via specific ligand-receptor

Biological effects of thyroid hormones

- Profound effect of increasing the metabolic rate of the body
 - Complete lack of TH secretion: BMR ↓ 40 to 50% below normal
 - Extreme excesses of TH secretion: BMR ↑ 60 to 100% above normal
- Inotropic and chronotropic effects on the heart
- Anabolic (in physiological quantities)
- Catabolic effects on muscle and adipose tissues (in excess)
 - e.g., hyperthyroidism
- Stimulate erythropoiesis
- Regulate cholesterol synthesis and degradation

Biological effects of thyroid hormones

- Play a major role in:
 - Differentiation and maturation of skin
 - Maintenance of normal cutaneous function
- Regulate the cornification process and sebaceous glands secretion
- Are required for initiation of anagen phase of the hair follicle cycle



Biological effects of thyroid hormones

- ▶ In hypothyroidism:
 - Epidermal atrophy and abnormal keratinization
 - Due to ↓ protein synthesis, mytotic activity and O_2 consumption
 - Abnormal lipogenesis and ↓ sterol synthesis by the keratinocytes
 - Sebaceous gland atrophy and ↓ sebum excretion rate
 - Glycosaminoglycans accumulate in the dermis (myxoedema)

Biological effects of thyroid hormones

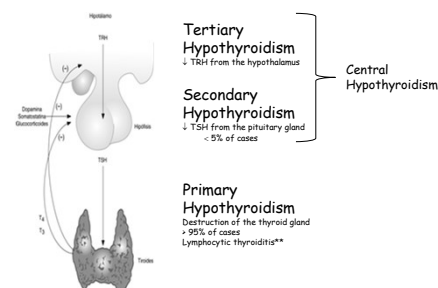
- ▶ Are required for normal development of lymphoid tissue
- ▶ Thyroidectomy leads to hypoplasia of lymphoid organs and thymus
- ▶ Depletion of thyroid hormones results in impaired neutrophils and B and T-lymphocytes function

Biological effects of thyroid hormones

Normal state	Deficiency
Catabolic effect on muscular and adipose tissues	Predispose to weight gain
Stimulate erythropoiesis	Non-regenerative anemia
Regulate cholesterol synthesis and degradation	Hypercholesterolemia
Required for initiation of anagen phase of the hair follicle cycle	Hair cycle arrest (hypotrichosis, alopecia)
Regulate the cornification process and sebaceous glands secretion	Cornification disorder
Required for normal development and function of lymphoid tissue	Infection

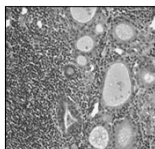
Etiopathology of canine hypothyroidism

- ▶ Hypothyroidism is the result of a ↓ production of T4 and T3 by the thyroid gland
- ▶ Can be acquired (most cases) or congenital (rare)



Etiopathology of canine hypothyroidism

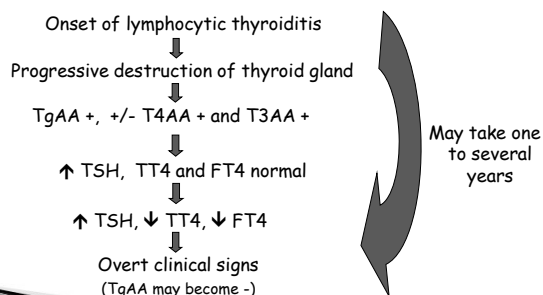
- ▶ Lymphocytic thyroiditis
 - Most frequent etiology (more than 95% of cases)
 - Highly heritable in many breeds
 - Immune mediated disorder characterized histologically by a diffuse infiltration of lymphocytes, plasma cells, and macrophages in the thyroid gland
 - Clinical signs develop between 3 and 8 years (~ never in dogs < 2 years)
 - Breed predisposed: Doberman, Golden retriever, Boxer, Gordon setter, English setter, OESD, etc..



Etiopathology of canine hypothyroidism

- ▶ The progressive destruction of thyroid follicles (and secondary fibrosis) eventually leads to a failure of thyroid hormone production
- ▶ > 70% of the thyroid tissue needs to be destroyed before changes in laboratory measures of thyroid function is seen
- ▶ This process can take months or years to cause clinical signs of hypothyroidism

Etiopathology of canine hypothyroidism



Etiopathology of canine hypothyroidism

- ▶ Congenital hypothyroidism (cretinism)
 - Can be primary, secondary or tertiary
 - Dysgenesis of the thyroid gland (aplasia, hypoplasia, ectasia)
 - Dyshormonogenesis (lack of iodine organization)
 - Poor dietary iodine intake
 - Mutation in the TPO gene
 - Congenital hypothyroidism with goiter
 - Autosomal recessive inheritance in wire fox terriers and rat terriers
 - Genetic testing available to identify carrier



Non-thyroidal illness syndrome (Euthyroid sick syndrome)

- ▶ Refers to changes in serum TH levels observed in sick animal in the absence of hypothalamic-pituitary-thyroid primary dysfunction
- ▶ Causes a ↓ TT4, TT3 and a ↑ rT3
 - ↓ production of T3 and T4 and ↓ degradation of rT3
- ▶ Metabolic change in sick animals
- ▶ Prevents excessive calorogenic effect of T3 in a catabolic state
- ▶ Frequent source of misdiagnosis
- ▶ Do not supplement in Levothyroxine!!!

Canine hypothyroidism: clinical features

- ▶ Myriad of clinical signs
- ▶ Dermatological signs in ~ 80% of cases
- ▶ Most organs or tissues are affected
- ▶ No clinical signs is pathognomonic
- ▶ Apparition is gradual and insidious

Canine hypothyroidism: clinical features

▶ Dermatological signs

- Alopecia tail and bridge of the nose



Canine hypothyroidism: clinical features

▶ Dermatological signs

- Alopecia tail and bridge of the nose
- Other areas of friction



Canine hypothyroidism: clinical features

► Dermatological signs

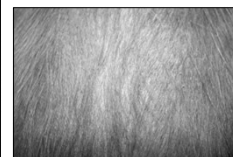
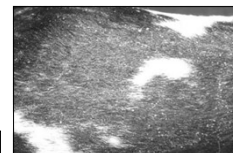
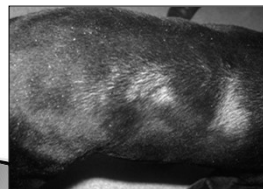
- Alopecia tail and bridge of the nose
- Other areas of friction



Canine hypothyroidism: clinical features

► Dermatological signs

- Dry, dull and sparse hair coat
- Scalling (dry or waxy)

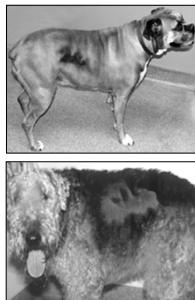


Canine hypothyroidism: clinical features

► Dermatological signs

Complete truncal alopecia ~ never !

... in spite of the fact that photos of hypothyroid dogs in Internal medicine textbook and in Endocrinology textbooks often look like this →



Canine hypothyroidism: clinical features

- However, simultaneous hypothyroidism and recurrent flank alopecia is possible!

Paradis M. Canine flank alopecia. *Derm Dialogue*. Summer 1998 pp10-13.

→ Concomitant hypothyroidism in 6 of 120 dogs suffering recurrent flank alopecia



Daminet S, Paradis M. Evaluation of thyroid function in dogs suffering from recurrent flank alopecia. *Can Vet J* 2000;41:699-703

Abstract — Thyroid function was assessed in euthyroid dogs (n = 20), dogs suffering from canine recurrent flank alopecia (CRFA, n = 18), and hypothyroid dogs (n = 21). Blood samples obtained from all dogs in each group were assayed for total thyroxine (TT4), thyrotropin (TSH), and thyroglobulin autoantibody (TgAA) serum concentrations. Total T4 and TSH serum concentrations were significantly decreased and increased, respectively, in the hypothyroid group compared with the other 2 groups. No significant differences in TT4 and TSH serum values were found between the euthyroid and CRFA groups. Thyroglobulin autoantibodies were detected in 10, 11, 1, and 61.9% of euthyroid dogs, dogs with CRFA, and hypothyroid dogs, respectively. In conclusion, dogs suffering from CRFA have a normal thyroid function, and the determination of TT4 and TSH serum concentrations allows differentiation of these dogs from dogs with hypothyroidism, in most cases. Occasionally, the 2 diseases can be concomitant.

Canine hypothyroidism: clinical features

► Dermatological signs

- Failure to regrowth hair after clipping
- Often a fortuitous finding

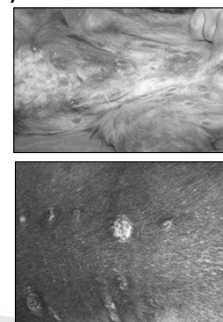


5 months post-clipping for a knee surgery

Canine hypothyroidism: clinical features

► Dermatological signs

- Secondary pyoderma
- Reported in < 10% of cases
- Mainly observed in severe, chronic cases



Canine hypothyroidism: clinical features

► Dermatological signs

◦ Secondary pyoderma

- Mainly observed in severe, chronic cases



Canine hypothyroidism: clinical features

► Dermatological signs

- Chronic or recurrent otitis externa secondary to hypothyroidism~ never! (unless suffering concomitant illness such as allergy)

... in spite of the fact that it is frequently mentioned in the literature ...

Canine hypothyroidism: clinical features

► Metabolic signs

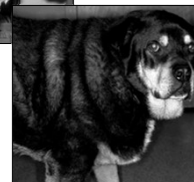
- Lethargy
- Weakness, exercise intolerance, etc...
- Bradycardia
- ↓ body T°



Canine hypothyroidism: clinical features

► Metabolic signs

- Obesity or weight gain (with low caloric intake)
 - Most hypothyroid dogs are not obese ... and
 - Most obese dogs are not hypothyroid !



Canine hypothyroidism: clinical features

► Myxoedema (tragic look)

- Mucin (mucopolysaccharide) accumulation in the dermis



Canine hypothyroidism: clinical features

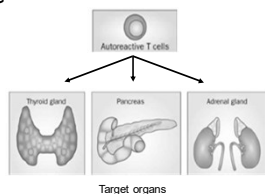
► Myxoedema (tragic look)

- Mucin (mucopolysaccharide) accumulation in the dermis



Canine hypothyroidism: clinical features

- ▶ Auto-immune polyglandular syndrome (Schmidt syndrome in humans)
 - Hypothyroidism + hypoadrenocorticism
 - Hypothyroidism + diabetes mellitus
 - Different from "euthyroid sick syndrome"



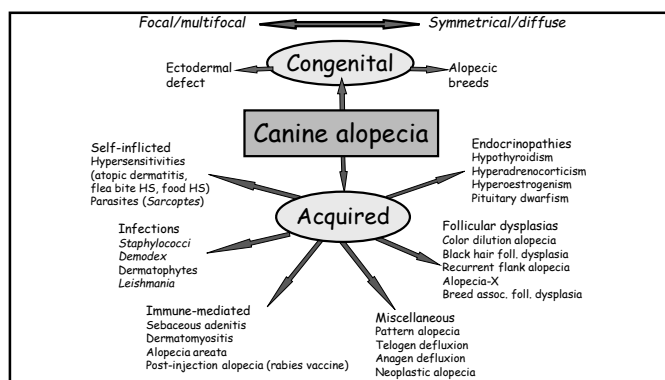
Canine hypothyroidism: clinical features

- ▶ Congenital hypothyroidism
 - Disproportionate dwarfism
 - Affected puppies have shorter limbs and shorter, broader heads than their littermates
 - Delayed skeletal maturation
 - Mental retardation (cretinism)
 - Affected puppies retain their coats and show the same dermatologic findings as adult hypothyroid dogs
 - Goiter in some dogs (Fox terrier)



Canine hypothyroidism: Differential diagnosis

- ▶ Most non-inflammatory alopecias (« Hair cycle arrest »)
 - Endocrinopathies
 - Follicular dysplasias
 - Pattern alopecia
 - Telogen defluxion
- ▶ Anagen defluxion
- ▶ Sebaceous adenitis



Tail alopecia

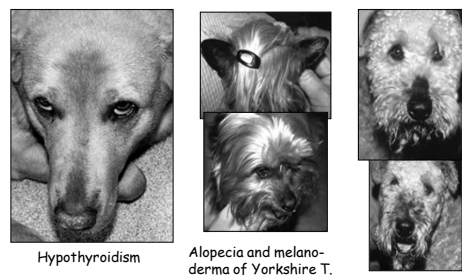


Hypothyroidism

Hyperadrenocorticism

Alopecia X

Alopecia on the bridge of the nose



Hypothyroidism

Alopecia and melano-
derma of Yorkshire T.

CRFA (rare)

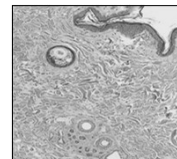
Alopecia on the bridge of the nose



Alopecia X

Canine hypothyroidism: diagnosis

- ▶ Nonspecific laboratory findings
 - Hemogram
 - Non-regenerative anemia: ~30% of cases
 - Biochemical panel
 - Fasting hypercholesterolemia in ~75% of cases often with hypertriglyceridemia
 - Skin biopsy
 - Non-specific changes of endocrinopathies
 - Dermal mucinosis in presence of myxedema
 - Useful to differentiate from some follicular dysplasias and sebaceous adenitis



Biological exploration of thyroid function

Baseline serum hormones

- Total thyroxine (TT4)
- Free thyroxine (FT4)
- Total triiodothyronine (TT3)
- Free triiodothyronine (FT3)
- Reverse T3 (rT3)
- Endogenous canine TSH (cTSH)

Dynamic tests

- TSH stimulation test
- TRH stimulation test

Miscellaneous

- Thyroglobulin autoantibodies (TgAA)
- TH autoantibodies (T4AA & T3AA)
- Thyroid biopsy
- Thyroid scintigraphy
- Thyroid ultrasound

Total thyroxine (TT4)

- ▶ $TT4 = FT4 + \text{protein-bound T4}$
- ▶ Commonly measured
- ▶ Significant overlap between hypothyroid and euthyroid dogs
 - Diagnostic errors in ~20-30% ?
- ▶ Often ↓ following certain drugs or NTI
- ▶ Declines with age
- ▶ Lower reference range in Sighthounds
 - Greyhound, Scottish Deerhound, Salukis, Afghan hounds, Whippets, Borzois, etc.
- ▶ Must be validated for dogs

Total thyroxine (TT4)

- ▶ May decrease with:
 - Drugs
 - Sulfa-trimethoprim (dermatologic dose), Phenobarbital
 - Glucocorticoids, Clomipramine, Aspirin
 - Non-thyroidal illnesses (NTI)
 - Renal, Cardiac and Hepatic failures, Hyperadrenocorticism, Diabetes mellitus, Neoplasm, Pyoderma

Total thyroxine (TT4)

- ▶ Before measuring TT4:
 - Avoid glucocorticoid excess (endogenous or exogenous)
 - Avoid drugs or NTI known to influence TT4
 - Age of the dog?
 - Compatible clinical signs?

Total thyroxine (TT4)

► Interpretation:

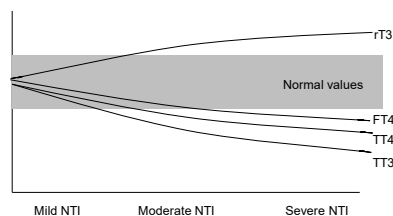
- > 99 % of dogs with a TT4 > 15 nmol/L are euthyroid
- > 95 % of dogs with a TT4 < 5 nmol/L are hypothyroid
- TT4 between 5-15 nmol/L = Grey zone

(example of reference values: ~ 15-45 nmol/L)

Free thyroxine (FT4)

- FT4 = active fraction, unbound to proteins
- < 1% of TT4
- Less overlap between euthyroid and hypothyroid dogs (?)
- Less influenced by drugs and NTI
- Preferably measured by equilibrium dialysis
 - Diagnostic precision > TT4 (in a small % of cases)
 - Not affected by T4AA
 - \$\$\$
- Usefulness similar to TT4 if FT4 is measure by other techniques

Effect of non-thyroidal illness (NTI) on thyroid function



Endogenous canine TSH (cTSH)

- Commercial cTSH assays since 1995
- Poor specificity and sensitivity
 - Remains within normal in ~25% of Hypothyroid dogs
 - ↑ into hypothyroid zone in ~10% of Euthyroid dogs
- Reference values ~ 0.02 to 0.6 ng/ml
- Always combine with TT4 or FT4

Thyroglobulin autoantibodies (TgAA)

- Positive in ~ 50-60% of hypothyroid dogs (~ 3% of euthyroid dogs)
 - TgAA may become negative after thyroid glands are destroyed
- TgAA strongly suggest the presence of an auto-immune lymphocytic thyroiditis but not necessarily hypothyroidism
 - It requires at least 75% of thyroid gland destruction for clinical signs
- Use for screening breeding stock
 - Breeds with hereditary predisposition for lymphocytic thyroiditis
 - OFA certification: FT4 (ed), TgAA and cTSH

Current recommendations

- Before testing, make sure that:
 - Compatible clinical signs ?
 - At least 2-year-old ?
 - Systemic illnesses ?
 - Drugs : glucocorticoids, sulfas, phenobarbital, clomipramine?
- Postpone testing after resolution of the systemic illness or withdrawal of the drug, if possible
- Use a Veterinary diagnostic laboratory that use canine kit and that has established reference values

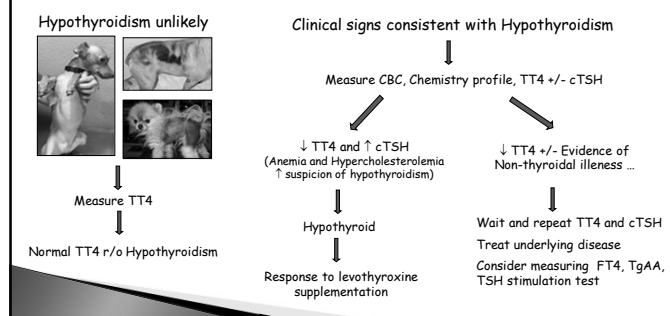
Current recommendations

- ▶ In humans, TSH is often used as screening and diagnostic accuracy is ~ 100% with combined measurements of TSH and FT4
- ▶ In dogs, no perfect test available and recommendations depend on availability of tests and reasons for testing
 - TT4 +/- cTSH
 - FT4 by equilibrium dialysis
 - TT4 or FT4 + TgAA
 - Thyroid (7 parameters) profile (Michigan state University VDL)
 - CBC and biochemistry profile including fasting cholesterol
 - TSH stimulation test
 - OFA certification: FT4 (ED) + cTSH + TgAA...

Current recommendations

- ▶ Reasons for testing:
 - Suggestive C/S, but hypothyroidism unlikely
 - Screening with TT4: rules out hypothyroidism if WNL
 - Suggestive C/S and hypothyroidism probable
 - TT4 + cTSH + CBC and Chemistry profile
 - Screening and OFA certification for breeding stock
 - FT4, cTSH and TgAA
- * Always interpret results carefully and with a healthy dose of skepticism!

Algorithm for hypothyroid testing



Canine hypothyroidism: diagnosis

- ▶ Definitive diagnosis is confirmed with a combination of:
 1. Compatible clinical signs
 2. Thyroid test results compatible with hypothyroidism
 - p.ej., very low T4T and elevated cTSH (in absence of NTI)
 3. Response to treatment
 - Very important to make sure the dog is truly hypothyroid
 - Return of mental and physical activity within 2 weeks of starting levothyroxine supplementation usually confirms the diagnosis

Canine hypothyroidism: Treatment

- ▶ Levothyroxine
 - Starting dose: **20-22 µg/kg** (or 500 µg/m²) **q12-24h**
 - After 4-6 weeks or when all C/S have resolved:
 - 4-6 hours post-pill TT4 concentration
 - Aim for high end of reference values
 - Maintenance dose: **20-22 µg/kg** (or 500 µg/m²) **q24h** for the majority of dogs
 - Co-ingestion with food may cause decrease absorption
 - Try to administer at consistent time



Canine hypothyroidism: Treatment

- ▶ Yearly recheck and TT4 measurement (?)
- ▶ Monitoring with FT4(ed) or cTSH ?
 - More expensive and no real benefit
- ▶ Thyrotoxicosis is rare in dogs
 - Pu/Pd, weight loss, panting, nervousness, tachycardia

Canine hypothyroidism: Take home message

- › Clinical hypothyroidism almost never seen before 2-3 years of age
- › Does not cause severe trunk alopecia or chronic otitis
- › When monitoring with TT4, always verify if and when levothyroxine was administered
- › Avoid supplementing dogs with "Euthyroid sick syndrome (NTI)"
- › Most dogs are well control with q24h levothyroxine administration

Canine hypothyroidism



The end