

Hyperadrenocorticism



The challenge of interpreting test results

LABOKLIN GmbH & Co. KG, Bad Kissinger, Germany

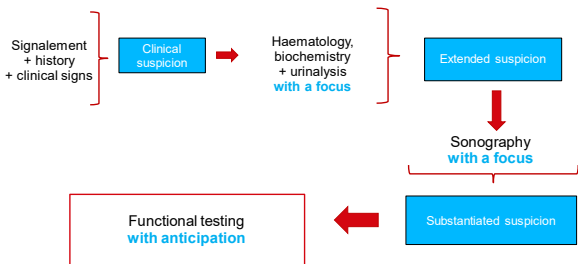
Dr Jennifer von Luckner

Hugo – Dachshund, mn, 11 years, 13 kg

- Hyperadrenocorticism was diagnosed
 - Clinical signs
 - Is drinking a lot
 - Is eating a lot
 - Bacterial pyoderma
 - Recurrent episodes of abdominal pain
 - Lethargy
 - LDDT positive
 - Ultrasonography
 - Inhomogenous liver with hypochoic lesions
 - Adrenal glands relatively large (0.8 cm) + rounded
- Vetoryl 30 mg SID (2.3 mg/kg)
- Clinical signs did not change



When searching for hyperadrenocorticism...

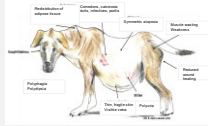


When searching for hyperadrenocorticism: **Signalement + History**

- Signalement
 - Elderly to older dog
 - Predisposed: Dachshund, Poodle, Terrier breeds, Schnauzer, Boxer
- Clinical signs
 - PU/PD
 - Polyphagia
 - Weight gain
 - Lethargy
 - Exercise intolerance
 - Panting
 - No heat
 - Changes of fur

When searching for hyperadrenocorticism: **clinical exam**

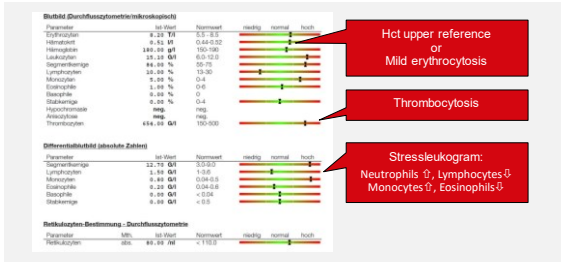
- Redistribution of adipose tissue: large belly + skinny legs
 - Typical love handles cranially to the hips
- Muscle wasting: large belly + skinny legs
 - Reduced temporal muscles
 - Vertebral column visible despite obesitas
 - Gluteal muscles decreased in size
- Muscle weakness: large belly + superficial breathing
- Skin
 - Thin skin/ visible veins
 - Flank alopecia
 - Comedones
 - Calcinosis cutis



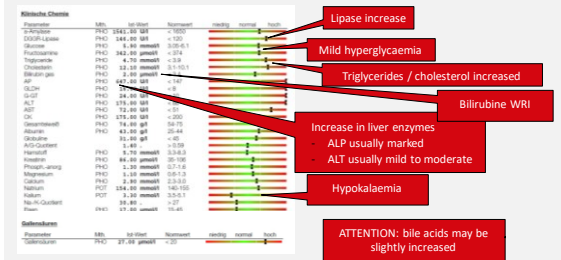
When searching for hyperadrenocorticism: **clinical exam**



When searching for hyperadrenocorticism: **Haematology**



When searching for hyperadrenocorticism: **biochemistry**



When searching for hyperadrenocorticism: **urinalysis**

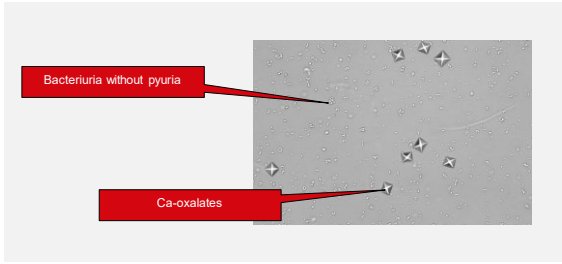
Low USG
Often isosthenuria (1008-1012/1015)
oder hyposthenuria (< 1008)

Urine specific gravity (REF)	1006	1016-1040
Protein (PHO)	++	negative
pH (PHO)	7.0	5.0-6.5
Bilirubin (PHO)	negative	negative
Urobilinogen (PHO)	negative	negative
Glucose (PHO)	negative	negative
Ketones (PHO)	negative	negative

Proteinuria

Protein urine (PHO)	210	mg/dl	< 100
Creatinine urine (PHO)	130	mg/dl	>
Index	1.6		< 0.2

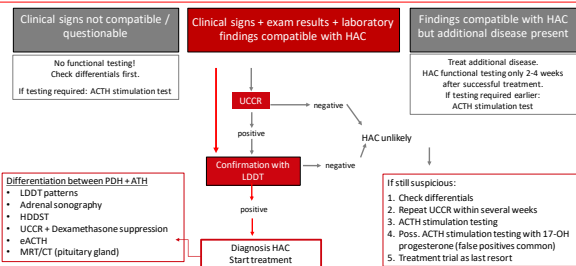
When searching for hyperadrenocorticism: **urinalysis**



When searching for hyperadrenocorticism: **sonography**

<ul style="list-style-type: none"> ○ Adrenal glands <ul style="list-style-type: none"> ▪ Enlarged, rounded ▪ Hypoechoic ○ Liver <ul style="list-style-type: none"> ▪ Enlarged, rounded ▪ Hyperechoic, may find hypoechoic lesions ○ Gallbladder <ul style="list-style-type: none"> ▪ Irregularities of the gallbladder wall ▪ Increased amount of sludge 	<ul style="list-style-type: none"> ○ Spleen + Kidney <ul style="list-style-type: none"> ▪ Miliar parenchymal mineralisations ▪ Precipitates within the pyelon ○ Pancreas <ul style="list-style-type: none"> ▪ Prominent, reduced echogenicity ▪ Surroundings slightly hyperechoic ○ Urinary bladder <ul style="list-style-type: none"> ▪ Irregular mucosal surface
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When searching for hyperadrenocorticism: **functional testing**



Back to Hugo – Dachshund, mn, 11 years, 13 kg

Hyperadrenocorticism was diagnosed

Clinical signs

- Is drinking a lot
- Is eating a lot
- Bacterial pyoderma
- Recurrent episodes of abdominal pain
- Lethargy

Signalement

- Elderly to old
- Predisposed breed

Clinical signs

- PU/PD
- Polyphagia
- Weightgain
- Exercise intolerance
- Lethargy
- Panting
- Anoestrus cycles
- Coat changes

Clinical exam

- Adipositas (rump)
- „Love handles“
- Reduced muscle mass
- Thin skin
- Alopecia
- Calcinosis cutis

HUGO

Parameter		Reference
Haematokrit %	38	44-55
Erythrocytes x10 ⁷ /µl	6.5	7 - 13
Haemoglobin g/dl	12.9	14.0-16.0
Eosinocytes x10 ³ /µl	8.0	6 - 12
Monocytes x10 ³ /µl	725	50-500
Lymphocytes x10 ³ /µl	1.450	1.000-4.000
Neutrophiles x10 ³ /µl	5.550	3.000-11.000
Eosinophiles x10 ³ /µl	75	40-500
Thrombocytes x10 ³ /µl	345	150-500

Haematology

- Hct upper reference/increased
- Stress leukogram
- Thrombocytosis

HUGO

ALT	: 293 UI	[< 90]
AST	: 56 UI	[< 44]
ALP	: 94 UI	[< 98]
GGT	: 3 UI	[< 7]
Bilirubin	: 0.4 µmol/l	[< 0.5]
Cholesterol:	3.26 mmol/l	[3.2 - 7.0]
BUN	: 7.33 mmol/l	[3.2 - 8.2]
Creatinine	: 68 µmol/l	[< 106]
Total protein	: 76 g/l	[55 - 76]
Albumin	: 38 g/l	[28 - 56]
Glucose	: 4.94 mmol/l	[bis 6.7]
K	: 4.2 mmol/l	[3.8 - 5.1]
Na	: 148 mmol/l	[148 - 156]
TCa	: 11.2 mg/dl	[10.8 - 12.8]

Biochemistry

- Increased liver enzymes (ALP)
- Triglycerides/cholesterol high
- Lipase increased
- Hypokalaemia
- Hyperglycaemia

HUGO

Urinalysis

USG 1043

pH 7

Trace protein

Sediment: erythrocytes 2/hpf (-6/hpf), Leukocytes 0/hpf (-6/hpf)

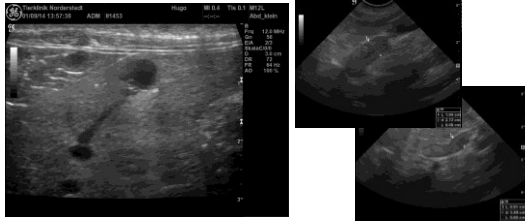
Urinalysis

- Low USG
- Proteinuria

HUGO

Ultrasonography

- Inhomogenous liver with hypochoic lesions
- Adrenal glands relatively large (0.8 cm) + rounded



HUGO

Ultrasonography

- Inhomogenous liver with hypochoic lesions
- Adrenal glands relatively large (0.8 cm) + rounded

Adrenal glands
 Enlarged + rounded
 Hypoechoic

Liver
 Enlarged + rounded
 Hyperechoic
 Maybe hypochoic lesions

Kidney + spleen
 Miliar parenchymal mineralisations
 Precipitates within pyelon

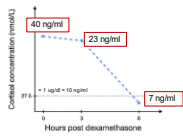
Pancreas
 Prominent/reduced echogenicity
 Surrounding mildly hyperechoic

Gallenbladder
 Irregularities of the wall
 Increased amount of sludge

Urinary bladder
 Irregularities of mucosal surface

Dexamethason-Screening-Test - CLA

Parameter	Mth.	Ist-Wert	Normwert	niedrig	normal	hoch
Cort. Basal	LIA	40,00 ng/ml	5-65			
Cort. Supp.	LIA	23,00 ng/ml	< 10			
Cort. 2.Supp	LIA	7,00 ng/ml	< 10			



UCCR (urinary cortisol/creatinine-ratio)

Cortisol/Kreatinin-Bestimmung im Harn - CLA/photometrisch

Tag 1

Parameter	Mth.	Ist-Wert
Cort. Tag 1	LIA	203,10 nmol/l
Krea. Tag 1	PHO	6117,00 µmol/l
Quotient	Tag1	34,17

Tag 2

Parameter	Mth.	Ist-Wert
Cort. Tag 2	LIA	243,00 nmol/l
Krea. Tag 2	PHO	7113,00 µmol/l
Quotient	Tag2	34,16

< 40: Normadrenocortizismus, ein M. Cushing ist unwahrscheinlich.
40 - 60: Fragliches Ergebnis
> 60: Hyperadrenocortizismus ist möglich und sollte durch einen Dexamethason-Low-Dose-Test bestätigt werden.

The case – the test

ACTH-Stimulationstest

Parameter	Mth.	Ist-Wert	Normwert	niedrig	normal	hoch
Cort. Basal	LIA	40,00 ng/ml	5-65			
Cort. Stim.	LIA	137,00 ng/ml	< 190			

Interpretation

M. Cushing:
typische Stimulationswerte liegen über 150 ng/ml. Chronischer Stress, andere Grunderkrankungen (z.B. D.M.) können ebenfalls zu einer abnormen ACTH-Antwort führen. Wahrscheinlich: Stimulationswerte >217 ng/ml (BDAVA Centre and Future Endocrinology, 2012)

Beachte:
ca. 15% mit Hypophysienem und ca. 40% mit adrenalem M. Cushing zeigen einen normalen, also keinen auffällig erhöhten Anstieg (W.A.Koel).

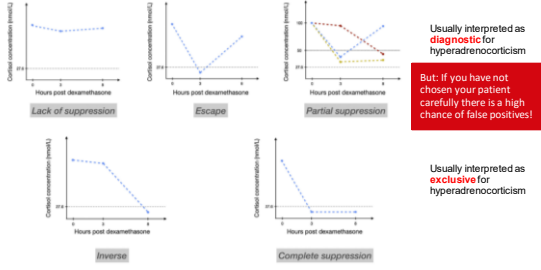
M. Addison oder iatrogenes M. Cushing:

Basalwerte liegen im unteren Normbereich oder darunter, Stimulation führt zu keinem bzw. nur zu geringfügigem Anstieg des Cortisolspiegels.

Therapiekontrolle

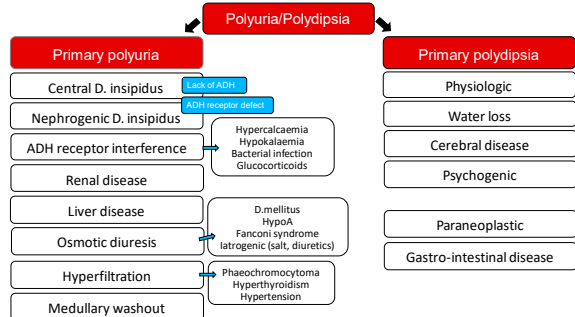
Bei einer Therapie mit Triostane (Vetonyl) wird ein Stimulationswert zwischen 18 und 73 ng/ml angestrebt.

Fig. 6. Illustration of different low-dose dexamethasone suppression test patterns, including the lack of suppression (C₀ at 4 h, and 8 h central concentrations above the laboratory cut-off of 100 nmol cortisol concentration), partial suppression (C₀ at 4 h, and 8 h central concentrations above the laboratory cut-off of 100 nmol cortisol concentration), escape (C₀ at 4 h, and 8 h central concentrations below the laboratory cut-off, and C₀ at 8 h central concentrations above the laboratory cut-off), complete suppression (C₀ at 4 h, and 8 h central concentrations below the laboratory cut-off), inverse (C₀ at 4 h, and 8 h central concentrations above the laboratory cut-off), and complete suppression (C₀ at 4 h, and 8 h central concentrations below the laboratory cut-off). A laboratory cut-off of 20 nmol/l was used. Bernheim et al., 2019



The verdict:

Hyperadrenocorticism unlikely



HUGO

- Gastrointestinal profile: TLI increased, PLI WRI, cobalamine decreased
- Endoscopy: eosinophilic enteropathy
- Liver biopsy: eosinophilic reactive hepatitis
- Treatment with diet + prednisolone successfull

TAKE HOME

- Take a close look at the whole picture when it comes to HAC
- Be aware of differentials
- Don't be scared of the diagnostic tests – in doubt combine them

The many faces of hypoadrenocorticism



A case study

LABOKLIN GmbH & Co. KG, Bad Kissingen, Germany

Dr Jennifer von Luckner

The great pretender...

1. Unspecific

- Listlessness
- Exercise intolerance
- Waxing + waning

2. Gastrointestinal

- Vomiting, regurgitation
- Diarrhoea (chronic, acute haemorrhagic possible)
- Abdominal pain
- Inappetence
- Eosinophilia
- Hypalbuminaemia

3. Renal

- PUPD
- Azotaemia
- Hyperkalaemia

4. Neurologic

- Tremor / Shivering
- Muscle cramping
- Seizures

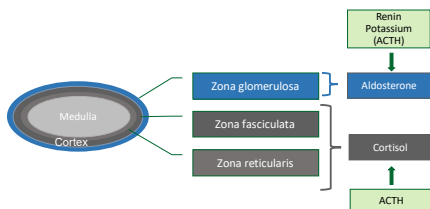
5. Anything else?

- Bradycardia
- Increase fur shedding

List not complete!

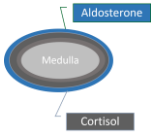
Peterson et al., 1996; Klein + Peterson, 2010

Short introduction



ALDOSTERONE

Hyperkalaemia + hyponatraemia



Klinische Chemie	Min.	lab Wert	Normwert	heftig	normal	hoch
Alaninase	PHO	1340.00 U/l	< 1600	→	→	→
Asparat	PHO	85.00 U/l	< 100	→	→	→
Glucose	PHO	2.80 mmol/l	3.00-6.1	→	→	→
Fructosamine	PHO	212.00 µmol/l	< 274	→	→	→
Thyroxin	PHO	1.10 mmol/l	< 1.9	→	→	→
Cholesterin	PHO	2.00 mmol/l	3.1-5.1	→	→	→
Bilirubin	PHO	1.70 µmol/l	< 3.4	→	→	→
AP	PHO	87.00 U/l	< 147	→	→	→
GGT	PHO	4.00 U/l	< 8	→	→	→
ALT	PHO	97.00 U/l	< 88	→	→	→
AST	PHO	47.00 U/l	< 91	→	→	→
Calcium	PHO	180.00 µg/l	< 200	→	→	→
Albumin	PHO	73.00 g/l	54-75	→	→	→
Bilirubin	PHO	24.00 µg/l	20-44	→	→	→
Urea	PHO	47.00 g/l	< 45	→	→	→
Kreatinin	PHO	9.50	< 0.20	→	→	→
Hämoglobin	PHO	17.40 mmol/l	3.3-6.3	→	→	→
Hämatocrit	PHO	532.00 g/mol	39-50	→	→	→
Phosphat	PHO	1.80 mmol/l	0.7-1.6	→	→	→
Magnesium	PHO	1.10 mmol/l	0.6-1.3	→	→	→
Calcium	PHO	12.00 mmol/l	2.3-3.0	→	→	→
Calcium	PHO	134.00 µmol/l	140-158	→	→	→
Natrium	PHO	5.30	3.5-5.1	→	→	→
Natrium	PHO	27.00	> 27	→	→	→
Eisen	PHO	10.40	10-40	→	→	→

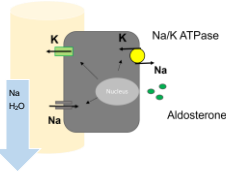
ALDOSTERONE

Hyperkalaemia + hyponatraemia:

- Aldosterone driven Na/K pump is not functioning
- Potassium (K) is not excreted into the urine
- Sodium (Na) is lost via the urine

⇒ Osmotic diuresis

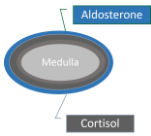
Polyuria / polydipsia



ALDOSTERONE

Pre-renal azotaemia

In the face of low USG / PU-PD

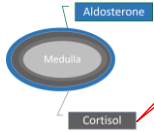


Klinische Chemie	Min.	lab Wert	Normwert	heftig	normal	hoch
Alaninase	PHO	1340.00 U/l	< 1600	→	→	→
Asparat	PHO	85.00 U/l	< 100	→	→	→
Glucose	PHO	2.80 mmol/l	3.00-6.1	→	→	→
Fructosamine	PHO	212.00 µmol/l	< 274	→	→	→
Thyroxin	PHO	1.10 mmol/l	< 1.9	→	→	→
Cholesterin	PHO	2.00 mmol/l	3.1-5.1	→	→	→
Bilirubin	PHO	1.70 µmol/l	< 3.4	→	→	→
AP	PHO	87.00 U/l	< 147	→	→	→
GGT	PHO	4.00 U/l	< 8	→	→	→
ALT	PHO	97.00 U/l	< 88	→	→	→
AST	PHO	47.00 U/l	< 91	→	→	→
Calcium	PHO	180.00 µg/l	< 200	→	→	→
Albumin	PHO	73.00 g/l	54-75	→	→	→
Bilirubin	PHO	24.00 µg/l	20-44	→	→	→
Urea	PHO	47.00 g/l	< 45	→	→	→
Kreatinin	PHO	9.50	< 0.20	→	→	→
Hämoglobin	PHO	17.40 mmol/l	3.3-6.3	→	→	→
Hämatocrit	PHO	532.00 g/mol	39-50	→	→	→
Phosphat	PHO	1.80 mmol/l	0.7-1.6	→	→	→
Magnesium	PHO	1.10 mmol/l	0.6-1.3	→	→	→
Calcium	PHO	12.00 mmol/l	2.3-3.0	→	→	→
Calcium	PHO	134.00 µmol/l	140-158	→	→	→
Natrium	PHO	5.30	3.5-5.1	→	→	→
Natrium	PHO	27.00	> 27	→	→	→
Eisen	PHO	10.40	10-40	→	→	→

CORTISOL

- Reduced hepatic gluconeogenesis
- Increased peripheral cellular uptake/consumption

Hypoglycaemia



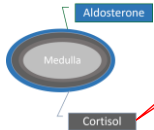
Parameter	Min.	Max. Wert	Normalwert	healthy	normal	hoch
z-Aminosäure	PHO 2.849.00 µMol	< 1500				
1000h Lipase	PHO 83.00 µMol	< 120				
Cortisol	PHO 9.00 nmol/dl	< 374				
Fructosamine	PHO 211.00 µmol/dl	< 374				
Triglyceride	PHO 2.10 mmol/dl	< 3.9				
Cholesterin	PHO 2.10 mmol/dl	3.1-5.1				
Bilirubin ges.	PHO 1.70 µmol/dl	< 3.4				
AP	PHO 87.00 µMol	< 147				
GLDH	PHO 4.00 µMol	< 8				
γ-GT	PHO 97.00 µMol	< 10				
ALT	PHO 87.00 µMol	< 88				
AST	PHO 47.00 µMol	< 31				
zweiwertiges Eisen	PHO 189.00 µMol	< 200				
Albumin	PHO 73.00 g/l	54-75				
Glukose	PHO 24.00 g/l	20-44				
Urea	PHO 47.00 g/l	< 45				
Acid-Quotient	PHO 8.55	> 8.59				
Harnstoff	PHO 37.40 mmol/dl	3.3-8.3				
Kreatinin	PHO 112.00 µmol/dl	35-106				
Phosphat-erhöht	PHO 1.80 mmol/dl	0.7-1.9				
Magnesium	PHO 1.10 mmol/dl	0.8-1.3				
Calcium	PHO 3.10 mmol/dl	2.3-3.0				
Natrium	POT 134.00 mmol/dl	140-155				
Kalium	POT 5.50 mmol/dl	3.5-5.1				
Na-K-Quotient	PHO 23.00	> 27				

Weakness, lethargy, gastrointestinal upset, GI bleeding

CORTISOL

- Reduced intestinal fat resorption

Hypocholesterolaemia



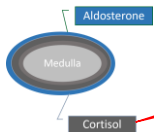
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Kalium	POT 5.50 mmol/dl	3.5-5.1				
Na-K-Quotient	PHO 23.00	> 27				

Weakness, lethargy, gastrointestinal upset, GI bleeding

CORTISOL

- Lack of nutrient intake (anorexia)
- Impaired synthesis
- Reduced absorption + gastrointestinal loss

Hypoalbuminaemia

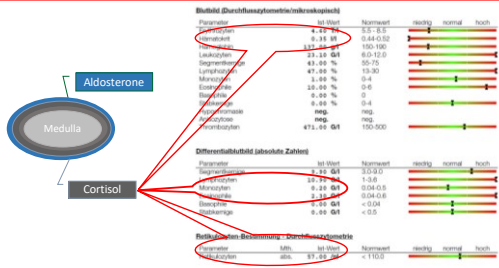


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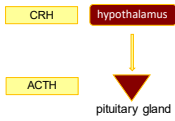
Weakness, lethargy, gastrointestinal upset, GI bleeding

CORTISOL

Loss of stress leukogram (absence of lymphopaenia) in a sick dog is a warning sign



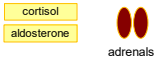
hypophysectomy *
exogenous steroids *



secondary hypoadrenocorticism
isolated cortisol deficiency *

* = Na + K within reference

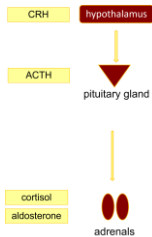
Trilostane overdose
Adrenal necrosis
- ACTH
- Trilostane
- Mitotane
surgical removal



primary hypoadrenocorticism
cortisol + aldosterone deficiency
isolated cortisol deficiency possible *

Diagnosis – Short introduction

- Screening
 - serum electrolytes (Na/K ratio)
 - basal cortisol
 - urine cortisol to creatinine ratio
- Confirmation
 - ACTH stimulation test
 - Cortisol/eACTH ratio
- Differentiation
 - endogenous ACTH
 - (aldosterone)



Lulu - Mix, 8 years, fs

Presented because of PU/PD + anorexia

- Imported from Rumania to Germany two years ago
- Positive *E. canis* antibody titer, was treated with Doxycycline
- Heavy flea infestation six months ago (treated with a spot on)
- Since then dull coat + increased shedding
- Increased water intake + reduced appetite for three weeks

- No vomiting, no diarrhoea
- No weight loss



Lulu - Mix, 8 years, fs

		SI	Reference
Erythrocytes	7.1	/fl	5.5-8.5
Haematocrit	0.47	/l	0.38-0.55
Haemoglobin	171	g/l	134-205
Leucocytes	12.3	/cfr	4.9-17.6
Neutrophils	45	%	55-75
Lymphocytes	43	%	13-30
Monocytes	5	%	0-4
Eosinophils	7	%	0-6
Basophils	0	%	0
Bands	0		0-4
Histiocytoma	neg.		neg.
Anisocytosis	neg.		neg.
Thrombocytes	279	/cfr	145-450
Differential count (absolute numbers)		SI	Reference
Neutrophils	5.6	/cfr	3.0-9.0
Lymphocytes	5.3	/cfr	1.9-6.6
Monocytes	0.6	/cfr	0.04-0.6
Eosinophils	0.8	/cfr	0.04-0.6
Basophils	0	/cfr	< 0.04
Bands	0	/cfr	< 0.5
Reticulocytes	32.6	/nl	< 110.0

Lulu - Mix, 8 years, fs

		SI	Reference
α-Amylase	1501	U/l	< 1500
DOG8-Lipase	28	U/l	< 120
Glucose	4	mmol/l	3.0-6.2
Fructosamine	292	umol/l	< 374
Triglycerides	2.0	mmol/l	< 1.9
Cholesterol	1.2	mmol/l	3.1-10.1
Bilirubin	1.9	umol/l	< 3.4
AP	24	U/l	< 147
GLDH	6	U/l	< 8
γ-GT	4	U/l	< 50
ALT	59	U/l	< 88
AST	81	U/l	< 91
CK	201	U/l	< 200
Total protein	71	g/l	54-75
Albumin	30	g/l	25-44
Globulins	41	g/l	< 45
A/G ratio	0.73		1.1-1.59
Urea	9.1	mmol/l	3.3-8.3
Creatinine	112	umol/l	35-106
Phosphorus	1.8	mmol/l	0.71-1.6
Magnesium	0.7	mmol/l	0.6-1.3
Calcium	3.3	mmol/l	2.3-3.0
Sodium	139	mmol/l	140-155
Potassium	5.0	mmol/l	3.5-5.1

		Reference
Urine specific gravity	1012	1010-1060
Protein	neg.	neg.
Haemo /Myoglobin	neg.	neg.
pH	7	5.0-8.5
Bilirubin	neg.	neg.
Urobilinogen	neg.	neg.
Glucose	neg.	neg.
Ketone bodies	neg.	neg.
Sediment		
Erythrocytes	3	0-5
Leukocytes	1	1-4
Bacteria	neg.	neg.
Yeast	neg.	neg.
Casts	neg.	
Epithelial cells	neg.	
Crystals	neg.	

Addison`s?

YES

NO



Lulu, Mix, 8 years, fs

These parameters raise suspicion for hypoA

- PU/PD
- Inappetence
- Dull coat/ shedding
- Positive E.canis antibodies

- Erythrogram + plt WRI
- **Lymphocytosis**
- Mild anaemia
- Mild hyperphosphataemia
- **Na + Cr slightly reduced**
- K WRI
- AST mildly increased
- Cholesterol reduced
- **Hypercalcaemia**
- Isosthenuria

Addison`s?

YES

NO



Lulu, Mix, 8 years, fs

What about...

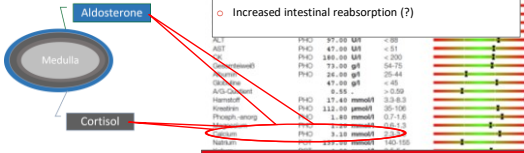
- PU/PD
- Inappetence
- Dull coat/ shedding
- Positive E.canis antibodies

- Erythrogram + plt WRI
- Lymphocytosis
- Mild anaemia
- Mild hyperphosphataemia
- **Na + Cr slightly reduced**
- **<K WRI**
- **AST mildly increased**
- Cholesterol reduced
- **Hypercalcaemia**
- Isosthenuria

Why hypercalcaemia?

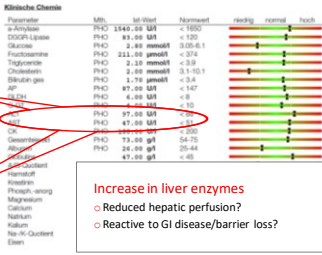
Hypercalcaemia

- Dehydration: Haemoconcentration
- Metabolic acidosis
- Reduced GFR: increased renal reabsorption (?)
- Increased release from bone (?)
- Increased intestinal reabsorption (?)



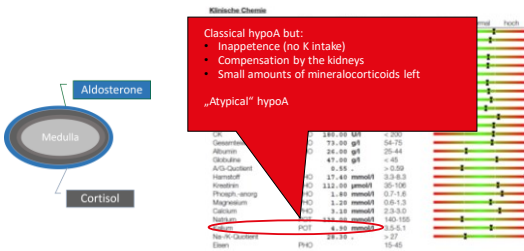
Usually total calcium – but may see ionized as well

Mild to moderate increases in AST + ALT activities reported



Increase in liver enzymes
 ○ Reduced hepatic perfusion?
 ○ Reactive to GI disease/barrier loss?

Hyperkalaemia is not evident in every case



Classical hypoA but
 • Inappetence (no K intake)
 • Compensation by the kidneys
 • Small amounts of mineralocorticoids left
 „Atypical“ hypoA

Site		
Primary	Secondary	
Electrolyte changes		
Hyperkalaemia, hyponatraemia or both	Sodium and potassium concentrations within reference interval	
Hormonal changes		
ACTH sufficient	ACTH deficient	
Aldosterone deficient	Aldosterone insufficient	Aldosterone sufficient
Nomenclature		
Typical primary hypoadrenocorticism (Addison's disease)	Atypical primary hypoadrenocorticism	Secondary hypoadrenocorticism
ACTH adrenocorticotrophic hormone		

Expected electrolyte and hormonal abnormalities in dogs with hypoadrenocorticism. Apparent isolated glucocorticoid deficiency (with reference interval electrolyte concentrations) can occur with sufficient, insufficient and deficient aldosterone production. Reproduced with permission of UK-Vet Companion Animal [53]

Guzman et al. 2022

Most eunatraemic/eukalaemic dogs are deficient in aldosterone

Evaluation of Aldosterone Concentrations in Dogs with Hypoadrenocorticism

M.E. Baumstark, N.S. Sieber-Ruckstuhl, C. Müller, M. Wenger, F.S. Boretti, and C.E. Reusch

Testing for possible mineralocorticoid deficiency is recommended!

Regardless of electrolyte status!

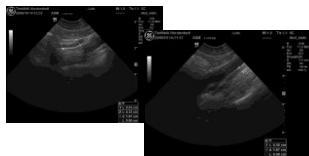
dogs. Additional blood samples were taken 15, 30, and 45 minutes after ACTH in 7 dogs with HA and in 22 with disease mimicking HA.

Results: Baseline and ACTH-stimulated aldosterone was significantly lower in dogs with HA than in the other groups. Aldosterone was low or undetectable in 67/79 dogs with HA independently of sodium and potassium levels. In 1 dog, sodium/potassium concentrations were normal, in 1 dog, sodium was normal and potassium decreased. In all 4, ACTH-stimulated aldosterone concentrations were below the detection limit of the assay. Aldosterone concentrations were not different at 15, 30, or 45 minutes after ACTH administration.

Conclusion and Clinical Implications: Cortisol and aldosterone secretion is compromised in dogs with HA with and without electrolyte abnormalities. The term atypical Addison's disease, used for dogs with primary HA and normal electrolytes, may be reconsidered; other mechanisms allowing normal electrolyte balance without aldosterone should be evaluated in these dogs.

Key words: adrenal insufficiency; canine; mineralocorticoids.

Lulu - Mix, 8 years, fs



ACTH Stimulation		Reference
Cortisol	< 1 ng/ml	5-65
Cortisol	< 1 ng/ml	

TAKE HOME

- HypoA is a differential diagnosis for hypercalcaemia
- Hyponatraemia (+ hypochloridaemia) can be indicative
- Not every patient with hypoA shows hyperkalaemia
- Increases in liver enzymes are possible with hypoA
- Increased fur shedding can be a clinical sign of hypoA



Sora – Australian Shepherd, 2 years, f

- Exercise intolerance for a while
 - Now especially weak
 - Has had diarrhoea a week ago
- Pale mucous membranes, heart rate 48/min, weak pulses



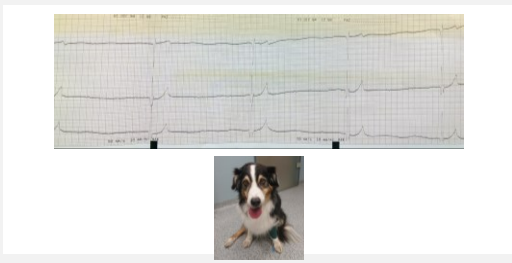
Sora – Australian Shepherd, 2 years, f

	SI	Reference
Erythrocytes	5.6 /fl	5.5-8.5
Haematocrit	0.4 /fl	0.38-0.55
Haemoglobin	139 g/l	134-205
Leucocytes	8.9 /fl	4.0-17.6
Neutrophils	62.1 %	50-75
Lymphocytes	38.7 %	13-30
Monocytes	0.1 %	0-4
Eosinophils	0.08 %	0-6
Basophils	0.02 %	0
Bands	0	0-4
Hypochromasia	neg.	neg.
Anisocytosis	neg.	neg.
Thrombocytes	neg.	145-450
Differential count (absolute numbers)	SI	Reference
Neutrophils	5.9 /fl	3.9-9.0
Lymphocytes	3.9 /fl	1.0-3.6
Monocytes	0.35 /fl	0.04-0.6
Eosinophils	0.4 /fl	0.04-0.6
Basophils	0.2 /fl	<0.04
Bands	0 /fl	<0.5
Reticulocytes	22 /fl	<110.0

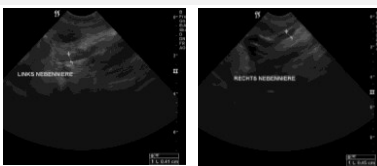
Sora – Australian Shepherd, 2 years, f

		SI	Reference
α-Amylase	678	IU/l	< 1850
DGCK-Lipase	108	IU/l	< 120
Glucose	6.1	mmol/l	3.0-6.1
Fructosamine	356	umol/l	< 374
Triglycerides	0.97	mmol/l	< 1.9
Cholesterol	4.1	mmol/l	3.1-10.1
Bilirubin	2.0	umol/l	< 1.4
AP	89	IU/l	< 147
GGT	1	IU/l	< 6
G-DT	8	IU/l	< 10
ALT	65	IU/l	< 88
AST	43	IU/l	< 51
CK	56	IU/l	< 200
Total protein	56.7	g/l	54-75
Albumin	39.1	g/l	25-44
Globulin	26.6	g/l	< 45
A/G ratio	1.47		1-0.59
Urea	7.3	mmol/l	3.3-8.3
Creatinine	90	umol/l	35-105
Phosphate	1.6	mmol/l	0.7-1.6
Magnesium	0.6	mmol/l	0.1-1.1
Calcium	2.5	mmol/l	2.3-3.0
Sodium	147	mmol/l	140-255
Potassium	4.0	mmol/l	3.5-5.1

Sora – Australian Shepherd, 2 years, f



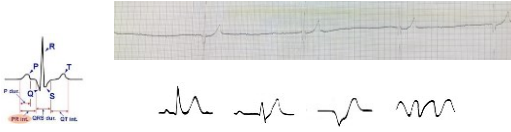
Sora – Australian Shepherd, 2 years, f



ACTH Stimulation			Reference
Cortisol	1.9	ng/ml	5-65
Cortisol	1.8	ng/ml	

Hyperkalaemia – clinical consequence bradycardia

- $K^+ > 6,5$ mmol/l can lead to bradycardia
- If there is no hyperkalaemia bradycardia is not due to Addison's!
- Hyperkalaemia does not necessarily lead to bradycardia



ACTH test – When to exclude Addison's

ACTH Stimulation			Reference
Cortisol	1.9	ng/ml	5-65
Cortisol	1.8	ng/ml	

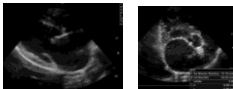
Cortisol

- Typical hypoA = no / nearly no stimulation
e.g. 0h: ≤ 1 ng/ml (0.1 ug/dl; 2.5 nmol/l)
1h: $\leq 1-3$ ng/ml (0.1-0.3 ug/dl; 2.5-5 nmol/l)
- Inadequate stimulation = moderate stimulation
1h < 20 ng/ml (2.0 ug/dl; 55 nmol/l)*
- No hypoA = normal stimulation
1 h > 20 ng/ml (2.0 ug/dl; 55 nmol/l)

BUT: cases with higher stimulation (up to 80 nmol/l, 29 ng/ml, 2.9 ug/dl) described

Sora – Australian Shepherd, 2 years, f

- Bradycardia induced by AV Block III (due to atrial myocarditis) – successfully treated by pacemaker implantation



- Upon intensive enquiry the owners stated that Sora had received ophthalmologic medication because of allergic/immune-mediated conjunctivitis...

ACTH test – What to do with questionable results

Exclude pre-treatment with glucocorticoids!

- o Even low dosages of glucocorticoids can influence test results
 - Ophthalmologic medications
 - Ear ointments
 - Skin creme/spray
 - Glucocorticoid injection (within the last 6-8 weeks)
 - A single tablet (even if 2-3 weeks ago)

ACTH test – What to do if pre-treated with glucocorticoids?

- o Negative feedback on pituitary-adrenal axis varies between individuals!
 - Decreased cortisol stimulation after ACTH
 - Reduced concentration of eACTH
- o Prednisolone + hydrocortisone will be detected by the assay + are reported als cortisol
- o 6-8-12 weeks may be needed for full recovery

ACTH test – What to do if pre-treated with glucocorticoids?

What I do:

A Pre-treated but without medication at the moment + clinically stable

- Perform ACTH stim 2 weeks after withdrawal (depending on the case even earlier)
 - Adequate stimulation = hypoA is excluded
 - Inadequate stimulation = monitor for clinical signs + repeat ACTH stim in 1-2 week intervals (as long as patient is stable)
- Consider measuring aldosterone with ACTH stimulation
- Consider measuring eACTH
 - very high = primary hypoA likely
 - low/normal not exclusive



ACTH test – What to do if pre-treated with glucocorticoids?

What I do:

B Currently treated with glucocorticoids + withdrawal not possible

- Perform ACTH stimulation with aldosterone measurement
 - No stimulation: hypoA confirmed
 - Normal stimulation: isolated cortisol deficiency possible*
- Consider measuring eACTH
 - high in the face of glucocorticoid treatment: primary hypoA likely
 - low not exclusive



*Not likely if electrolyte imbalance was reason to consider hypoA

TAKE HOME

- o Bradycardia seen with hypoA usually is due to hyperkalaemia
- o If there is no hyperkalaemia look for another disease
- o Even the smallest amounts of exogenous glucocorticoids can influence ACTH stimulation test



Before we are allowed a break – a last question from a colleague...

Dear Jenny,

a 6 years old, male neutered mixed breed dog about 10kg of body weight with chronic diarrhoea, normal appetite, normal heart rate. Last week blood profile: GLDH mildly increased, NaK 32.8

Cortisol very low

IS this (atypical) hypoadrenocorticism or do I need to investigate further?

Faecal exam for parasites + Giardia negative. Have given prednisolone once. Shall I start him on Exortol?

Thank you very much!!!

?

ENDOCRINOLOGIE		Result
Cortisol	* 6.3	0.8-4.1 µg/dl

Basal cortisol – When to exclude Addison`s

⇒ If high = hypoA excluded

⇒ If low = hypoA possible => **ACTH stimulation test necessary***

Accepted cut-off: > 20 ng/ml
> 2 ug/dl
> 55 nmol/l (SI)

* Even undetectable cortisol possible in non-hypoA dogs (Gallego et al., 2021)

Basal cortisol – When to exclude Addison`s

Table 1. Calculated sensitivities and specificities of routine serum or plasma basal cortisol concentrations for the diagnosis of hypoadrenocorticism in dogs.

Basal Cortisol (nmol/L), n = 163	Dogs with HSA (n = 51)		% Sensitivity (95% CI)	% Specificity (95% CI)
	HA	NAI		
≤5.3	133	3	81.6 (74.8-87.2)	99.3 (97.5-99.8)
≤7.0	144	4	83.3 (76.4-87.2)	99.9 (97.1-99.7)
≤7.7	158	5	86.9 (81.0-90.9)	95.7 (93.0-97.9)
≤8.4	168	5	88.2 (84.5-90.9)	91.5 (89.0-94.2)
≤9.1	162	6	89.4 (86.4-90.9)	82.6 (78.2-86.9)
≤9.8	162	7	89.4 (86.4-90.9)	67.8 (61.8-71.8)

Gold et al., 2016

28 nmol/l (10 ng/ml, 1 ug/dl) probably excludes hypoA

- with a reasonable specificity
- without major forfeit in sensitivity

My personal cut-off: 18 ng/ml, 1.8 ug/dl, 50 nmol/l

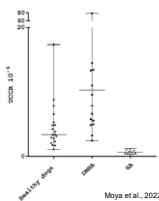
Greyzone but never had one: 15 ng/ml, 1.5 ug/dl, 40 nmol/l

* only 2/162 hypoA dogs had a basal cortisol > 28

UCCR – What is the value?

○ UCCR < 1.4 indicative for hypoA (Del Baldo et al., 2021)*

○ UCCR ≤ 10 indicative for hypoA (Moya et al., 2022)**

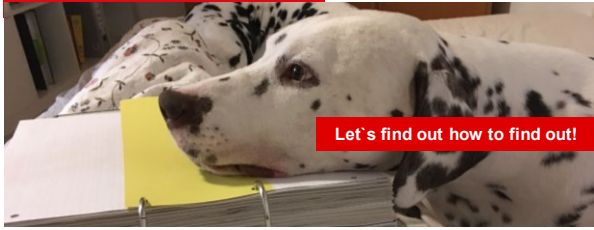


Moya et al., 2022



* CLIA, Immulle 2000 cortisol nmol/l / creatinine umol/l
** CLIA, Immulle 2000 (cortisol nmol/l / creatinine umol/l)x100

Is this really hypothyroidism?



LABOKLIN GmbH & Co. KG, Bad Kissingen, Germany

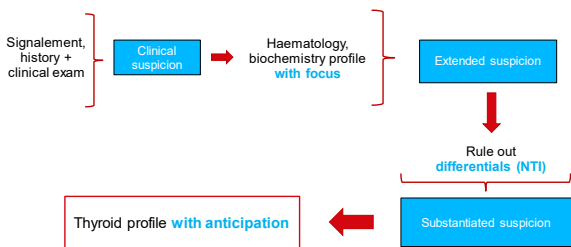
Dr Jennifer von Luckner

Chap – Jack Russel Terrier, 10 years, mc

Recurrent episodes with abdominal pain
Intermittent vomiting



When searching for **hypothyroidism**...



Clinical suspicion

Typical presentation

Typical breeds: Labrador/Golden Retriever, Dobermann, Rhodesian Ridgeback, Dalmatiner, Cocker Spaniel, Shetland Sheepdog

Labrador Retriever, 5 years, mc

- Tired, listless
- Weight gain despite normal (little) food intake
- Dull coat with colour fading
- Thick skin
- Looks somehow sad

Typical age: 5-8 years



REMINDER: clinical signs

Common

Signs related to decreased metabolic rate

- Lethargy or dull mentation
- Inactivity or unwillingness to exercise
- Weight gain
- Cold intolerance or heat seeking

- Normal to reduced appetite
(**NOT** polyphagia!)
- **NOT**: polyuria/polydipsia

Dermatologic changes

- Symmetric, nonpruritic hair loss
- Post-clipping alopecia
- Dry, dull hair coat
- Scaling
- Hyperpigmentation
- Recurrent pyoderma or otitis externa

REMINDER: clinical signs

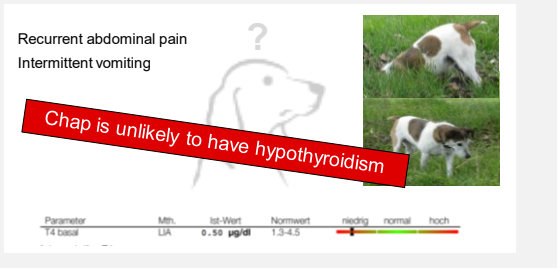
Uncommon

- **Ocular** signs: Lipid corneal deposits
- **Peripheral nervous system** signs
 - Facial nerve paralysis
 - Laryngeal paralysis
 - Polyneuropathy
- **Vestibular** signs
- **Oesophageal dysmotility** (?)
- **Reproductive** effects
 - Periparturient mortality, low birth weights
 - Lactatio falsa
 - Irregularities in oestrus?

- **Cardiovascular** abnormalities
 - Bradycardia
 - Exacerbation of other cardiac signs
 - Atherosclerosis
- **Myxoedema coma**
 - Depressed mental status
 - Altered thermoregulation
 - Bradycardia
 - Hypoventilation
 - Thickened skin

Chap – Jack Russel Terrier, 10 years, MC

Recurrent abdominal pain
Intermittent vomiting



Parameter	Min.	ist-Wert	Normwert	reading	normal	hoch
T4 basal	LIA	0.50 $\mu\text{g/dl}$	1.3-4.5	←		

Euthyroid Sick Syndrom = Non-Thyroidal Illness (NTI)

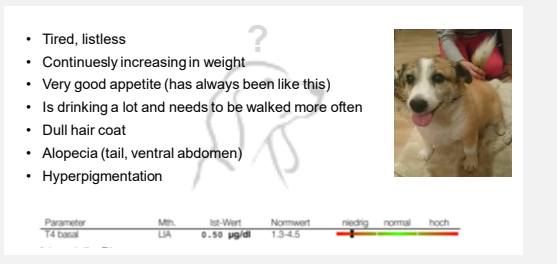
**Reduction of serum TT4 concentration
caused by non-thyroidal disease**

- ⇒ Pathophysiologic reaction (induced slowing of metabolic rate)?
- ⇒ Change in transport proteins?

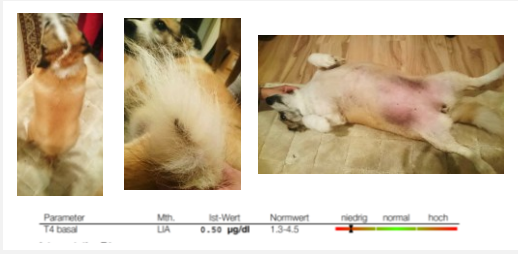
TT4 can fall below the detection limit!

Mandy – Mix, 6 years, fS

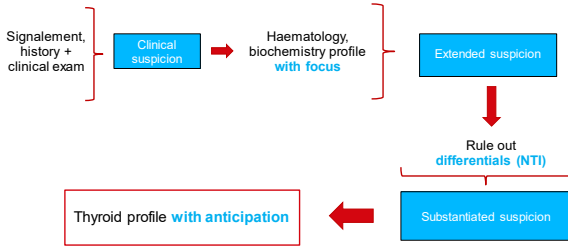
- Tired, listless
- Continuesly increasing in weight
- Very good appetite (has always been like this)
- Is drinking a lot and needs to be walked more often
- Dull hair coat
- Alopecia (tail, ventral abdomen)
- Hyperpigmentation



Parameter	Min.	ist-Wert	Normwert	reading	normal	hoch
T4 basal	LIA	0.50 $\mu\text{g/dl}$	1.3-4.5	←		



When searching for hypothyroidism...



REMINDER: haematology

What to expect

		SI unit	Reference Interval
Leukocytes	5.900	G/l	4.900-17.600
Haematocrit	0,42	l/l	0,38-0,55
Haemoglobin	132	g/l	134-205
Erythrocytes	5,6	T/l	5,4-8,7
MCV	74,4	fl	59-76
MCH	23,6	pg	21,9-26,1
MCHC	31,7	g/dl	32,6-39,2
Thrombocytes	440	G/l	145-450
Reticulocytes	1	%	
Reticulocytes	55900	/ul	

Erythrocyte parameters low reference or mild anaemia (non-regenerative)

REMINDER: biochemistry

What to expect

	SI units	Reference interval
ALP	175 U/l	< 150
AST	56 U/l	< 60
ALT	154 U/l	< 125
G-GT	17 U/l	< 15
Bilirubin	3.4 µmol/l	< 6.4
Cholesterol	18.7 mmol/l	2.5-10.0
Triglycerides	4.1 mmol/l	0.25-3.5
Creatinin	79.5 µmol/l	80-200
Urea	3.4 mmol/l	2.7-4.8
Na	150 mmol/l	142-153
K	4.6 mmol/l	3.9-5.8
Calcium	2.3 mmol/l	2.2-2.9
Phosphate	1.4 mmol/l	0.9-1.7
Glucose	4.7 mmol/l	3.5-7.8
Fructosamin	397 µmol/l	200-375
Total protein	72 g/l	66-84
Albumin	32 g/l	35-50
Globulins	40 g/l	23-52
Amylase	635 U/l	330-1265
Lipase	145 U/l	140-400
CK	430 U/l	40-380

- Mild increase in liver enzymes possible
- Increase in cholesterol
- Increase in triglycerides
- Increase in fructosamin possible
- Increase in CK possible

Extended suspicion in Mandy?

Blutbild (Durchflusszytometrie/akroskopisch)

Erythrozyten	6.6 T/l	5.5 - 8.5
Hämatokrit	0.45 l/l	0.44-0.52
Hämoglobin	170 g/l	150-190
Leukozyten	15.3 G/l	+ 6.0-12.0
Segmentkernige	85 %	+ 55-75
Lymphozyten	6 %	+ 13-30
Monozyten	9 %	+ 0-4
Eosinophile	1 %	0-6
Basophile	0 %	0
Stäbchenige	2 %	0-4
Hypochromasie	neg.	neg.
Anisokytose	neg.	neg.
Thrombozyten	401 G/l	150-500

Differentialblutbild (absolute Zahlen)

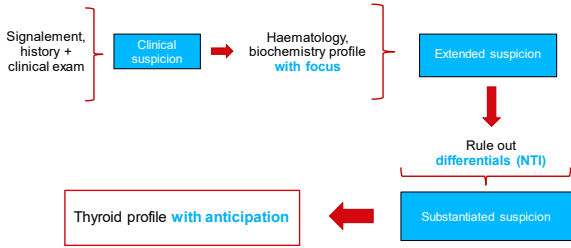
* Segmentkernige	13.0 G/l	+ 3.0-9.0
* Lymphozyten	0.9 G/l	- 1-3.6
* Monozyten	1.4 G/l	+ 0.04-0.5
* Eosinophile	0.2 G/l	0.04-0.6
* Basophile	0.0 G/l	< 0.04
* Stäbchenige	0.3 G/l	< 0.5

Extended suspicion in Mandy?

Klinische Chemie

Parameter	Mth.	lab Wert	Normalwert	niedrig	normal	hoch
β-Amylase	PHO	121.00 U/l	< 100		█	
DDP/Lipase	PHO	90.00 U/l	< 100		█	
Glucose	PHO	4.20 mmol/l	3.00-6.1		█	
Fructosamin	PHO	272.00 µmol/l	< 374		█	
Triglyceride	PHO	1.50 mmol/l	< 3.9		█	
Cholesterin	PHO	9.80 mmol/l	3.1-10.1		█	
Bilirubin ges.	PHO	6.20 µmol/l	< 3.4		█	
AP	PHO	142.00 U/l	< 147		█	
ALDH	PHO	4.90 U/l	< 8		█	
G-GT	PHO	2.00 U/l	< 10		█	
ALT	PHO	24.00 U/l	< 88		█	
AST	PHO	14.00 U/l	< 91		█	
CK	PHO	67.00 U/l	< 200		█	
Oxalantkreatin	PHO	62.00 µg/l	04-75		█	
Albumin	PHO	44.00 g/l	28-44		█	
Globuline	PHO	22.00 g/l	< 45		█	
AVG-Quotient		1.80	> 0.50		█	
Harnstoff	PHO	5.14 mmol/l	3.0-8.3		█	
Kreatinin	PHO	58.00 µmol/l	35-108		█	
Phosphat-serum	PHO	5.90 mmol/l	0.7-1.6		█	
Magnesium	PHO	1.20 mmol/l	0.6-1.3		█	
Calcium	PHO	2.40 mmol/l	2.3-3.0		█	
Natrium	POF	147.00 mmol/l	140-155		█	
Kalium	POF	5.00 mmol/l	3.5-5.1		█	
Na-K-Quotient		29.40	> 27		█	
Eisen	PHO	17.00 µmol/l	10-45		█	

When searching for hypothyroidism...

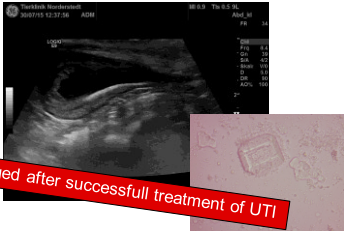


Extended suspicion in Mandy?

Urinalysis

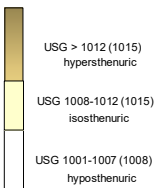
Specific gravity	1007
pH	8
Protein	(+)
Glucose	neg
Ketones	non
Bilirubin	

Bacterial culture (cystocentesis):
 > 1 Mio KBE/ml
 > Staphylococcus pseudintermedius



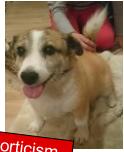
The most common differentials for very low USG

- D. mellitus
- Renal disease
- Bacterial infection
- Hyperadrenocorticism
- Hypercalcaemia
- Central D. insipidus
- Psychogenic



Mandy – Mix, 6 years, fs

- Tired, listless
- Continued increasing in weight
- Very good appetite (has always been like this)
- **Is drinking a lot and needs to be walked more often**
- Dull hair coat
- Alopecia (tail)
- Hyperpigmentation



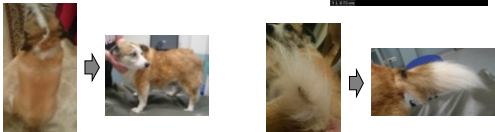
We need to consider hyperadrenocorticism

Parameter	Min.	ist-Wert	Normwert	reading	normal	hoch
TT4 basal	UA	0.50	1.3-4.5	0.15		

Hyperadrenocorticism may mimic hypothyroidism

Glucocorticoids can lead to decreased TT4 serum concentration

- Treatment trial with Levothyroxine unsuccessful
- Unresolved PU/PD after treatment of UTI
- Enlarged adrenal glands, large and hyperechoic liver
- Treatment with Trilostane successful



Nike – Golden Retriever, 11 years, fs

- Reduced activity level
- Unenthusiastic to exercise / lazy
- Being treated with meloxicam for osteoarthritis



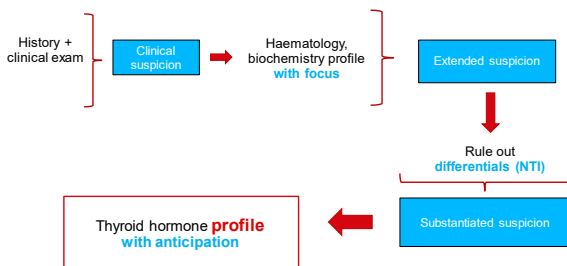
Nike – Golden Retriever, 11 years, fs

	SI	Reference
Erythrocytes	4.0	T/L 5.5-8.5
Haematocrit	0.27	I/L 0.38-0.55
Haemoglobin	144	g/l 134-205
Leucocytes	7.0	G/l 4.0-12.6
Neutrophils	66	% 55-75
Lymphocytes	24	% 13-30
Monocytes	8	% 0-4
Eosinophils	1.5	% 0-6
Basophils	0.5	0
Bands	0	0-4
Hypochromasia	neg.	neg.
Anisocytosis	neg.	neg.
Thrombocytes	478	G/l 145-450
Differential count (absolute numbers)		
Neutrophils	4.65	G/l 3.0-9.0
Lymphocytes	1.63	G/l 1.0-3.6
Monocytes	0.55	G/l 0.04-0.6
Eosinophils	0.12	G/l 0.04-0.6
Basophils	0.05	G/l < 0.04
Bands	0	G/l < 0.5
Reticulocytes	28.1	/ml < 110.0

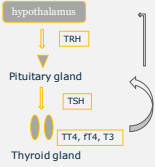
Nike – Golden Retriever, 11 years, fs

	SI	Reference
α Amylase	654	U/l < 1650
DGCR Lipase	42	U/l < 120
Glucose	4.3	mmol/l 3.0-6.1
Fructosamin	297	umol/l < 374
Triglycerides	3.8	mmol/l < 3.9
Cholesterol	10.7	mmol/l 3.1-10.1
Bilirubin	1.2	umol/l < 3.4
AP	30	U/l < 147
GLDH	4	U/l < 8
γ-GT	2	U/l < 10
ALT	24	U/l < 88
AST	36	U/l < 51
CK	69	U/l < 200
Total protein	59	g/l 54-75
Albumin	28	g/l 24-44
Globulin	31	g/l < 45
A/G ratio	0.9	1.0-1.5
Urea	3.9	mmol/l 3.3-8.3
Creatinine	78	umol/l 35-106
Phosphate	1.1	mmol/l 0.7-1.6
Magnesium	0.8	mmol/l 0.6-1.3
Calcium	2.8	mmol/l 2.3-3.0
Sodium	146	mmol/l 140-155
Potassium	3.8	mmol/l 3.5-5.1

When searching for hypothyroidism...

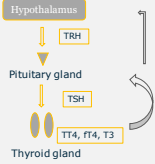


	TT4	FT4	TSH	TT3
Sensitivity	very good			
Specificity	low			
Expected result	↓			



	TT3	TT4	FT4	TSH
Sensitivity		very good		moderate
Specificity		low		good
Expected result		↓		↑

What if:
TT4 ↓, TSH ↑
Hypothyroidism likely
TT4 normal, TSH normal
Hypothyroidism unlikely



What if
TT4 ↓ + TSH normal
 ?

In most cases NTI related decrease of TT4...
BUT: in 25 – 40% of hypothyroid dogs TSH is WRI

Thyroid hormone profile

Großes Schilddrüsenprofil (Hund) - CLIA/ELISA



Small Schilddrüsen-Hormon (T4) - CLIA



Can it just be the age?

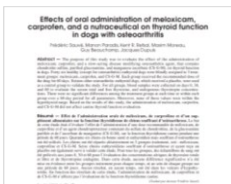
- T4 higher in young dogs
- Decreases with age
- Usually does not fall below reference interval

In some breeds T4 declines much faster than in others

Peter Graham, ECVIM Congress 2021
Scott-Moncrieff, 2014

What about Meloxicam?

Conflicting results on NSAIDs



Can osteoarthritis cause NTI?

Effects of moderate to severe osteoarthritis on canine thyroid function

Manon Parada, Fabrice Souvli, Julie Chiquet, Karol B. Refsal, Moamr Moreau, Jacques Dupuis

Abstract – Several osteoarthritis (OA) cases in collared dogs can affect the results of thyroid function testing, making interpretation of the results more difficult with an increased risk of misdiagnosing hypothyroidism. The purpose of this study was to evaluate the effect of chronic, moderate to severe osteoarthritis on canine thyroid function. Twenty-six healthy, clinically normal dogs, 13 of which were collared dogs, and 13 canine osteoarthritis and 1 collared dog without any physical evidence of osteoarthritis, were used in this study. Blood samples were collected to evaluate unbound total thyroxine (TT4), free thyroxine (FT4), and thyroxine (TT4) concentration. Bound serum TT4 concentration was not affected by osteoarthritis in dogs. Mild, but statistically significant differences were noticed for FT4 and TT4 concentrations among the 2 groups. However, this had no clinical effect. Osteoarthritis could possibly be confounding when the collared dogs, but no dogs would have been misdiagnosed as hypothyroid. Therefore, based on the results of our study, osteoarthritis does not appear to be considered a major confounding thyroid function evaluation in dogs.

Résumé – Effet de l'arthrose modérée à grave sur la fonction thyroïdienne canine. Plusieurs ostéopathies chez les chiens collés peuvent affecter les résultats des tests de la fonction thyroïdienne, rendant l'interprétation des résultats plus difficile et augmentant le risque de mal-diagnostiquer l'hypothyroïdisme. Le but de cette étude était d'évaluer l'impact de l'arthrose chronique, modérée à grave, sur la fonction thyroïdienne canine. Quarante-six chiens sains, 13 chiens collés et 13 chiens souffrant d'arthrose et 1 chien collé sans preuve physique d'arthrose, ont été utilisés dans cette étude.

Des échantillons sanguins ont été prélevés afin d'évaluer la concentration totale de thyroxine (TT4), de la thyroxine libre (FT4) et de la thyroxine liée (TT4) dans le sérum. La concentration de TT4 n'a pas été affectée par l'arthrose chez les chiens. Des différences légères mais statistiquement significatives ont été observées pour la concentration de FT4 et de TT4, mais elles n'ont eu aucun effet clinique. L'arthrose pourrait être un facteur confondant lors de l'évaluation de la fonction thyroïdienne canine. Cependant, basé sur les résultats de notre étude, il ne semble pas raisonnable de mal-diagnostiquer l'hypothyroïdisme chez les chiens collés.

Conclusion: L'arthrose ne semble pas être un facteur confondant majeur de l'évaluation de la fonction thyroïdienne canine.

Does not look like it!

Can ft4 help us?

Free thyroxine (FT4)

→ Sensitivity 90-100 %

→ Specificity 90 %

With consistent clinical signs!

When measured with RIA!

- Within reference ⇒ euthyroidism
- Moderate reduction ⇒ hypothyroidism possible
- Marked reduction ⇒ consistent for hypothyroidism

Low FT4 (CLIA) more reliable than low TT4 (CLIA)

- Low T4 binding capacity in NTI (= increase in FT4)
- TGAA interference can cause false increase in FT4

BUT: severe NTI + drugs (e.g. sulfonamides, phenobarbital, prednisolone) can decrease FT4!

When to use fT4 equilibrium dialysis?

- Differentiation from NTI when
 - functional thyroid testing not possible
 - clinical signs/laboratory abnormalities consistent with hypothyroidism
 - NTI not evident (differentials excluded)
 - concurrent disease/drugs present

Drawback: fT4 disseminates from TT4 (= fT4 ↑) with

- Prolonged transportation times
- High temperatures

= false increase of fT4

Thyroid hormone profile

Deutsches Schilddrüsenprofil (Shard): CL431204

Thyreoid-Schilddrüsenprofil (Shard)

Parameter	Wert	Referenzbereich	Abweichung
fT4	17,38 pmol/l	12,0 - 16,0 pmol/l	erhöht
fT3	3,71 pmol/l	2,3 - 4,2 pmol/l	normal
fT4i	17,38 pmol/l	12,0 - 16,0 pmol/l	erhöht
fT3i	3,71 pmol/l	2,3 - 4,2 pmol/l	normal

Interpretation fT4
Bei Abweichung im Thyroxin (Schilddrüsenhormon) oder -derivat weist die Veränderung nicht automatisch auf eine Beeinträchtigung von fT4 und fT3i oder auf Funktionsstörungen hin. Diese Werte über dem Referenzbereich können auf eine gestörte Hormonbindung (z.B. durch Nieren- oder Lebererkrankungen) oder auf eine Beeinträchtigung der Hormonbindung (z.B. durch Nieren- oder Lebererkrankungen) hinweisen. Eine vorliegende Erkrankung kann die Messergebnisse beeinflussen.

Thyreoid-Schilddrüsenprofil (Shard): CL4

Parameter	Wert	Referenzbereich	Abweichung
fT4	17,38 pmol/l	12,0 - 16,0 pmol/l	erhöht
fT3	3,71 pmol/l	2,3 - 4,2 pmol/l	normal
fT4i	17,38 pmol/l	12,0 - 16,0 pmol/l	erhöht
fT3i	3,71 pmol/l	2,3 - 4,2 pmol/l	normal

Interpretation fT4
Bei Abweichung im Thyroxin (Schilddrüsenhormon) oder -derivat weist die Veränderung nicht automatisch auf eine Beeinträchtigung von fT4 und fT3i oder auf Funktionsstörungen hin. Diese Werte über dem Referenzbereich können auf eine gestörte Hormonbindung (z.B. durch Nieren- oder Lebererkrankungen) oder auf eine Beeinträchtigung der Hormonbindung (z.B. durch Nieren- oder Lebererkrankungen) hinweisen. Eine vorliegende Erkrankung kann die Messergebnisse beeinflussen.

Freie Thyroxin-Bestimmung (fT4)

Parameter	Wert	Referenzbereich	Abweichung
fT4	17,38 pmol/l	12,0 - 16,0 pmol/l	erhöht
fT3	3,71 pmol/l	2,3 - 4,2 pmol/l	normal
fT4i	17,38 pmol/l	12,0 - 16,0 pmol/l	erhöht
fT3i	3,71 pmol/l	2,3 - 4,2 pmol/l	normal

Freie fT4-Werte (ng/dl) 0,73 0,47 3,32 ng/dl

Text: Weiterleitung an Speziallabor

What about TGAA?

Thyroglobulin antibodies

- Thyroglobulin antibodies indicate thyroiditis
- Around 20% of dogs develop hypothyroidism at some time point
- 80-90% destruction of thyroid gland before dogs show clinical signs
- Autoantibodies often are not present anymore when hypothyroidism manifests itself

TgAA are not equivalent to hypothyroidism!

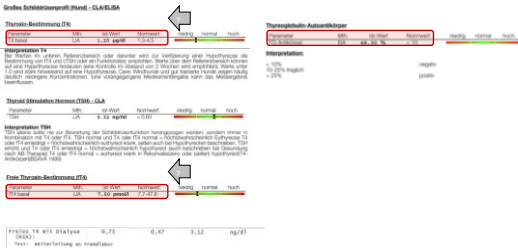
But: hypothyroidism in young dogs is unusual without positive TgAA

But: positive TgAA in an old dog indicate ongoing thyroid disease

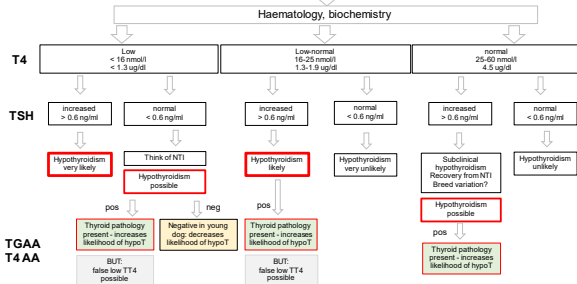
TgAA can lead to false measurements of TT4 (+TT4!)

Photo credit: 1995 JNMA, Dixon + Money 1999, JSAP

Thyroid hormone profile



Hypothyroidism suspected based on history and clinical signs



TGAA
T4 AA

What about functional testing?

1. Stimulation with TSH (recombinant human TSH)

- 50-75 µg per dog IV
- Blood sampling before + 6 hours after injection

Expensive

2. Stimulation with TRH

Many euthyret dogs do not show adequate response (differentiation not possible)

% increase in TSH after injection may be helpful

3. Scintigraphy

Journal of Veterinary Internal Medicine ACVIM

Use of basal and TRH-stimulated plasma growth hormone concentrations to differentiate between primary hypothyroidism and nonthyroidal illness in dogs

Tara Pipavack | Hans S. Koostra | Cathelipe F. Vermeulen | Merel van der Weide | Marit Prins | Sara Galic | Jan A. Muij

Background: A low plasma total thyroxine (TT₄) concentration in combination with plasma growth hormone (GH) concentrations that are not elevated in response to recombinant human TSH (rhTSH) in all cases (NTI) dogs. Hypothyroidism associated with TSH-releasing hormone (TRH) is increased when a parallel increase in GH is observed.

Objective: Test and TRH-induced plasma GH concentrations can be used to differentiate hypothyroid dogs.

Animals: Twenty-one dogs with signs consistent with hypothyroidism or low plasma TT₄ (NTI) were included in the study.

Methods: Case-control study. Thyroid scintigraphy was performed in healthy dogs in which hypothyroidism or NTI was confirmed. GH concentrations were measured at a combination of GH and TRH before and 30 and 60 minutes after TRH administration of TRH.

Results: Data of the dogs were divided in hypothyroid and NTI showing GH secretion concentration in the hypothyroid dogs (2.0) and range 0.0-10.0 and non-significantly increased in NTI after TRH administration in hypothyroid dogs, whereas it did not change over time. In NTI dogs GH concentrations in hypothyroid dogs and NTI dogs did not change. Plasma TSH concentrations did not change significantly after TRH administration in hypothyroid dogs, whereas it increased in NTI dogs. In NTI dogs, there was no overlap in percentage.

Principle

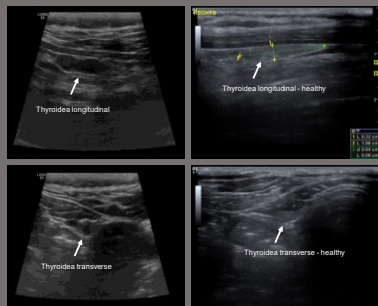
Recombinant human TRH (10 µg/kg IV)
Blood sample (serum) for TSH before injection + 45 min later

→ Stimulates the pituitary to produce TSH (+ GH)

Interpretation

Increase in TSH < 57% = hypothyret
Increase in TSH > 57% = euthyret or NTI

plasma TSH concentration did not change significantly after TRH administration in hypothyroid dogs, whereas it increased ($p < .001$) in NTI dogs. At T=45, there was no overlap in percentage TSH increase from baseline between hypothyroid dogs.



Is ultrasonography the solution?

Not able to clearly differentiate healthy from hypothyroid

Diagnostic treatment trial

Treatment trial – How to treat

- Tablets or oral solution
- 20 (10-40) ug/kg PO SID to BID
- Ideally, on an empty stomach
- If given with food do this constantly + pay attention when monitoring

Be aware:

- ⊕ Functional testing not possible anymore
- ⊕ Activity level + dermatological signs may improve independently


Treatment trial – How to monitor

Clinical signs	Lethargy	Few days
	Adipositas	Approx. 10% weight loss within the first few months
	Dermatology	Improvement within one month, normalization within 2-3 months
	Neurology	2-3 (up to 6) months
TT4	Sampling	4-6 hours after pilling
	Aim	Mid to upper reference range
TSH	Aim	Reference range or below
	Disadvantage	Not helpful if not increased at diagnosis

Nike – Golden Retriever, 11 years, fs

74	2.2	pp/dl	1.5-4.0
74 (Serum)	5.9	pp/dl	

?

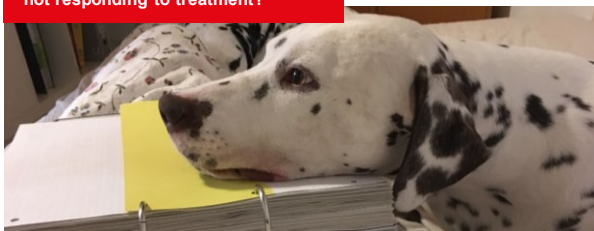


- Joint disease
- Recheck haematology 4 weeks later: unchanged
- Ultrasonography: evidence for chronic enteropathy
- Activity level improved after change of diet, anaemia resolved.

TAKE HOME

- Do not test for hypothyroidism, if there are no supportive findings
- Erythrogram: low reference or below very common
- Biochemistry: hypercholesterolaemia very common
- Combine thyroid hormones for a better interpretation
- Low ft4 may be more specific, as TT4 but influence by NTI as well
- TGAA indicate thyroid pathology, but not necessarily hypothyroidism
- TGAA can influence concentration of thyroid hormones

What to do if the hypothyroid dog is not responding to treatment?



LABOKLIN GmbH & Co. KG, Bad Kissingen, Germany

Dr Jennifer von Luckner

Short reminder – standard treatment

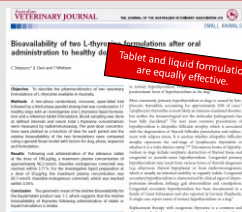
L-Thyroxine (T4)

T4 is converted to T3 which is the main active hormone within the cells

10-20 (-40) ug/kg SID-BID

Oral as well as liquid formulations available

Diet can influence intestinal drug absorption:
Consistent interval between pilling + feeding is essential for monitoring T4.



Short reminder – standard treatment

Once daily pilling has similar efficacy as twice daily.

Some dogs will need twice daily pilling.

A Pivotal Field Study to Support the Registration of Levothyroxine Sodium Tablets for Canine Hypothyroidism

Victoria A. Lumb, DVM, MS, CAE, DACVIM, MRCV, CDE, DACVP, MRCV, DVM, PhD, DABVP, Jeffrey A. Janowski, DVM, MS, DABVP, DACVIM, DAB, PhD, DABVP

ABSTRACT

A prospective, parallel, multicenter field study to evaluate the dose regimen, effectiveness, and safety of levothyroxine sodium tablets (L-T4) for the treatment of canine hypothyroidism and hypercholesterolemia. The study included 100 dogs with confirmed canine hypothyroidism and hypercholesterolemia. The study was conducted in 10 different locations across the United States. The study included 100 dogs with confirmed canine hypothyroidism and hypercholesterolemia. The study was conducted in 10 different locations across the United States. The study included 100 dogs with confirmed canine hypothyroidism and hypercholesterolemia. The study was conducted in 10 different locations across the United States.

Pharmacokinetics of Total Thyroxine after Repeated Oral Administration of Levothyroxine Solution and its Clinical Efficacy in Hypothyroid Dogs

IC: van Dijk, G. Le Thiec, B.D.M., van der Meulen, S., Bergsma, L.H., Burger, and H.G. Schrijver

Background: The pharmacokinetics of L-thyroxine in a solution and in a tablet formulation were compared.

Objective: The objective of this study was to compare the pharmacokinetics of L-thyroxine in a solution and in a tablet formulation.

Methods: The study included 10 dogs with confirmed canine hypothyroidism and hypercholesterolemia. The study was conducted in 10 different locations across the United States.

Results: The study showed that the pharmacokinetics of L-thyroxine in a solution and in a tablet formulation were similar.

Conclusion: The study showed that the pharmacokinetics of L-thyroxine in a solution and in a tablet formulation were similar.

Short reminder – monitoring

Timing

a) In relation to start of treatment/change of dose

- 2-4 (-6) weeks after starting treatment
- 2-4 (-6) weeks after change of dose
- As soon as the patient is well controlled:
q 6-12 months

b) In relation to pilling

- 4-6 hours post pill
- Through level (directly pre pill)
- Peak concentration (3 h post pill)

Parameters

o T4

- 4-6 hours postpill
 - Upper half of reference interval
 - 20-47 nmol/l (2.3-5.6 ug/dl)
- Peak concentration (3 h post pill)
 - High end of reference interval or slightly above
- Trough level (directly pre pill):
 - Recommended by some authors for once daily pilling
 - Within reference / slightly above lower end
 - 19 nmol/l (1.5 ug/dl)

o TSH

- Within reference or below lower limit
- Usually not needed
- May be helpful in case of difficulties with controlling disease

o Clinical signs

- o Improvement within 4-8 weeks after starting treatment/reaching T4 goal

What to expect

Clinical signs	Lethargy	Some days
	Adipositas	Approx. 10% weight loss within the first few months
	Skin + fur	Improvement within first months Normalisation after 2-3 months (possibly longer)
	Reproduction	Several months
	Neurologic	Several months
Haematology / biochemistry	Anaemia	2-4 weeks
	Hypercholesterolaemia	
	Hypertriglyceridaemia	
TT₄	Time of sampling	4-6 hours pp // 3 Stunden pp
	Aim	Upper half of reference // upper limit of reference or slightly above
TSH	Aim	Within reference or below

Inadequate response to treatment

1. Is this hypothyroidism after all?
2. There a factors that can reduce serum TT4 concentration
3. Laboratory error
4. Keep T4 pharmacokinetic in mind!
5. Compliance
6. Is T3 the solution?

Treatment trial – Withdrawal to do functional testing

How to withdraw?

Likely best to do it abrupt.

How long to wait before performing functional testing?

J Vet Intern Med 2013;38:705-710

Effects of Levothyroxine Administration and Withdrawal on the Hypothalamic-Pituitary-Thyroid Axis in Euthyroid Dogs

V. Zigelbo, D.L. Panciera, G.C. Troy, W.E. Monroe, K.M. Boss, and K.R. Refsal

- Healthy dogs
- Treatment for 8 or 16 weeks (20 ug/kg q 24 h)
- Abrupt withdrawal
- T4, fT4, T3, TSH measurement 1 + 4 weeks later
- After 1 week all values were what they had been originally

Factors that may reduce serum TT4 concentration

- NTI – especially hyperadrenocorticism!
- Drugs
 - Glucocorticoids
 - Non-steroidal antiplogistics? (phenylbutazone, acetylsalicylic acid)
 - Phenobarbital
 - Barbiturates, diazepam
 - Sulphonamides
 - Furosemide
- Influence on resorption:
 - Antacids
 - Diet rich in fibre
 - Diet high in minerals

Laboratory error

- a) Antibodies
 - Interference with TT4 measurement possible
 - No influence on effect of Levothyroxine
- b) Haemolysis
- c) Lipaemia
- d) In-house measurements?

The effect of lipaemia

- ⇒ Sample inhomogeneity
 - ⇒ Optic interference
 - ⇒ Interference with antibody affinity
- = Turbidity (chylomicrons: triglycerides > 3,4 mmol/l)
 - = Lipid content



In-house vs external laboratory



- In-house underestimates TT4
- Differences may affect interpretation at higher serum TT4 concentrations

Peter Graham at ECVIM Congress 2021:
Effect may be more relevant
+ non-linear discrepancies

Consider pharmacokinetics

- Appropriate pilling – blood sampling interval? Serum T4 concentration will decline substantially 6-12 hours post pill
- Sufficient time to reach serum levels? Will not be the case after one week.
- Differences in bioavailability between human and veterinary formulations discussed
- Pilling in combination with food decreases bioavailability
- Individual drug absorption and elimination properties possible
- Loss with faeces – may cause decreased serum levels with enteropathies
- Some dogs may need BID even if recommended otherwise in the leaflet

Consider pharmacokinetics

- a) Compliance?
 - Dosing recommendation understood and correctly put into practice?
 - Correct tablet concentration sold?
 - How often is medication skipped / not given regularly?
 - Are tablets really going into the dogs stomach?
- a) Minimum durability
- b) Did the dog receive medication on the day of blood sampling?

Is T3 the solution?

- a) Problems with conversion of T4 to T3 theoretically possible but not described in dogs
- b) Measurement of T3 instead of T4?
 - May be of help if T4 antibodies are interfering with T4 measurement (but may be an issue with T3 as well)
 - Not helpful with glucocorticoid induced T4 reduction
 - Drugs (and NTI) can influence T3 as well
- c) Can treatment of individual dogs with T3 instead of T4 be make sense?
 - Only in very rare cases with lack of clinical response despite adequate serum T4 concentration + reliable diagnosis
 - 4-6 ug/kg q 8 hours
 - Increased risk of thyreotoxicosis
- d) Human T4/T3 combination preparations should not be used in dogs

What to ask myself, if the patient is not responding to treatment as anticipated?

1. Is this hypothyroidism after all?
2. Factors that may influence serum TT4 concentration
3. Consider TT4 pharmacokinetics
4. Compliance



Take Home
