KEY POINTS

A. Thyroid Hormone
- T4 accounts for the majority of the thyroid hormone secreted by the thyroid gland
  - Small quantities of T3 released – primary hormone that induces physiologic effects
  - Minor amounts of rT3 released
- More than 99% of T4 is bound to plasma proteins
- <1% of T4 and T3 circulate in unbound ‘free’ state (fT4, fT3)
  - Biologically active, capable of entering cells throughout the body
  - fT4 Exerts negative feedback inhibition on pituitary TSH secretion
- Thyroid hormones entrance into cells is mediated by transporter proteins. Hormones bind to receptors in nuclei

B. Physiologic Function of Thyroid Hormones
- Stimulate calorigenesis
- Stimulate protein and enzyme synthesis
- Regulates every aspect of carbohydrate and lipid metabolism (synthesis, mobilization, degradation)
- Have marked chronotropic and inotropic effects on the heart
- Increase the number and affinity of beta-adrenergic receptors
- Enhance the response to catecholamines
- Necessary for normal hypoxic and hypercapnic drive to the respiratory centers
- Stimulate erythropoiesis
- Stimulate bone turnover

C. Hypothyroidism in the Dog
- Acquired primary hypothyroidism is most common cause (2 forms: lymphocytic thyroiditis, idiopathic atrophy)
- Common in middle age to older dogs. Golden Retrievers and Dobermans are most at risk

D. Clinical Signs of Canine Hypothyroidism
- 80% of the gland must be destroyed before clinical signs are evident
- Most consistent clinical signs are those due to decreased cellular metabolism and dermatologic manifestations
- Cardiovascular system
  - Can induce ECG and echo abnormalities. Rarely causes heart failure without preexisting heart condition
  - Hemodynamic effects caused by direct effect of thyroid hormone deficiency on myocardium
    - Decreased cardiac muscle myosin adenosine triphosphatase (ATPase) activity
    - Decreased sarcoplasmic reticulum calcium-ATPase activity
    - Decreased calcium channel activity
    - Decreased sodium-potassium ATPase activity
    - Reduced β-adrenergic receptors in the myocardium
- Neuromuscular system
  - Causal relationship between hypothyroidism, laryngeal paralysis, megaesophagus and myasthenia gravis has not been established
- Gastrointestinal and Reproductive system

E. Diagnosis and Treatment
- Recommendation for assessment of hypothyroidism in dogs: consider serum T4, fT4 and serum TSH
- Concurrent illness, drugs (especially glucocorticoids), and random fluctuations in thyroid hormone concentrations are most common factors resulting in lower baseline thyroid hormone concentrations in euthyroid dogs
- Initial treatment of choice is synthetic L-T4 sodium
- Severity of suppression of serum thyroid hormone concentrations can be used as a prognostic indicator
  - Lower serum thyroid hormone concentrations are associated with a higher mortality rate
Thyroid Gland and Regulation

• Functional unit of thyroid gland is the follicle, which contains a proteinaceous colloid called thyroglobulin (Tg)
  o Tg is a large glycoprotein dimer that serves as a reservoir for thyroid hormone
• Parafollicular cells (C cells) lie in the interstitium between the follicles
  o Synthesize and secrete calcitonin

*Hypothalamic production and release of TRH is controlled by poorly understood neural pathways from higher brain centers.

**FIGURE 3-5** Regulation of thyroid hormone concentration by the hypothalamo-pituitary-thyroid axis. Thyroid hormone concentrations are controlled by the hypothalamic-pituitary-thyroid axis, which operates as a negative feedback loop. Thyrotropin (TSH) causes synthesis and release of thyroxine (T4) and lesser amounts of 3,5,3'-triiodothyronine (T3) from the thyroid gland. Intracellular T3, derived from de-iodination of T4 within the pituitary gland, causes decreased TSH synthesis and secretion and is the main determinant of TSH concentration. Thyrotropin-releasing hormone (TRH), secreted by the hypothalamus, modulates TSH release from the pituitary gland. Increased thyroid hormone concentrations are also believed to decrease TRH synthesis and secretion. Hormones that inhibit TSH secretion include dopamine, somatostatin, serotonin, and glucocorticoids. TRH, prostaglandins, and alpha-adrenergic agonists increase TSH secretion. rT3, Reverse 3,3',5'-triiodothyronine; +, stimulation; —, inhibition.

**FIGURE 3-4** Structure of the thyroid hormones and their precursors.
• Thyroid hormones entrance into cells is mediated by transporter proteins
  o Thyroid hormones bind to receptors in nuclei
• Within the cell, fT4 is de-iodinated to form either T3 or rT3, depending on the metabolic demands of the tissues
• T3 is primary hormone that induces physiologic effects
  o Enters cells more rapidly
  o Has more rapid onset of action
  o 3-5x more potent than T4 (greater biologic activity)
• T3 is preferentially produced during normal metabolic states
• rT3, which is biologically inactive, is produced during periods of illness, starvation, or excessive endogenous catabolism

Physiologic Function of Thyroid Hormones
1. Stimulate calorigenesis
2. Stimulate protein and enzyme synthesis
3. Regulates every aspect of carbohydrate and lipid metabolism (synthesis, mobilization, degradation)
4. Have marked chronotropic and inotropic effects on the heart
5. Increase the number and affinity of beta-adrenergic receptors
6. Enhance the response to catecholamines
7. Necessary for normal hypoxic and hypercapnic drive to the respiratory centers
8. Stimulate erythropoiesis
9. Stimulate bone turnover

CANINE HYPOTHYROIDISM

Classification
• Acquired primary hypothyroidism is most common cause is the dog
  o Two histologic forms recognized in dogs: lymphocytic thyroiditis and idiopathic atrophy
• Common in middle age to older dogs
• Golden Retrievers and Dobermans are most at risk
Clinical Signs

- 80% of the gland must be destroyed before clinical signs are evident
- Most consistent clinical signs are those due to **decreased cellular metabolism** and **dermatologic manifestations**
- Additional clinical signs can affect:
  - Cardiovascular system
  - Neuromuscular system
  - Gastrointestinal system
  - Reproductive system

### BOX 3-1 Potential Causes of Hypothyroidism in the Dog

**Primary Hypothyroidism**
- Lymphocytic thyroiditis*
- Idiopathic atrophy*
- Neoplastic destruction*
- Iodine deficiency*
- Goitrogen ingestion
- Iatrogenic*
  - Surgical removal*
  - Anti-thyroid medications/potentiated sulfonamides*
  - Radioactive iodine treatment*

**Congenital**
- Thyroid gland dysgenesis*
- Dys hormonogenesis*
- Defective thyroid hormone transporters/receptors
- Iodine deficiency
- Maternal antibodies
- Maternal medications

**Secondary Hypothyroidism**
- Pituitary malformation*
- Pituitary cyst
  - Pituitary hypoplasia
  - Pituitary destruction*
- Neoplasia
- Defective TSH molecule
- Defective TSH-follicular cell receptor interaction
- Iatrogenic*
  - Drug therapy, most notably glucocorticoids
  - Radiation therapy
  - Hypophysectomy

**Tertiary Hypothyroidism**
- Congenital hypothalamic malformation
- Acquired destruction of hypothalamus
  - Neoplasia*
  - Hemorrhage
  - Abscess
  - Granuloma
  - Inflammation
- Deficient/defective TRH molecule
- Defective TRH-thyrotroph receptor interaction
### Dermatologic Signs
- Occur in 60-80% of hypothyroid dogs
- Most commonly observed abnormalities in dogs with hypothyroidism
- Bilaterally symmetric, nonpruritic truncal alopecia
  - Thyroid hormone is necessary to initiate and maintain the anagen phase (growing) of the hair cycle
  - With thyroid hormone deficiency hair follicles prematurely enter the telogen phase of the hair cycle
- Hyperpigmentation
- Myxedema or cutaneous mucinosis occurs in severe cases
  - Hyaluronic acid accumulates in the dermis, bind water, and results in increased thickness and non-pitting edema of the skin
  - Predominantly affects the forehead, eyelids, and lips (contributes to “tragic facial expression”)
- Depletion of thyroid hormone suppresses humoral immune reactions, impairs T cell function, and reduces the number of circulating lymphocytes
  - Predisposes to adult demodecosis and otitis externa

### Neurologic Signs
- Can affect both CNS and PNS
- Neurologic dysfunction may be multifocal, acute or chronic, and static or progressive
- Other physical examination findings consistent with hypothyroidism may be absent
- The reason for neurologic dysfunction is poorly understood and likely multifactorial
- Laryngeal paralysis, megaesophagus and myasthenia gravis may occur in association with hypothyroidism
  - Causal relationship has not been established
  - Treatment of hypothyroidism does not consistently result in improvement of clinical signs
Myxedema coma
- Extremely rare
- Characterized by profound weakness, hypothermia, bradycardia, and decreased consciousness (progress to stupor and then coma)

Cardiac abnormalities
- Usually reversible with supplementation
- Hypothyroidism can induce echocardiographic changes BUT rarely causes heart failure without underlying condition
- ECG abnormalities:
  - Sinus bradycardia
  - Decreased amplitude of the P and R waves
  - Inversion of the T waves
  - First-degree and second-degree atrioventricular block
- Echo abnormalities:
  - Increased left ventricular end systolic diameter
  - Prolonged preejection period
  - Decreases in left ventricular posterior wall thickness during systole
  - Percentage change in left ventricular posterior wall from diastole to systole
  - Interventricular wall thickness during systole and diastole
  - Aortic diameter
  - Velocity of circumferential fiber shortening
  - Fractional shortening
- Hemodynamic effects attributable to direct effects of hypothyroidism on the myocardium
  - Decreased cardiac muscle myosin adenosine triphosphatase (ATPase) activity
  - Decreased sarcoplasmic reticulum calcium-ATPase activity
  - Decreased calcium channel activity
  - Decreased sodium-potassium ATPase activity
  - Reduced β-adrenergic receptors in the myocardium

Ocular signs
- Rare in hypothyroid dogs
- Most commonly are secondary to hyperlipidemia

Gastrointestinal Signs
- Not common
- Megaesophagus
  - No cause and effect relationship
  - Likely result of hypothyroid induced myopathy or neuropathy

Coagulopathy
- Humans:
  - Reduction in concentration of factors VIII and IX
  - Reduction in factor VIII–related antigen (von Willebrand factor)
  - Reduced platelet adhesiveness
  - Increased capillary fragility
- No evidence noted in dogs

Diagnostics
CBC
- Normocytic, normochromic, nonregenerative anemia (packed cell volume [PCV], 28% to 36%)
  - In 30% of dogs
  - Cause unknown
Biochemistry
- Fasting hypercholesterolemia (75% of hypothyroid dogs) AND Fasting hypertriglyceridemia
  - Synthesis and degradation of lipids are depressed in hypothyroidism (degradation >> synthesis)
- Mild to moderate increase in LDH, AST, ALT, ALP
  - Associated with hypothyroid myopathy

Nuclear Imaging
- 99m-TcO4 is concentrated but not organified by the thyroid gland
  - Most commonly used isotope used for thyroid scintigraphy in veterinary medicine
  - Parotid salivary glands concentrate isotope too
  - A 1:1 thyroid-to-salivary ratio is considered normal in the dog,

Serology
- Total serum T4 concentrations represent the sum of the protein-bound and free levels circulating in the blood
- fT4 concentration is a measure of the free hormone only
- Recommendation for assessment of hypothyroidism in dogs:
  - Serum T4
  - fT4
  - Serum TSH
- Serum T3 concentration is a poor gauge of thyroid gland function because of its predominant intracellular location and the minimal amount of T3 secreted by the thyroid gland compared with T4
- Baseline serum T4 is best to RULE OUT hypothyroidism
  - Nonthyroidal illness can suppress the baseline serum T4 concentration to < 0.5 μg/dL in a euthyroid dog
  - Hypothyroid dogs rarely have serum T4 concentrations > 1.5 μg/dL
- Baseline serum T3 is not useful when differentiating euthyroidism from hypothyroidism
- Measurement of T3 may be justified in Greyhounds
  - Tend to have low concentrations of T4 and fT4 but normal T3 concentrations
Factors Affecting Thyroid Gland Function Tests

- Factors that affect baseline thyroid hormone and endogenous TSH concentrations
  - Age
  - Breed
  - Body size
  - Diurnal fluctuations

FIGURE 3-20 Algorithm for diagnosis of canine hypothyroidism.
Most common factors that result in lower baseline thyroid hormone concentrations in euthyroid dogs are concurrent illness, use of drugs (especially glucocorticoids), and random fluctuations in thyroid hormone concentrations.

Age
- Progressive decline in T4 with age
- Serum T4 highest in puppies
- Older dogs have higher mean TSH concentration than younger dogs
- Reasons for decline with age not fully understood. Proposed mechanisms:
  - Effect of concurrent illness
  - Change in responsiveness of the thyroid gland to TSH
  - Subclinical thyroid pathology (fibrosis, atrophy, degenerative changes)
  - Decreased biologic activity of TSH with age

Body size
- Mean serum T4 greater in small than in medium-sized and large dogs

Breed
- Sighthounds (see table 3-5)

Concurrent illness (Non-Thyroidal Illness Syndrome)
- Mechanisms:
  - Decreased TSH secretion
  - Decreased synthesis of T4
  - Decreased concentration or binding affinity of circulating binding proteins
  - Presence of serum protein binding inhibitors
  - Inhibition of the de-iodination of T4 to T3
  - Any combination of these factors
- Disorders that are frequently associated include:
  - Neoplasia
  - Renal disease
  - Hepatic disease
  - Cardiac failure
  - Neurologic disease
  - Inflammatory disorders
  - Diabetic ketoacidosis
  - Diabetes Mellitus
  - Addison’s
- Severity of suppression of serum thyroid hormone concentrations can be used as a prognostic indicator
  - Lower serum thyroid hormone concentrations are associated with a higher mortality rate
- Supplementation not recommended in NTIS as it is suspected to be a protective mechanism to reduce cellular metabolic demands

Drugs
- Glucocorticoids are the most commonly used drugs that influence serum thyroid hormone concentrations
  - Decreases serum T4, fT4, and T3 (often into the hypothyroid range)
- Sulfonamide antibiotics, anticonvulsants and NSAIDs can also affect thyroid hormone concentrations
### Table 3-12: Mechanisms by Which Drugs Influence Thyroid Function in Humans

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease TSH secretion</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>Change thyroid hormone secretion</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Decrease gastrointestinal absorption</td>
<td>Sucralfate</td>
</tr>
<tr>
<td>Alter serum binding</td>
<td>Phenylbutazone</td>
</tr>
<tr>
<td>Change hepatic metabolism</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Inhibit TPO</td>
<td>Sulfonamides</td>
</tr>
</tbody>
</table>

*TPO, Thyroid peroxidase; TSH, thyroid-stimulating hormone (also known as thyrotropin).

### Table 3-13: Drugs That Have Been Demonstrated to Influence Thyroid Function in Dogs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total Thyroxine (I or N)</th>
<th>Free Thyroxine (I or N)</th>
<th>Thyrotropin (+ or N)</th>
<th>Clinical Signs of Hypothyroidism? (Y/N)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoids</td>
<td>I</td>
<td>(I or N)</td>
<td>N</td>
<td>N</td>
<td>Effect dose and duration dependent</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>I</td>
<td>I</td>
<td>slight t</td>
<td>N</td>
<td>TSH not increased outside reference range</td>
</tr>
<tr>
<td>Trimethoprim/sulfonamides</td>
<td>I</td>
<td>I</td>
<td>t</td>
<td>Y</td>
<td>Effect dose and duration dependent</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Effect varies depending on specific drug used</td>
</tr>
<tr>
<td>Aspirin</td>
<td>I</td>
<td>N or I</td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Deracoxib</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Meloxicam</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Carprofen</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Etofibrate</td>
<td>N or I</td>
<td>N</td>
<td>N or T</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Clomipramine</td>
<td>I</td>
<td>I</td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
</tbody>
</table>

*TSH, Thyroid-stimulating hormone (also known as thyrotropin).

### Box 3-5: Proposed Alterations in Thyroid Hormone Physiology Caused by Glucocorticoids

- Decreased 5'-monodeiodination enzyme activity
- Decreased binding affinity of plasma proteins for T₄, T₃
- Decreased cellular binding of T₄, T₃
- Increased metabolic clearance rate of T₄
- Decreased metabolic clearance rate of T₃, rT₃
- Inhibition of TSH secretion (secondary hypothyroidism)
- Inhibition of TRH secretion

*T₃, Triiodothyronine; T₄, thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone (also known as thyrotropin).
**NSAIDs may decrease serum T₄, fT₄, T₃, and TSH concentrations. Proposed mechanisms include:**

- Displacement of thyroid hormone binding to plasma proteins
- Decreased thyroid hormone de-iodination
- Inhibition of binding of thyroid hormone to receptors in the plasma membrane, cytoplasm, and nucleus

**Treatment**

- Initial treatment of choice is synthetic L-T₄ sodium
- The dose in dogs is 10x higher than the dose used in humans
  - Because of poorer gastrointestinal absorption and a shorter serum half-life of T₄ in dogs
FIGURE 3-33 Algorithm for treatment of canine hypothyroidism.

TABLE 3-14 ANTICIPATED TIME OF CLINICAL RESPONSE TO SODIUM LEVOTHYROXINE TREATMENT IN DOGS WITH HYPOTHYROIDISM

<table>
<thead>
<tr>
<th>AREA OF IMPROVEMENT</th>
<th>TIME TO IMPROVEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mentation and activity</td>
<td>2 to 7 days</td>
</tr>
<tr>
<td>Lipemia and clinical pathology</td>
<td>2 to 4 weeks</td>
</tr>
<tr>
<td>Dermatologic abnormalities</td>
<td>2 to 4 months</td>
</tr>
<tr>
<td>Neurologic abnormalities</td>
<td>1 to 3 months</td>
</tr>
<tr>
<td>Cardiac abnormalities</td>
<td>1 to 2 months</td>
</tr>
<tr>
<td>Reproductive abnormalities</td>
<td>3 to 10 months</td>
</tr>
</tbody>
</table>
Treatment of myxedema coma

- IV thyroid hormone as absorption of therapeutic agents from the gut or from SQ/IM sites is unpredictable
  - Because of the sluggish circulation and severe hypometabolism
  - Recommended initial dosage for injectable L-T4 sodium: 4 to 5 μg/kg q 12 hours
- Correct electrolyte abnormalities and supplement with dextrose

Thyrotoxicosis

- Rare
- May develop in dogs receiving excessive amounts of L-T4 sodium (iatrogenic hyperthyroidism)
- May develop in dogs with impaired metabolism of L-T4 sodium (e.g., concurrent renal or hepatic insufficiency)
- Clinical signs of thyrotoxicosis:
  - Panting
  - Nervousness
  - Anxiety
  - Tachycardia
  - Aggressive behavior
  - Polyuria
  - Polydipsia
  - Polyphagia
  - Weight loss
    - Sinus tachycardia, atrial flutter, syncope (iatrogenic hyperthyroidism dogs with concurrent cardiac disease)
- Supplementation may have to be discontinued for a few days if the clinical signs are severe
  - Signs of thyrotoxicosis should resolve within 1 to 3 days if iatrogenic

FELINE HYPOTHYROIDISM

- Rare naturally occurring disease in the cat
- Iatrogenic hypothyroidism is common

Questions

1. What % of the thyroid gland must be destroyed before clinical signs of hypothyroidism are evident?
   a. 60%
   b. 50%
   c. 70%
   d. 80%
2. Clinical signs related to which organ system is most common in dogs affected by hypothyroidism
   a. Neurologic system
   b. Dermatologic system
   c. Cardiovascular system
   d. Gastrointestinal system

3. True or False. Treatment of hypothyroidism can result in improvement in signs of laryngeal paralysis, megaesophagus and myasthenia gravis.

   False. Causal relationship has not been established
   Treatment of hypothyroidism does not consistently result in improvement of clinical signs

4. Name 4 clinical signs or physical exam abnormalities identified in dogs with myxedema coma.

5. Why is serum T3 concentration NOT recommended for assessment of thyroid gland function? (Provide 2 reasons)

6. Which combination represents the most common factors that cause lower baseline thyroid hormone concentrations in euthyroid dogs?
   a. Concurrent illness, drugs, random fluctuations
   b. Diurnal fluctuations, concurrent illness, age
   c. Age, drugs, random fluctuations
   d. Age, breed, gender

7. True or False. Severity of suppression of serum thyroid hormone concentrations can be used as a prognostic indicator.

8. Name 2 direct effects of hypothyroidism on the myocardium that can cause altered hemodynamic effects.

9. Bonus. Why is the dosage of L-T4 sodium in dogs so much higher than that used for treatment of human hypothyroidism?

**Answers**

1. What % of the thyroid gland must be destroyed before clinical signs of hypothyroidism are evident?
   a. 60%
   b. 50%
   c. 70%
   d. 80%

2. Clinical signs related to which organ system is most common in dogs affected by hypothyroidism
   a. Neurologic system
   b. **Dermatologic system**
   c. Cardiovascular system
   d. Gastrointestinal system

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   Treatment of hypothyroidism does not consistently result in improvement of clinical signs

4. Name 4 clinical signs or physical exam abnormalities identified in dogs with myxedema coma.
Characterized by profound weakness, hypothermia, bradycardia, and decreased consciousness (progress to stupor and then coma)

5. Why is serum T3 concentration NOT recommended for assessment of thyroid gland function? (Give 2 reasons)
   a. Because of its predominant intracellular location
   b. Due to minimal amount of T3 secreted by the thyroid gland compared with T4

6. Which combination represents the most common factors that cause lower baseline thyroid hormone concentrations in euthyroid dogs?
   a. Concurrent illness, drugs, random fluctuations
   b. Diurnal fluctuations, concurrent illness, age
   c. Age, drugs, random fluctuations
   d. Age, breed, gender

7. True or False. Severity of suppression of serum thyroid hormone concentrations can be used as a prognostic indicator.
   True. Lower serum thyroid hormone concentrations are associated with a higher mortality rate

8. Name 2 direct effects of hypothyroidism on the myocardium that can cause altered hemodynamic effects.
   Hemodynamic effects caused by direct effect of thyroid hormone deficiency on myocardium
   a. Decreased cardiac muscle myosin adenosine triphosphatase (ATPase) activity
   b. Decreased sarcoplasmic reticulum calcium-ATPase activity
   c. Decreased calcium channel activity
   d. Decreased sodium-potassium ATPase activity
   e. Reduced β-adrenergic receptors in the myocardium

9. Bonus. Why is the dosage of L-T4 sodium in dogs so much higher than that used for treatment of human hypothyroidism?
   Because of poorer gastrointestinal absorption and a shorter serum half-life of T4 in dogs