Hypothyroidism in dogs

Hypothyroidism is a commonly occurring endocrinopathy of dogs. Correct diagnosis represents a challenge in some patients, because the disease can develop gradually over years and the clinical specificity varies a great deal. Moreover, all available laboratory diagnostic tests have their limitations. In particular, other illnesses and the administration of medications can influence the outcome of tests, so that their correct interpretation can be difficult. By itself, evidence of a lowered total T₄ concentration (TT₄) is not sufficient to make the diagnosis of hypothyroidism.

Etiology

We can differentiate 3 forms of acquired hypothyroidism, depending on the localization of the defect within the hypothalamus-hypophysis-thyroid gland axis.

Primary hypothyroidism

More than 95% of acquired hypothyroidism cases in dogs are traced back to reduced thyroid hormone synthesis and release in the thyroid gland. In most cases the cause of this is a lymphocytic thyroiditis (about 50%) (Graham et al. 2007) or an idiopathic atrophy.

In lymphocytic thyroiditis there is an immune-mediated inflammation of the thyroid gland and thyroglobulin antibodies (Tg-Ab), and in some cases antibodies against T₃ and T₄ can be detected. The inflammation-conditioned progressive destruction of thyroid gland follicles is a long-term process, and clinical signs become obvious only when more than 75% have been destroyed.

In idiopathic atrophy, there is replacement of functional thyroid gland tissue by connective tissue, and Tg-Ab are no longer detectable. Other, rare causes are neoplasias and adenomatous hyperplasia.

Starting from the assumption that idiopathic atrophy represents the final stage of lymphocytic thyroiditis, 4 different stages can be distinguished on the path of development of atrophic hypothyroidism (Graham et al. 2007):

1. Sub-clinical thyroiditis
   - No clinical symptoms
   - Tg-Ab positive, TT₄ in the reference range,
   - TSH < 0.5 ng/mL

2. Sub-clinical hypothyroidism
   - No clinical signs
   - about 60 – 70% of the thyroid gland destroyed
   - Tg-Ab positive, TT₄ in the reference range, TSH elevated

3. Antibody-positive hypothyroidism
   - Clinical signs
   - about 75% of the thyroid gland destroyed
   - Tg-Ab detectable, TT₄ reduced, TSH elevated

4. Non-inflammatory atrophic hypothyroidism
   - Clear clinical signs. Thyroid gland tissue replaced by fatty and connective tissue. Tg-Ab no longer detectable, TT₄ decreased, TSH elevated

Secondary hypothyroidism (reduced release of TSH from the hypophysis) is a very rare cause of hypothyroidism (< 5%). Causes described include a hypophysis hypoplasia with hypophyseal dwarfism, trauma, neoplasia or cystic changes (Scott-Moncrieff 2015). Diagnosis is quite difficult, because the diagnostic sensitivity of the currently available TSH assay is not sufficient to differentiate between physiological and low TSH concentration. In this respect it can't be excluded that the frequency of secondary hypothyroidism may be still higher (Scott-Moncrieff 2015).
Tertiary hypothyroidism (reduced release of TRH from the hypothalamus) has up to now been described only once as a case report (Shiel et al. 2007) in the literature. Congenital hypothyroidism is considered rare in dogs, although it is possible that the actual incidence is underestimated, since it rarely leads to premature death of affected puppies. (Scott-Moncrieff 2015).

**Regulation**

Synthesis and release of thyroid hormone is subject to control by TSH from the hypophysis anterior lobes (adenohypophysis), which is controlled in turn by the release of TRH from the hypothalamus.

Under the influence of TSH there is an increased release of T\(_3\) and T\(_4\) from the thyroid gland. T\(_3\) is synthesized exclusively in the thyroid gland, about 80% of T\(_4\) originates in the periphery through deiodination in the target cells.

Thyroid hormone is bound to plasma proteins in the circulation. Only a very small portion (about 1%) is unbound and represents the metabolically active fraction of thyroid hormone, the free T\(_3\) (fT\(_3\)) and free T\(_4\) (fT\(_4\)).

fT\(_3\) and fT\(_4\) are solely responsible for the negative feedback to the hypophysis and hypothalamus. If the concentration of free thyroid hormone in the circulation drops, a lapse in the negative feedback leads to an increased synthesis of TSH in the hypophysis.

**Clinical**

Hypothyroidism is a disease of middle-aged to old dogs, but clinical signs can appear earlier in predisposed breeds. Gender or castration has no influence on the appearance of the disease. The disease primarily affects middle-sized to large dogs. Golden and Labrador Retrievers and Dobermans are listed in Anglo-American professional literature as predisposed breeds (Scott-Moncrieff 2015). However a breed predisposition could not be identified in the patient population at the University of Zürich (Boretti et al. 2003).

The clinical signs of hypothyroidism are multifarious and reflect both the manifold effects of the thyroid hormone on total metabolism, and its influence on many organ systems.

The primary signs are metabolic changes (lethargy, weight gain, exercise intolerance), some 80% of patients also exhibit dermatological changes (altered coat structure or color, alopecia, hypertrichosis, seborrhea, Otitis externa).

Due to the long-term progression of the disease, the changes are frequently not detected early by the owner of the patient, and are attributed to the ageing process. In isolated cases neurological symptoms may also appear, which have been described both alone and co-existing with other symptoms of hypothyroidism (Cizinauskas et al. 2000).

The periphery can be affected (peripheral neuropathy as paresis or paralysis, peripheral vestibular syndrome, facial paresis, mega-esophagus) or the central nervous system as well (myxedema coma, epileptic seizures). Currently the direct causal connection between peripheral neuropathy and
hypothyroidism is being critically discussed, since a peripheral neuropathy could not be reproduced in an experimental model for hypothyroidism (Rossmeisl 2010).

On the other hand, cases have been described in the literature in which the neurological deficits disappeared again after administration of T₄ (Scott-Moncrieff 2015).

By contrast, a sub-clinical myopathy has been documented many times in dogs with hypothyroidism, and is evidenced by an elevated CK, elevated AST and LDH. This presumably contributes to the hypothyroid dog’s exercise intolerance. Gastrointestinal, cardiac and ocular signs are more rarely seen. Fertility dysfunction has been described in female dogs in connection with hypothyroidism (Panciera et al. 2012).

**Diagnosis**

**Changes in haematology and clinical chemistry in hypothyroid dogs**

The most common change is a pronounced hypercholesterolemia and hypertriglyceridemia in fasted patients (Boretti et al. 2003, Mooney et al. 2012). When fructosamine is co-determined, a concentration in the upper reference ranges is frequently seen, or even above it with concomitant euglycemia. The cause of this is the slower metabolization of fructosamine in hypothyroid patients (Reusch et al. 2002).

About 50 – 70% of hypothyroid dogs exhibit a mild, at most moderate, non-regenerative anemia. Leptocytes can frequently be detected in the smear (Panciera 2001).

- **Triglycerides**  
  - (50 – 88%)
- **Cholesterol**  
  - (70 – 80%)
- **Fructosamine**  
  - (0 – 70%)
- **mild, non-regenerative anemia**  
  - (50 – 70%)
- **CK**  
  - (30 – 35%)
- **Liver enzymes**  
  - (0 – 30%)


**Thyroid function test**

**Before determination of the thyroid hormone and cTSH levels, it is essential:**
- that non-thyroid illnesses (NTI) be ruled out, and
- that a careful pharmaceutical medical history be collected, because many medications influence the concentrations of thyroid hormone and TSH directly.

In particular, the use of sulfonamides can lead to a clinical and laboratory diagnostic picture supportive of hypothyroidism. It has been possible to show in animal experiments (Williamson et al. 2002), that sulfonamides inhibit thyroid peroxidase, and thus actually lead to a reduced thyroid hormone synthesis, with resulting reduction in total T₄ concentration and, in compensation, an increased synthesis and release of TSH.

**Total T₄ (TT₄), Factors influencing baseline TT₄, fT₄ and TSH concentration**


<table>
<thead>
<tr>
<th>Factor</th>
<th>Influence on TT₄</th>
<th>Influence on fT₄</th>
<th>Influence on TSH</th>
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<tbody>
<tr>
<td>Age: &lt; 3 months/6 years</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight: &lt; 10 kg/30 kg</td>
<td>↑</td>
<td></td>
<td>Φ Φ</td>
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<tr>
<td>Breed: (e.g. Greyhound)</td>
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<td>Obesity</td>
<td></td>
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<tr>
<td>Fasting</td>
<td>↓</td>
<td>= or ↓</td>
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<tr>
<td>Great physical exertion</td>
<td>↑</td>
<td>=</td>
<td>↓</td>
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<tr>
<td>Pregnancy (progesterone)</td>
<td>↑</td>
<td></td>
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<tr>
<td>Carprofen</td>
<td>↓</td>
<td>= or ↓</td>
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<td>Aspirin</td>
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<td>Glucocorticoids</td>
<td>↓</td>
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<td>Furosemide</td>
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<td>Methimazole</td>
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<td>↑</td>
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<tr>
<td>Phenobarbital</td>
<td>= or ↓</td>
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<td>= or ↑</td>
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<tr>
<td>Phenyl butazone</td>
<td>↓</td>
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<tr>
<td>Sulfonamides</td>
<td>↓</td>
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<td>↑</td>
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<tr>
<td>Iodine supplementation</td>
<td>↓</td>
<td></td>
<td>↑</td>
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<tr>
<td>T₄ auto-antibodies</td>
<td>↑ or ↓ depending on the assay used</td>
<td>vFT₄ (immunoassay); ↑ fT₄ (dialysis-procedure); uninfluenced</td>
<td>Only if simultaneously hypothyroid</td>
</tr>
</tbody>
</table>

Total T₄ (TT₄) is composed of a free (fT₄) and a protein-bound portion. In measuring TT₄, both parts are recorded. Endogenous T₄ is, unlike T₃, formed exclusively in the thyroid gland and is thus a very reasonable parameter for use in ruling out hypothyroidism, since very few dogs with hypothyroidism exhibit TT₄ concentrations within the reference range (high sensitivity) (Scott-Moncrieff 2015). Values below the reference range do not confirm hypothyroidism (low specificity), because a large number of other causes, such as natural fluctuation, a drop resulting from age, breed-dependency, almost every other disease, and many medications can lead to low T₄ concentrations.
Even topical administration of glucocorticoids can cause a short-term drop in TT4 concentration (Gottschalk et al. 2011). If TT4- auto-antibodies are present, assay interferences dependent upon test methods can cause falsely elevated or falsely decreased TT4 values. Elevated values can, in individual cases result in failure to recognize hypothyroidism, as due to assay interference TT4 levels are measured within the reference range or above it. Fortunately, T4 auto antibodies appear distinctly more rarely (8%) than T4 auto-antibodies (28%) in hypothyroid dogs (Graham et al. 2007). In addition, it appears that in spite of the theoretically possible interference, actual clinically relevant influence on the measured T4 concentration is rare (Pichotta et al. 2010).

If a high TT4 is measured in a dog which exhibits no clinical signs of hypothyroidism, a nutritional medical history should be urgently advised. It is common for raw food from slaughterhouse waste with gullet to cause an increase of the TT4 concentration (Köhler et al. 2012). Fortunately, T4 auto-antibodies are present distinctly more rarely (8%) than T4 auto-antibodies (28%) in hypothyroid dogs (Graham et al. 2007). In addition, it appears that in spite of the theoretically possible interference, actual clinically relevant influence on the measured T4 concentration is rare (Pichotta et al. 2010).

**Free T4**
Free T4 (fT4) is the non-protein-bound, metabolically active form of T4, and is responsible for the negative feedback on release of TSH from the hypophysis. Because fT4 represents the biologically active form of T4, great hope has been placed in the diagnostic value of analysis of fT4. However, it has been shown that even the concentration of free T4 (fT4) is influenced by administration of medication and by non-thyroid illnesses, if not to the same degree as TT4.

**Analogue procedures (immunological assays)**
Here it has been shown that the veterinary fT4 assay used by IDEXX Laboratories compares very well to the fT4 results calculated by means of dialysis procedures (Scott-Moncrieff 2014). Only in the presence of T4 auto-antibodies are the dialysis procedures superior for veterinary fT4, because there is no assay interference in the case of dialysis. Other analogous assays from human medicine are, in principle, not recommended (Scott-Moncrieff 2014).

**Dialysis procedure**
Analysis of fT4 by the dialysis procedure is to be recommended in patients with suspicion of the presence of T4 auto-antibodies, because only this test procedure is able to establish a correct result for fT4 concentration in these circumstances (Scott-Moncrieff 2014).

**cTSH**
Reduced circulating thyroid hormone leads, by nullifying the negative feedback mechanism, to increased secretion of TSH from the hypophysis.

With a supporting preliminary report and consistent clinical signs, the combined appearance of a lowered TT4 and an elevated TSH is, in many cases, entirely sufficient to make the diagnosis of hypothyroidism.

But unfortunately, some 30% of hypothyroid dogs exhibit no elevation in TSH (Scott-Moncrieff 2014). It is currently being debated whether the occurrence of a secondary hypothyroidism, and thus a reduced synthesis and secretion of TSH, is underestimated (Scott-Moncrieff 2015). There is further speculation that not all isomers of TSH are recorded by the highly specific TSH assay (Boretti et al. 2015). Even fluctuations in TSH secretion, exhaustion of the hypothysis in long-term hypothyroidism (Diaz-Espineira et al. 2008) or a hypophysial myxedema are discussed as possible causes (D. C Ferguson 2007).

On the other hand, the TSH can also be elevated without clinically relevant hypothyroidism being present. This happens in the phase of convalescence from a non-thyroid illness, with sub-clinical hypothyroidism (TT4, fT4 D in the reference range, TSH elevated) and after administration of several medications, particularly of sulfonamides or trilostane (Williamson et al. 2002, Boretti et al. 2015).

**T3**
T3 is formed only to a small extent in the thyroid gland itself; the larger portion originates through deiodination from T4 in the target cells. With reduced T4 production there is frequently, by way of compensation, an augmented conversion of T4 into T3 (hormonally active form, faster acting), so that T3 concentrations in the hypothyroid dog are frequently calculated within the reference range. Therefore the T3-measurement is less meaningful for diagnosis of hypothyroidism.

**Thyroglobulin antibodies (Tg-Ab)**
Thyroglobulin AB are frequently detected as a consequence of lymphocytic thyroiditis. They are not suitable as evidence of a thyroid function defect, because they can be present in euthyroid dogs. Likewise they are often not detectable in end-stage thyroiditis or in cases of idiopathic atrophy of the thyroid gland. The absence of Tg-Ab does not exclude hypothyroidism, equally the presence of Tg-Ab does not necessarily imply hypothyroidism. Graham et al 2007 demonstrated that around 20% of dogs that were Tg-Ab positive developed hypothyroidism in the course of one year, but at the same time about 15% of the dogs became Tg-Ab negative again during this period (Graham et al. 2007).

Elevated concentrations of thyroglobulin-AB can be consistent with an early stage of a lymphocytic thyroiditis. Moreover it has been possible to show that dogs with T4 auto-antibodies simultaneously exhibit Tg-Ab in 95% of cases (Graham et al. 2007).
Their additional determination can contribute to clarifying the etiology or, as a “second line test,” strengthen the diagnosis of hypothyroidism. False positive results are possible, especially shortly after vaccinations and after a viral infection.

**TSH stimulation test**
The TSH stimulation test is based on the fact that by administering a supraphysiological dose of TSH, a maximal stimulation of the thyroid gland is achieved and thus the reserve capacity can be assessed. Since TSH is no longer available in medicinal product quality, recombinant human TSH has to be used. The Zürich Working Group (Boretti et al. 2009) were able to show that by using a distinctly higher dose (150 µg/dog) than previously described, it was possible to differentiate accurately between actual hypothyroidism and an NTI in many more patients.

**Test procedure:**
- Blood sample and analysis of the baseline concentration of T4
- Application (im or iv) of 150 µg rh TSH
- Blood sample 6 h later and analysis of the T4 concentration

**Interpretation:**
- post-TSH T4:
  - <19.3 nmol/L (1.5 µg/dL) indicates hypothyroidism
  - >32.2 nmol/L (2.5 µg/dL) and at least 1.5 times increase of the baseline value indicates an adequate stimulation.

**Treatment**
For treatment of hypothyroidism, synthetic L-thyroxine is administered orally daily; the dosage information varies among manufacturers between 10 – 20 µg/kg one to two times a day. In the Consensus Statement of 1996 an initial dosage of L-thyroxine at 20 µg/kg twice a day is recommended. The bioavailability varies greatly among individuals and is stated at 10% – 50% and depends on the time of feeding. Therefore the tablet should always be given as closely as possible before or after eating (Scott-Moncrieff 2014). The maximal initial dose is 800µg/dog. Patients with heart disease or concurrent kidney or liver disease, the initial dose should be reduced to half or one-quarter of the manufacturers recommendations and then successively increased as required (Scott-Moncrieff 2015).

**Monitoring treatment**
The first check is done 4 – 8 weeks after the start of treatment, on the basis of clinical signs and the TT4 concentration in the blood. After this period, an improved exercise tolerance and a normalization of the altered laboratory parameters of the clinical chemistry are to be expected in nearly all patients (Scott-Moncrieff 2015).

To test the L-thyroxine dose, a blood sample is taken 4 – 6 hours after administering the tablet, and TT4 is analysed. The target is a TT4 concentration in the upper part of the reference range or slightly above it. (Scott-Moncrieff 2015). This is a target value; the final adjustment is done on an individualized basis and takes into account the clinical success of the treatment, as well as individual circumstances such as, concurrent diseases or administration of additional medications (Scott-Moncrieff 2014).

If TSH was also elevated at the time the diagnosis was made, the parallel analysis of TSH also makes sense. With adequate supplementation it is expected that the TSH concentration will normalize again. However, since the diagnostic sensitivity of the TSH assay unfortunately does not allow correct measurement of very low TSH concentrations, reviewing the TSH concentration cannot detect an over supplementation. If L-thyroxine is applied only once daily, the blood sample to analyze TT4 and TSH is taken immediately before the next tablet is administered. Here the goal is a TT4 concentration in the reference range (Scott-Moncrieff 2015). If a dosage adjustment is required, the next treatment check-up is done after 4 – 8 weeks.

If the patient exhibits T4 auto-antibodies, assay interference has made it necessary to monitor the treatment by means of fT4 in the dialysis procedure.

If the diagnosis of hypothyroidism is correct, nearly all clinical signs are reversible under adequate treatment. Increased physical activity and changed behavior can already be identified in the first weeks.

The normalization of changed laboratory parameters (e.g., hypercholesterolemia) can be expected after 2 – 4 weeks. On the other hand, improvement of dermatological and neurological changes frequently takes 3 – 4 months (Scott-Moncrieff 2015).

If a complex of symptoms persists even after a sufficient period of treatment, the diagnosis of hypothyroidism must be critically questioned.

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Exclusion of other illnesses
(no evidence from haematology, clinical chemistry and urinalysis)
Wherever possible the animal should not have received any medication in the last 4-6 weeks

Measurement of TT₄

- TT₄ < 1,0 µg/dL 
  (<13,0 nmol/L)
- TT₄ 1,0 - 2,0 µg/dL 
  (<13,0 - 26,0 nmol/L)
- TT₄ 2,0 - 4,0 µg/dL 
  (26,0 - 51,0 nmol/L)
- TT₄ > 4,0 µg/dL 
  (>51 nmol/L)*

Very probable
Euthyroid

Measurement of cTSH (+vfT₄)

(vfT₄ ↓ +) cTSH ↑
Hypothyroidism very possible

(vfT₄ ↓ +) cTSH normal
Hyothyroid

(vfT₄ ↑ +) cTSH ↑
TSH stimulation test
or “diagnostic” treatment
with clear clinical indication

↓
hypothyroid

↓
euthyroid

With presence of TT₄ auto-antibodies, assay interference possible
False high TT₄ value with measurement of TT₄ on the Catalyst or Snap-Shot
False low value in the IDEXX Laboratory test

List of References:
Scott-Moncrieff JC: Canine Hypothyroidism. In: Bonagura JD & Twedt, DC (eds), Kirk’s Current Veterinary Therapy XV (2014)