# A retrospective study of musculoskeletal pain in hypothyroid dogs and cats

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Swedish University of Agricultural Sciences, SLU
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Veterinary Medicine Programme

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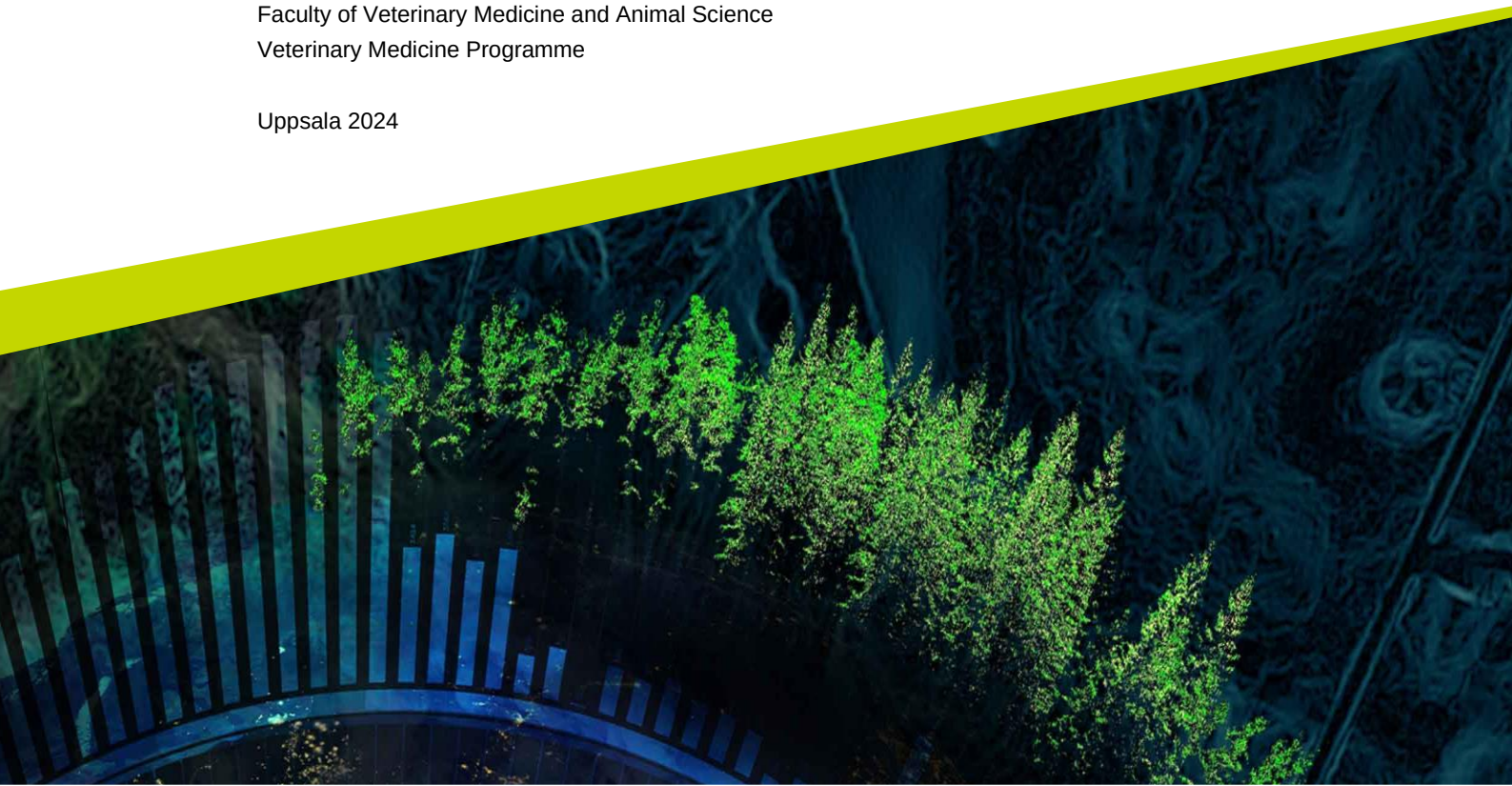

# A retrospective study of musculoskeletal pain in hypothyroid dogs and cats

*En retrospektiv studie över muskuloskeletal smärta hos hundar och katter med hypotyreos*

Greta Dagfjäll

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## Abstract

Musculoskeletal symptoms are commonly described in hypothyroid humans but are rarely described in dogs with hypothyroidism. In this retrospective study, medical records of dogs and cats with hypothyroidism during the time period 2009 till 2019 at the University Animal Hospital, Swedish University of Agricultural Sciences (SLU), Sweden, were reviewed to investigate the prevalence of signs of musculoskeletal pain. The following musculoskeletal manifestations were recorded as signs of musculoskeletal pain; signs of pain from the locomotory apparatus in the clinical history and presence of lameness or reactions at the clinical examination that implicate pain from the locomotory apparatus at the time of diagnosis.

Of the identified 107 hypothyroid dogs, 39% showed musculoskeletal pain before or at the time of diagnosis. 14% of the dogs had only a clinical history (anamnestic or veterinary consultation) of pain before diagnosis, and 25% presented with signs of musculoskeletal pain at the time of diagnosis. Of all dogs, both those with only a history of musculoskeletal pain and those presenting with clinical signs of pain at the time of diagnosis of hypothyroidism, the musculoskeletal signs diminished in 31% after hormone therapy for hypothyroidism according to what could be found in the medical recordings. Of the dogs with lameness at the time of diagnosis musculoskeletal signs diminished in 41% after hormone therapy. Of the dogs with persistent musculoskeletal pain after hormone therapy there were other concurrent diagnoses or descriptions in the medical records such as old trauma and severe osteoarthritis.

Among the identified 9 hypothyroid cats, one cat was described to have musculoskeletal signs in the form of stiffness. The clinical notes post diagnosis and treatment with hormone therapy indicated improved mobility in the patient, but statistics could not determine the effect from hormone therapy on musculoskeletal pain due to the small study group.

The prevalence of musculoskeletal signs in hypothyroid dogs were higher than previously reported in the literature. With hormone therapy, the musculoskeletal signs resolved in more than a third of the dogs that exhibited lameness at the time of diagnosis. However, the change in comparison to the control group of hypothyroid dogs without musculoskeletal signs was not statistically significant. Therefore, it remains to be established whether hypothyroidism can cause musculoskeletal pain in dogs that resolves after therapy, although such a relationship exists in humans. The result of this retrospective study indicates that musculoskeletal pain is more common in hypothyroid dogs than previously reported, and testing for thyroid function is indicated in dogs with diffuse musculoskeletal pain. A prospective or longitudinal study of dogs at-risk could reflect the development of musculoskeletal manifestations in hypothyroidism.



*Keywords:* Hypothyroidism, musculoskeletal, neuromuscular, pain, myalgia, arthralgia

## Sammanfattning

Muskuloskeletal smärta vid hypotyreos är vanligt förekommande hos människa, men finns inte dokumenterat hos hundar i samma utsträckning i litteraturen. I denna retrospektiva studie har journalunderlag från tidsperioden 2009 till 2019 vid Universitetsdjursjukhuset, Sveriges lantbruks-universitet, granskats för att undersöka prevalensen av muskuloskeletal smärta vid hypotyreos hos hundar och katter. Förekomst av muskuloskeletal smärta har bedömts utifrån huruvida det finns anamnestiska uppgifter om smärta före och/eller vid diagnostillfället, samt hälta eller reaktion som kan tyda på smärta från rörelseapparaten vid klinisk undersökning vid diagnostillfället.

Av de 107 hundar med hypotyreos som identifierades, uppvisade 39 % av hundarna tecken på lokal eller generell smärta från rörelseapparaten före eller i anslutning till diagnostillfället, 14 % hade en klinisk historik (utifrån anamnestiska uppgifter eller veterinär konsultation) om smärtförekomst innan hypotyreos diagnostiserades och 25 % av hundarna visade tecken på muskuloskeletal smärta vid klinisk undersökning i samband med diagnostillfället. Av samtliga hundar som haft historik eller uppvisade smärta i någon form vid diagnosställandet hade de kliniska tecknen som kopplades till smärta minskat hos 31 % av patienterna efter behandling med sköldkörtelhormon, vilket kunde utläsas från noteringar i journalerna. Av de hundar som uppvisat tecken på smärta i rörelseapparaten vid diagnostillfället hade dessa tecken enligt journalerna minskat hos 41 % av patienterna efter hormonbehandling. Bland de hundar som det inte gick att utläsa en förbättring hos efter hormonbehandling fanns andra muskuloskeletala sjukdomar beskrivna som t ex trauma eller osteoartrit av allvarligare grad.

Av de 9 katter med hypotyreos som identifierades, beskrevs muskuloskeletala sjukdomstecken i form av stelhet hos en katt, och viss förbättring kunde ses avseende detta efter att hormonbehandling satts in. Det saknades generellt information om uppföljning efter hormonbehandling hos katterna och studiegruppen var förhållandevis liten och inga slutsatser kunde därmed dras om smärtan försvann efter det att normal sköldkörtelhormonstatus uppnåtts eller inte.

Prevalensen av muskuloskeletala tecken hos hundar med hypotyreos var högre än vad som tidigare rapporterats och enligt vad som gick att utläsa från journalerna förbättrades de kliniska tecknen på muskeloskeletal smärta i över en tredjedel av fallen. Förändringen var dock inte statistiskt signifikant, jämfört med gruppen utan tecken på smärta vid diagnostillfället, vilket skulle kunna bero på ett så kallat typ-II fel, det vill säga det var ett för litet antal hundar för att avgöra om det finns ett samband eller inte. Det går därför inte, i denna retrospektiva studie, att statistiskt fastställa om en del av den smärta som noterats innan och i samband med diagnosställandet och som försvunnit efter behandling, sannolikt är relaterad till hypotyreos eller inte, även om ett sådant samband har fastställts på människa. En prospektiv eller longitudinell studie av hundar ”at-risk” behövs för att studera fenomenet i närmare detalj.



*Nyckelord:* Hypotyreos, muskuloskeletal, neuromuskulär, smärta, myalgi, artralgi

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# Abbreviations

| | |
|---|---|
| $^{99}$Tc | Technetium-99 |
| CK | Creatine kinase |
| GAGs | Glycosaminoglycans |
| T3 | Triiodothyronine |
| T4 | Thyroxine |
| TgAA | Thyroglobulin autoantibody |
| TRH | Thyrotropin-releasing hormone |
| TSH | Thyroid stimulating hormone |
| TT4 | Total T4 |

# 1. Introduction

Hypothyroidism is one of the most common endocrine disorders in dogs, resulting in low levels of thyroid hormones. This can result in various clinical manifestations e.g., lethargy, weight gain and alopecia. In humans, musculoskeletal pain and joint stiffness are common symptoms in patients with hypothyroidism. It is suggested that the term hypothyroid myopathy should be used in hypothyroid patients presenting with predominantly musculoskeletal symptoms (Sindoni et al. 2016). Some early studies have shown up to 88-100% reversibility in musculoskeletal symptoms after thyroid hormone treatment (Wilson & Walton 1959; Golding 1970; Abiodun et al. 1973). In dogs, musculoskeletal pain is not as frequently described in association with hypothyroidism. In a literature study in the form of a Bachelor's thesis (Eklund 2017) signs of musculoskeletal or neuromuscular pain were only described in 4 of 140 hypothyroid dogs. This contrast between reported frequencies of musculoskeletal pain in humans, compared to dogs, led to the hypothesis that signs of pain from the locomotor apparatus is underreported in dogs with hypothyroidism. One reason for this could be that the signs of musculoskeletal pain are most prominent in dogs with hypothyroidism at time of diagnosis.

In this retrospective study, dogs and cats with hypothyroidism during the period 2009 – 2019, were identified in the clinical data system of the University Animal Hospital in Uppsala, Sweden. The medical records were then evaluated regarding descriptions of musculoskeletal pain in dogs with hypothyroidism before and at time of diagnosis, and whether signs of pain in the locomotor apparatus improved after initiation of treatment of hypothyroidism.

# 2. Literature

## 2.1 Thyroid anatomy and function

The thyroid gland in dogs and cats consists of two separate lobes located on the left and right lateral side of trachea, at the level just below the larynx. It consists of follicular cells responsible for synthetizing and releasing of thyroid hormones – thyroxine (T4) and triiodothyronine (T3), and C-cells in the connective tissue responsible for the synthesis of calcium regulating hormone (Sjaastad et al. 2010). The release of thyroid hormones is stimulated by thyroid-stimulating hormone (TSH) from the pituitary gland, which in turn is stimulated by thyrotropin-releasing hormone (TRH) from the hypothalamus (Figure 1). Thyroid hormones play a major role for cell function by increasing metabolism, and oxygen consumption. They stimulate growth and are important for development of the nervous system and function of the gonads. The skeletal muscle is a major target for thyroid hormones, which are crucial for myogenesis and contractile function by regulating expression of myosin (Salvatore et al. 2014; Bloise et al. 2018).

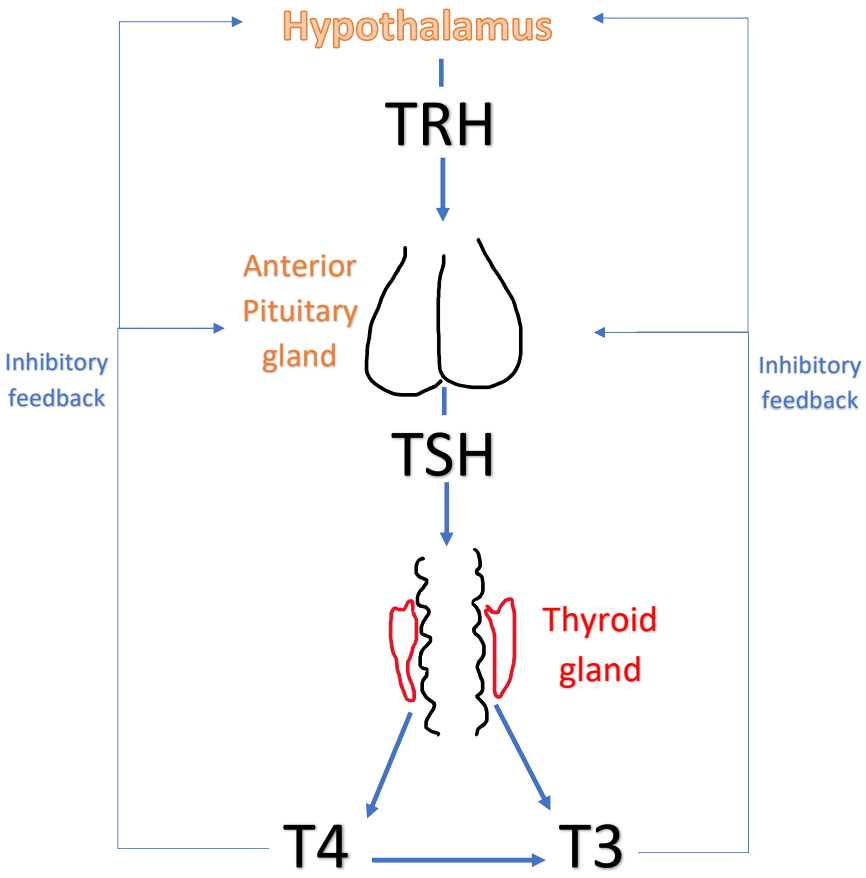


*Figure 1. The interplay between the hypothalamus, the pituitary gland and the thyroid gland. TRH, thyrotropin-releasing hormone; TSH, thyroid stimulating hormone; T4, thyroxine; T3, triiodothyronine. Illustration by the author.*

## 2.2 Etiopathogenesis

The most common form of hypothyroidism in dogs is primary hypothyroidism, which in most cases is the result of lymphocytic thyroiditis, an autoimmune process against thyroid structures, e.g., thyroglobulin, which leads to thyroid destruction and eventually hypofunction (Nelson 2020). The initiating factor(s) for the immunological response remains unknown. Release of thyroid hormones will gradually decrease, resulting in an increased release of TSH from the pituitary gland, to which the thyroid gland will be unable to respond. Hypothyroid patients are therefore most likely to present with high levels of TSH and low levels of thyroid hormones. However, there are exceptions. It has been shown that chronic hypothyroidism is associated with gradual decrease in TSH-concentrations. (Diaz-Espiñeira et al. 2008)

Secondary hypothyroidism occurs when there is a hyposecretion of TSH from the pituitary gland (Kooistra et al. 2000; Voorbij et al. 2016). The cause for reduced TSH synthesis and secretion could be tumors, malformation or other diseases affecting the pituitary gland. Secondary hypothyroidism is rare in dogs but is described in cases of pituitary dwarfism.

Tertiary hypothyroidism is a very rare condition and has only been documented with certainty once (Shiel et al. 2007). In this condition the thyroid hormones are low due to reduced synthesis and secretion of TRH from hypothalamus thus even the synthesis and secretion of TSH from the pituitary gland.

Hypothyroidism in cats is not as common, most cases are iatrogenically caused by radioactive iodine treatment for hyperthyroidism (Scott-Moncrieff 2007). Congenital hypothyroidism is also seen sometimes and is often secondary due to pituitary gland malformation. Recently, non-iatrogenically caused hypothyroidism in adult cats has been reported (Peterson et al. 2018).

## 2.3 Clinical signs of hypothyroidism in dogs

Since thyroid hormones have central regulating functions in cellular metabolism, there are many clinical manifestations, which can vary in clarity and severity from being very subtle and vague to more conspicuous. Clinical signs include obesity or weight gain due to reduced metabolism, changes in behavior, fatigue and exercise intolerance, reduced resistance to cold (Panciera 1994; Dixon et al. 1999) and sometimes gastrointestinal signs (Panciera 2001). Dermatologically, the hair follicles remain in resting phase (telogen phase) which with time result in a generalized or local (typically the tail or sides of the body) alopecia and a dull haircoat (Panciera 2001). In addition, thickening of the skin due to accumulation of mucopolysaccharides may be seen (myxedema) (Scott-Moncrieff 2007). Myxedema is usually localized subcutaneous to the forehead causing a characteristic "puffy face". Some individuals also develop seborrhea and pyodermia (Dixon et al. 1999).

## 2.4 Diagnosis

Clinical signs of hypothyroidism are often subtle and unspecific without pathognomonic clinical signs. To support the diagnosis of hypothyroidism, thyroid hormone measurements are often used. Typically, low serum concentrations of T4 support the diagnosis of hypothyroidism. However, low serum concentrations of the total T4 (TT4) alone do not necessarily equal hypothyroidism because con-

current disease may lower the serum concentrations of TT4, without any deficiency of thyroid hormone at the cellular level, so called “euthyroid-sick-syndrome” (von Klopmann et al. 2006). This can be explained by the fact that the large proportion of serum TT4 is protein bound, and only a small proportion remain unbound and active (free T4). In some situations, the result of serum TT4 concentration measurements can be within normal reference range, spite of the existence of hypothyroidism at the cellular level e.g., if the dog has developed anti T4 antibodies (Mooney 2011). In that situation, measurement of the free-hormone fraction with equilibrium dialysis is indicated. Another situation with falsely high hormone concentration is in the presence of so called heterophilic antibodies which interfere with the laboratory analysis (Bergman et al. 2020).

To overcome the risk of over-diagnosing hypothyroidism based on a single TT4 measurement, concurrent measurement of serum-TSH is usually performed (Diaz-Espiñeira et al. 2008). Typically, presence of primary hypothyroidism is supported by low serum TT4, and elevated serum TSH, unless diagnosis is made late in the progress of disease when TSH has already been downregulated.

Sometimes serum is tested for presence of autoantibodies against thyroid globulin (TgAA) (Mooney 2011; Nelson 2020). Presence of TgAA indicate autoimmune thyroiditis and can support a diagnosis of hypothyroidism. However, thyroid gland function can still be sufficient in the presence of TgAA.

When there are doubts about diagnosis, a stimulation test using synthetic TSH can be used to evaluate thyroid gland function (Daminet et al. 2007, Mooney 2011). In the test, TT4 is measured before and after administration of TSH. However, the test result is not definitive and synthetic TSH is expensive. Therefore, the test is not routinely used in veterinary practice.

Scintigraphy is another method of measuring thyroid function that can be used when serum hormone measurements are not diagnostic for hypothyroidism (Pinilla et al. 2009). In this test, radioactive technetium-99 ($^{99}$Tc) is used. The $^{99}$Tc accumulates in the thyroid gland by the iodine pumps and the intensity of radioactivity in the thyroid gland is compared with the intensity of accumulated material in the salivary gland, which is used as a control.

## 2.5 Treatment

Even though thyroid hormones are important for many functions in the body, supplementation with synthetic thyroid hormones on a daily basis is not vital, but recommended to avoid the negative effects of hypothyroidism (Sjaastad et al. 2010). For most dogs with hypothyroidism, treatment is lifelong (Dixon et al.

2002). The patient will need follow-up visits on a regularly basis, to ensure that the serum concentrations of thyroxin is within reference interval, with concurrent normalization of TSH. Follow-up sampling and evaluation is usually made three to four hours after medication is given, when serum concentrations are at the highest level. Treatment usually has a good effect and prognosis for the patient is generally good.

## 2.6 Musculoskeletal and neuromuscular symptoms in human patients

Musculoskeletal symptoms in humans with hypothyroidism were described already in 1959 in three patients who underwent thyroidectomy (Wilson and Walton, 1959). All patients developed muscular dysfunction which was reversible with treatment with T3. In a study on nine hypothyroid patients in 1970, all patients described pain in various forms (Golding 1970). The pain sensation was generalized and/or localized to specific areas e.g., neck, back, wrists, limbs and ankles. Eight out of nine of the patients also had stiffness, seven displayed cramps and five experienced acroparaesthesiae (an abnormal sensation of tingling, numbness, pins and needles in hands and fingers). In another study, administration of phenylbutazone aggravated the symptoms in one patient since phenylbutazone has an antithyroid effect and antagonizes peripheral T4 (Abiodun et al. 1973). In all nine patients described by Golding 1970, symptoms were alleviated by thyroid hormone administration within a few weeks of administration. Relief of stiffness was more pronounced than relief in pain. Acroparaesthesiae was completely reversible (Golding 1970). The suggestion based on this study is that hypothyroidism should be considered a differential diagnosis in patients presenting with pain and stiffness in the body. Furthermore, there are cases where human patients with hypothyroidism may have musculoskeletal symptoms as the major or only presenting symptoms indicating hypothyroidism. In one study the described musculoskeletal symptoms were muscle cramps, aches, proximal symmetrical muscle weakness, stiffness, polymyositis, and exercise intolerance which were relieved by T4 treatment (Kumar et al. 2023).

There are several studies revealing high prevalence of musculoskeletal symptoms in hypothyroid human patients (Cakir et al. 2003). Many hypothyroid patients have significant elevations of serum muscle enzymes most commonly creatine kinase (CK) in 37-60% of the patients (Sindoni et al. 2016) and studies has shown an occurrence of myopathy in 30-80% of cases (Ozker et al. 1960; Nickel et al. 1961). The elevation of CK indicate muscular degradation, for instance presenting as painful muscles, weakness, cramps and “sluggish” movements. However, the serum CK and severity of myopathy is not always related.

Based on the common occurrence it is suggested that the term hypothyroid myopathy should be used in hypothyroid patients presenting with predominant musculoskeletal syndromes, or musculoskeletal symptoms alone (Sindoni et al. 2016). The muscle abnormities in this review were asymptomatic elevations of CK, myalgia, myoedema, muscular pseudohypertrophy, proximal myopathy or rhabdomyolysis and they presented with various clinical manifestations and pain were described in several of them.

Arthralgia is commonly described in humans (McLean & Podell 1995; Cakir et al. 2003). In addition, myxedema is commonly formed in the subcutis and connective tissue, commonly accumulating in the forehead, but also in joints causing swelling of the joints which may be one of the causes to arthralgia. The production of mucopolysaccharides (glycosaminoglycans, GAGs) rich in hyaluronic acid, in the connective tissue is stimulated by TSH, whereas T3 inhibits formation of GAGs (McLean & Podell 1995). Accordingly, high levels of TSH and low levels of T3 increases the production of hyaluronic acid in the subcutaneous tissue, which attracts water molecules resulting in myxedema.

Neuromuscular symptoms are commonly described by humans with hypothyroidism (Duyff et al. 2000). As many as 79% of hypothyroid patients that participated in the prospective study by Duyff et al. (2000) described neuromuscular symptoms in various forms.

## 2.7 Musculoskeletal signs in dog patients

The number of studies is limited regarding how the hypothyroidism affects the locomotor apparatus in dogs. Musculoskeletal and neuromuscular effects are known in dogs, but pain is rarely described in hypothyroid dogs. Like in humans, increased serum concentrations of CK has been described in several studies, and was observed in all 6 included dogs in one study (Rossmeisl et al. 2009). Neuromuscular pain has been described in four dogs presenting unilateral lameness (Budsberg et al. 1993). Thyroid hormones stimulate mitochondrial function by influencing sodium-potassium pumps and ATP-production which can lead to reduced neural transduction in a hypothyroid state (Miller 2017). Changes in sodium-channels alters neural activity and muscular denervation can quickly lead to muscular atrophy. The signs of neuropathy are similar to those of myopathy, and it is therefore difficult to differentiate between the two.

In a literature study (Eklund 2017) based on case reports and retrospective studies (Kaelin et al. 1986; Indrieri et al. 1987; Budsberg et al. 1993; Panciera 1994; Delauche et al. 1998; Dixon et al. 1999) musculoskeletal manifestations in hypo-

thyroid dogs were reviewed. The studies together included in total 140 dogs. Of these, musculoskeletal signs were described in 24 dogs. In 4 dogs, pain was described in the form of unilateral lameness (Budsberg et al. 1993). Stiffness, lethargy and muscular atrophy were other descriptions when musculoskeletal involvement was described. The musculoskeletal signs reported in human and dog patients are listed in table 1.

*Table 1. Comparison of musculoskeletal signs generally described in hypothyroid human patients versus hypothyroid dogs from previous literature studies (Sindoni et al. 2016; Eklund 2017).*

| | Humans | Dogs |
|---|---|---|
| Musculoskeletal signs | Generalized pain | Stiffness |
| | Aches | Lethargy |
| | Muscle weakness | Lameness |
| | Polymyositis | Muscular atrophy |
| | Pain in specific areas | |
| | Stiffness | |
| | Cramp | |
| | Acroparaesthesiae | |
| | Exercise intolerance | |
| | Carpal tunnel syndrome | |

# 3. Material and methods

Clinical records from hypothyroid dogs and cats from the University Animal Hospital, Swedish university of Agricultural Sciences, Sweden between 2009 and 2019 were reviewed. The animals were identified by a search in the clinical database Trofast for dogs and cats that had received a diagnosis code for hypothyroidism, EA2371, based on the national diagnostic registry (Olson et al. 1993), during the period of 2009-01-01 to 2018-12-31.

The animals were excluded if data from the time of diagnosis of hypothyroidism were not present and in cases where the diagnosis of hypothyroidism were not confirmed. To be regarded as a confirmed case of hypothyroidism, the clinical data from the time of diagnosis needed to be present including measurement of serum TT4 concentration below reference range in combination with elevated serum TSH concentrations, with or without presence of TgAA. In case the serum TSH concentration was within reference ranges, serum TT4 below detection limit in combination with typical clinical signs of hypothyroidism including lethargy, alopecia, hyperpigmentation of the skin or hypofunctioning thyroid gland confirmed by scintigraphy. Dogs and cats that had undergone iodine treatment or had their thyroid glands surgically removed were included in the study if the diagnostic criteria for hypothyroidism was fulfilled.

The history and findings from clinical examination in the clinical records were screened for description indicating lameness and/or musculoskeletal pain before, at the time of, and after the diagnosis of hypothyroidism. Only musculoskeletal pain or lameness with an obvious underlying cause, e.g., acute trauma, were excluded. Other related findings such as generalized weakness or loss of neurological function, and any analgesic drug that was administered together with thyroid hormone supplementation were also registered.

When screening the clinical records for each patient, the time of diagnosis were firstly determined and noted in Microsoft Excel. To determine if musculoskeletal findings were present at time of diagnosis, the clinical notes from the veterinary examination from the same date were evaluated. In the search of history of musculoskeletal signs, eventual notes from the same visit that indicated earlier problems have been noted. This could be information given by the owner or

clinician. All available medical record from earlier visits were also gone through in search for historic musculoskeletal signs.

To determine if musculoskeletal signs were present after hormonal treatment started the following medical records were evaluated. Only if there was a clear notification in the medical journal of musculoskeletal improvement present the patient were considered improved. If no information were given regarding musculoskeletal improvement, the patient was considered as not improved.

For the literature study, search was made in databases such as PubMed, Web of Science and Google Scholar using search criteria (hypothyroidism OR hypothyroid) AND (canine OR dog OR dogs OR human) AND (musculoskeletal OR muscular OR muscle OR joint OR joints OR limbs) AND (pain OR stiffness OR symptoms OR manifestations). In addition, medical textbooks were also used for the literature part.

Descriptive data include species, gender and neuter status, breed, age by the time of diagnosis, cause of hypothyroidism and description of presence of musculoskeletal pain according to the criteria above, before diagnosis, and/or at the time of diagnosis and/or after treatment for hypothyroidism, and analgesics drugs that were administered together with thyroid hormone supplementation. The categorial data are presented as numbers and percentages.

## 3.1 Statistical analysis

Statistical analysis was performed in R studio version 1.3.1093. The presence of lameness before and after treatment of hypothyroidism was tested with McNemars test, used to compare paired samples with binary responses. A continuity correction was included if the cell counts in the four-fold table were less than five. A p-value $<0.05$ was considered statistically significant.

Statistics were performed on various selections from the study group to test the correlation between hormone therapy and musculoskeletal relief and are presented under different headings. The selections were sorted according to when musculoskeletal signs occurred based on information from the medical records in relation to time of diagnosis.

# 4. Results

After the initial search, 7 dogs and 2 cats were excluded leaving 107 dogs and 9 cats remaining for the study. 42 of the dogs and 5 of the cats showed musculoskeletal clinical signs before and/or at the time of diagnosis. The selection process and results are illustrated in figure 2 as an organigram. The individuals presenting with musculoskeletal signs are grouped according to when in time related to time of diagnosis signs expressed and are separated by species.

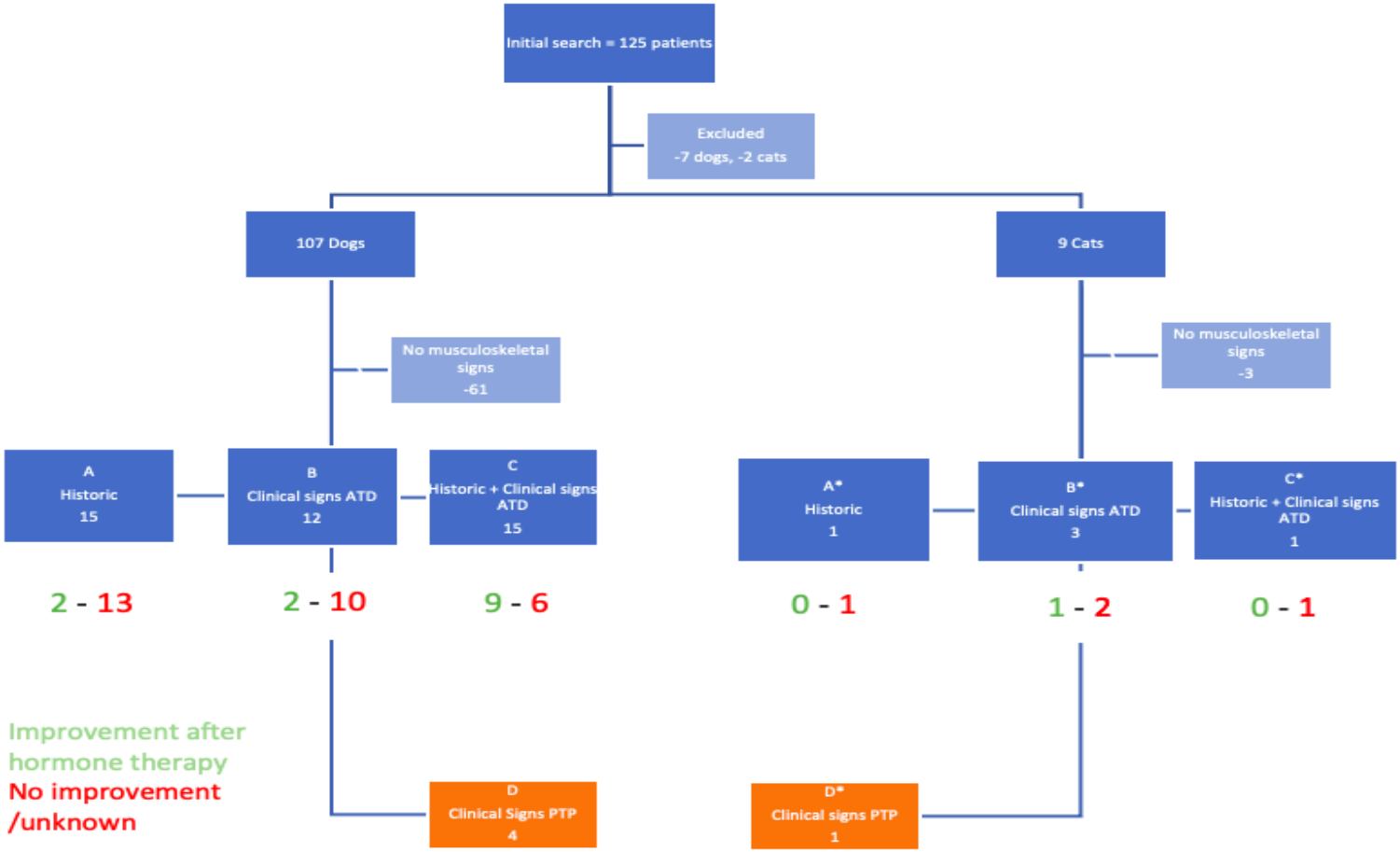


*Figure 2. Overview of the selection of study groups and findings from medical recordings of hypothyroid patients presenting musculoskeletal signs. ATD= At time of diagnosis. Historic = History of musculoskeletal signs. PTP= Post Treatment Period (patients for which the first documentation of musculoskeletal signs came after treatment for hypothyroidism was initiated.)*

## 4.1 Dogs

The total number of included dogs was 107. There were 53 (49.5%) male dogs and 54 (50.4%) female dogs of which 16 (30%) of the male dogs and 12 (22%) of the female dogs were castrated. There were 54 different breeds represented of which mixed breed, Golden Retriever, Boxer, Welsh Springer Spaniel, Riesenschnauzer and Shetland Sheepdog were the most common (Table 2). In addition to the breeds displayed in table 2 there was one dog each from 32 additional breeds.

*Table 2. Breed distribution of 107 hypothyroid dogs treated at the Swedish University of Agricultural Sciences during 2009-2019 and included in the retrospective study of musculoskeletal signs in dogs with hypothyroidism.*

| **Breed** | *n* | | |
|---|---|---|---|
| Golden Retriever | 7 | Lagotto Romagnolo | 3 |
| Mixed breed | 6 | Nova Scotia Duck Tolling Retriever | 3 |
| Boxer | 5 | Australian Kelpie | 2 |
| Welsh Springer Spaniel | 5 | Bichon Havanais | 2 |
| Shetland Sheepdog | 5 | Cocker Spaniel | 2 |
| Riesenschnauzer | 4 | Doberman Pincher | 2 |
| Labrador Retriever | 4 | Finnish Lapphund | 2 |
| German Shepherd | 4 | Swedish Elkhound | 2 |
| Papillon | 3 | German Pinscher | 2 |
| Toy Poodle | 3 | Other | 32 |
| English Springer Spaniel | 3 | | |
| Eurasier | 3 | | |
| Hovawart | 3 | | |

Of the dogs, 73% had the diagnosis of primary hypothyroidism or the more specific diagnosis lymphocytic thyroiditis confirmed. In one dog, secondary hypothyroidism was suspected. Seven dogs suffered from iatrogenic hypothyroidism after iodine treatment due to hyperthyroidism (5) or thyroidectomy for treatment of thyroid carcinoma (2).

The median age of diagnosis for dogs with primary hypothyroidism was 6.1 years (range 1.5 years to 12 years), the dog suspected to have secondary hypothyroidism was 5 years, median age for dogs with iatrogenically caused hypothyroidism after iodine treatment was 6 years (range 3.7 to 12.6 years). For the dogs that underwent treatment for thyroid carcinoma, the range of age at diagnosis was 7.5 to 8.5 years. The inclusion and exclusion process is visualized in figure 2 as an organigram. In total 42 dogs (39%) displayed musculoskeletal signs before or at time of diagnosis. Of these, 15 dogs (14%) only had history of musculoskeletal signs (information from owner noted in the medical record or earlier visits regarding musculoskeletal

problems in the medical records, confirmed by clinician) (Group A); 12 (11%) dogs had no history of musculoskeletal problems found in the medical records but displayed pain in the form of lameness or painful reaction during the clinical examination at time of diagnosis (Group B); and 15 dogs (14%) had both history of musculoskeletal problems and presented with musculoskeletal signs at time of diagnosis (Group C). Four dogs had no history of and did not show musculoskeletal problems at time of diagnosis but presented musculoskeletal signs during the post-treatment period (Group D).

The musculoskeletal signs noted in the medical records were lameness (57%), stiffness (19%), reduced range of motion (14%), and painful reaction during examination (extending and flexing of joints and palpation of the locomotor apparatus) (26%). Some dogs displayed a combination of these musculoskeletal signs.

Musculoskeletal problems were documented to diminish in 13 dogs after initiation of hormone therapy. The highest proportion of documented improvement of musculoskeletal signs during hormone therapy was seen in group C where musculoskeletal signs improved in 9 of 15 dogs (60%) (Figure 2).

### 4.1.1 Statistical analysis – persistence of musculoskeletal manifestations after initiation of hormone therapy in hypothyroid dogs

*Dogs presenting with musculoskeletal signs before and at time of diagnosis*

This group consists of all dogs which had history of musculoskeletal signs and/or presented musculoskeletal signs at time of diagnosis (group A+B+C). They are presented in numbers in the 2 x 2 table (Table 3). The chance that the lameness decreased after treatment as a result from a random outcome could not be excluded (McNemar's test, p=0.05).

*Table 3. Presence of a clinical history of, and/or musculoskeletal signs at the time of diagnosis in 107 hypothyroid dogs treated at the Swedish University of Agricultural Sciences during 2009-2019, and documented improvement of the musculoskeletal signs after initiation of therapy for hypothyroidism.*

| *Musculoskeletal signs* | | *Before hormone therapy* | | |
|---|---|---|---|---|
| | | **Y** | **N** | |
| *After hormone therapy* | **Y** | 29 | 4 | 33 |
| | **N** | 13 | 61 | 74 |
| | | 42 | 65 | 107 |

*Dogs presenting with musculoskeletal signs at time of diagnosis*

In this group, only the dogs which showed musculoskeletal signs at time of diagnosis, regardless of previous history of musculoskeletal problems, are included (group B + C). The dogs with only historic musculoskeletal problems (group A) were added to the group of dogs which did not show musculoskeletal signs. The numbers are presented in table 4. The chance that the lameness decreased after treatment as a result from a random outcome could not be excluded (McNemar's test, $p = 0.12$)

*Table 4. Presence of musculoskeletal signs at the time of diagnosis in 107 hypothyroid dogs treated at the Swedish University of Agricultural Sciences during 2009-2019, and documented improvement of the musculoskeletal signs after initiation of therapy for hypothyroidism.*

| *Musculoskeletal signs* | | *Before hormone therapy* | | |
|---|---|---|---|---|
| | | **Y** | **N** | |
| *After hormone therapy* | **Y** | 16 | 4 | 20 |
| | **N** | 11 | 76 | 87 |
| | | 27 | 80 | 107 |

*Dogs with diffuse musculoskeletal signs*

Among the total 42 dogs presenting with musculoskeletal signs (A + B + C), 6 dogs had concurrent registered diagnoses related to the musculoskeletal system e.g., osteoarthritis, polyarthritis, patellar luxation, hip dysplasia and traumatic injuries. When these 6 individuals were excluded, there were 36 dogs with a history of musculoskeletal signs and/or presented musculoskeletal signs at time of diagnosis, of which 12 (33%) had documented relief of the signs after hormone therapy (Table 5).

*Table 5. Presence of a clinical history of, and/or musculoskeletal signs at the time of diagnosis in 101 hypothyroid dogs treated at the Swedish University of Agricultural Sciences during 2009-2019, and documented improvement of the musculoskeletal signs after initiation of therapy for hypothyroidism. In this population, 6 dogs with a concurrent registered diagnosis related to the musculoskeletal system e.g., osteoarthritis, polyarthritis, patellar luxation, hip dysplasia and traumatic injuries were excluded.*

| *Musculoskeletal signs* | | *Before hormone therapy* | | |
|---|---|---|---|---|
| | | **Y** | **N** | |
| *After hormone therapy* | **Y** | 24 | 4 | 28 |
| | **N** | 12 | 61 | 73 |
| | | 36 | 65 | 101 |

The chance that the lameness decreased after treatment as a result from a random outcome could not be excluded (McNemar's test, p=0.08).

## 4.2 Cats

In total nine cats with hypothyroidism were included in the study. There were four males and five females. Two cats were suspected to suffer from congenital form of hypothyroidism. Six cats had iatrogenically caused hypothyroidism after treatment of hyperthyroidism with radioactive iodine, one cat underwent thyroidectomy due to carcinoma.

The age at time of diagnosis for primary hypothyroidism were 14.9 and 16 years. Age at diagnosis for the cats which underwent iodine treatment ranged between 10.8 to 16 years, and median age was 11.4 years. The cat with thyroid carcinoma had the thyroid gland removed by surgery at eight months of age.

The breeds presented in the study group were eight Domestic shorthair and one Siberian.

The selection of cats for the study are presented in figure 2. There were in total five cats presenting musculoskeletal signs. One cat had history of musculoskeletal signs (group A*). Three cats lacked history of but presented musculoskeletal signs at the clinical consultation at time of diagnosis (group B*). One cat had history of and presented musculoskeletal signs at the clinic at time of diagnosis (group C*). One cat lacked history of musculoskeletal signs but developed signs after diagnosis was made and hormone therapy had begun (group D*).

The musculoskeletal signs described in the cats were lameness, painful reaction during palpation of the spine, pain during extending and flexing of joints and general stiffness.

One cat had improved mobility and pain relief after hormone therapy. For the rest of the cats, in the medical records, there was no information about musculoskeletal improvement after hormone therapy or not, and therefore, in this study, considered not improved.

### 4.2.1 Statistical analysis – persistence of musculoskeletal manifestations after initiation hormone therapy in hypothyroid cats

McNemar's test was performed on the whole study group of all cats presenting musculoskeletal signs and the numbers are presented in table 6. The chance that the lameness decreased after treatment as a result from a random outcome could not be excluded (p=1).

*Tabell 6: Presence of a clinical history of, and/or musculoskeletal signs at the time of diagnosis in 9 hypothyroid cats treated at the Swedish University of Agricultural Sciences during 2009-2019, and documented improvement of the musculoskeletal signs after initiation of therapy for hypothyroidism. Two cats had primary hypothyroidism, 7 cats had iatrogenically caused hypothyroidism after treatment of hyperthyroidism.*

| *Musculoskeletal signs* | | *Before hormone therapy* | | |
|---|---|---|---|---|
| | | **Y** | **N** | |
| *After hormone therapy* | **Y** | 4 | 1 | 5 |
| | **N** | 1 | 3 | 4 |
| | | 5 | 4 | 9 |

# 5. Discussion

The aim of this retrospective study was to investigate the occurrence of musculoskeletal pain in dogs diagnosed with hypothyroidism, and whether the signs of musculoskeletal pain was relieved by hormone therapy. In total 42 dogs (39%) displayed musculoskeletal signs before or at time of diagnosis. Fifteen dogs (14%) only had recorded history of musculoskeletal signs (as stated by the owner or clinician in previous visits at clinic), 12 (11%) dogs no clinical history of musculoskeletal problems but displayed pain during the clinical examination at time of diagnosis. Fifteen dogs (14%) had both a clinical history of musculoskeletal problems and presented also with musculoskeletal signs at time of diagnosis. In 13 (31%) of the 42 dogs, the clinical signs of pain from the locomotor apparatus were documented to diminish after treatment with thyroid hormone supplementation.

The signalements of the included dogs in the study are in agreement with previous studies. The proportion of male (49.5%) and female (50.4 %) dogs was basically equal. In humans, middle aged women are at higher risk of developing hypothyroidism (Garber et al. 2012), or women during pregnancy (Teng et al. 2013). Sixteen (30%) male dogs and 12 (22%) female dogs were neutered. In dogs, no significant difference between sexes or neuter status has been described (Dixon et al. 1999), though in one study, neutered animals had a significant higher risk of developing hypothyroidism (Panciera 1994).

The most common breeds in the present study were mixed breed and Golden retriever followed by Boxer, Riesenschnauzer, Welsh springer spaniel and Shetland sheepdog. The result was expected, since these breeds are reported to be predisposed for developing hypothyroidism in previous studies (Panciera 1994; Dixon et al. 1999).

The mean age at diagnosis of primary hypothyroidism (6.1 years) is in agreement with the mean age of 7 years reported in previous studies (Panciera 1994; Dixon et al. 1999).

In the present study, 27 (25%) of the dogs presented with musculoskeletal signs at time of diagnosis (dogs from group B + C), which is higher than what previously has been reported. In a previous review, only 2.8% out of 140 hypothyroid dogs

were described to show signs of pain (Eklund 2017). One possible explanation may be that previous publications focused on the clinical signs more traditionally known to be associated with hypothyroidism, e.g., clinical signs such as alopecia, exercise intolerance, and fatigue. Concurrent musculoskeletal pain may have been unrecorded. In the present study, the aim was to investigate whether dogs and cats had signs of musculoskeletal pain or lameness in their clinical records.

The noted musculoskeletal signs were in the form of lameness, stiffness, weakness and painful reactions during manipulation and palpation of joints, which agrees with what has been frequently reported in humans. Other musculoskeletal symptoms described in humans, such as cramps, acroparaesthesiae, aches and polymyositis (Golding 1970; Kumar et al. 2023) were rare or absent in the dogs, which can be explained by true absence of these clinical signs or, again, the retrospective nature of the present study, in which the clinicians may not have been attentive to these signs even if they were present.

Of the dogs with lameness at the time of diagnosis (group B+C), there were clinical recordings at follow-up visits that the signs were relieved after hormone supplementation in about 41% of the dogs. In the subset of dogs with no relief of musculoskeletal signs there was a description of more defined locomotory problems such as old trauma and severe osteoarthritis. It is possible that there may have been more dogs in which the musculoskeletal signs improved after hormone therapy since the dogs without clinical recordings of musculoskeletal improvement were regarded as not improved in this study. The improvement of the dogs after treatment approached, but was not below, the set level of statistical significance ($p<0.05$). The retrospective nature of the study where the documentation of musculoskeletal pain on history and clinical examinations were performed in a non-standardized way, may have reduced the power in the study.

Muscular pain, some of which is related to elevated serum CK concentrations, is commonly found in humans with hypothyroidism (McKeran et al. 1975; Sindoni et al. 2016) and also in dogs (Rossmeisl et al. 2009). However, CK was not included in the biochemical panel for any of the dogs included in the present study and therefore it is unknown to what extent the dogs with musculoskeletal pain had CK elevations or not. In the study by Rossmeisl et al. 2009, morphological changes in skeletal muscle were confirmed in all dogs with induced hypothyroidism, and CK was elevated in 2/6 dogs. The changes of skeletal muscle were subclinical but was discussed to be related to nonspecific clinical signs such as lethargy and exercise intolerance. In this study 25% of the dogs showed musculoskeletal signs at time of diagnosis, and it is likely to believe there may be a tangible impact on skeletal muscle morphology in these dogs as well.

The limitations of the present study are partly related to the retrospective nature of the study design. Some patients were diagnosed at other clinics and medical recordings have been absent or lacking information before diagnosis was made. In these cases, they have not been marked as presenting with lameness or pain before diagnosis. For some dogs, there was uncomplete follow-up data.

The medical records often lacked information whether the locomotor system was examined or not. In those cases where examination was performed, there was no standardized procedure. Also, there was no objective method used for determining pain in the animal which may interfere with the result of the study since it might have led to uncertain prevalence to musculoskeletal pain to the study result. An objective, easy to use method for determining musculoskeletal pain in the animal would be preferred to ensure all animals being examined in a similar manner. This might lead to greater inclusion of individuals presenting vague pain symptoms (aches and generalized pain that are not easily detected in regular locomotory clinical examination). Furthermore, an objective and structured clinical examination to exclude other reasons for musculoskeletal signs is necessary.

This study only included dogs with a registered diagnosis of hypothyroidism and did not consider the potential undiagnosed hypothyroid dogs presenting with musculoskeletal signs. It would be of interest to follow a different study model similar to Rossmeisl et al. 2009, e.g., cohort-study focusing on clinical musculoskeletal signs development in patients at risk for developing hypothyroidism, how they express and when. If there may be a certain characteristic to musculoskeletal signs in hypothyroid dogs, it could be of importance for the clinician if these could be recognized.

The number of cats in this study were too few for any conclusion, even though one cat was described as significantly improved in musculoskeletal signs. Spontaneous hypothyroidism is rare in cats, although congenital secondary hypothyroidism is described in cats (Scott-Moncrieff 2007). In older cats hyperthyroidism is a common disease (McLean et al. 2014). A subset of cats treated for hyperthyroidism developed iatrogenic hypothyroidism. This group of cats might be interesting to study focusing on musculoskeletal function. However, determining pain in cats can be challenging since they can be shy and vague in their expression of pain (Mathews 2000). The follow up visits were not as frequent in cats post diagnosis compared to dog patients and did not always include clinical examination of the locomotor apparatus. Since the phenomenon of musculoskeletal symptoms in hypothyroid human patients is well known in human medicine and based on what has been found in both veterinary literature and this study, it is likely to believe musculoskeletal pain could exist in hypothyroid cat patients as well.

In conclusion, there was a high proportion of dogs that were diagnosed with hypothyroidism that had a history of musculoskeletal pain or lameness (stated by owner or at earlier visits at clinic) of which about a third of these dogs had documented records of improvement after hormone therapy. Given the large presence of painful musculoskeletal symptoms in humans with hypothyroidism, future studies in hypothyroid dogs are of interest.

# 6. Conclusion

Based on this study, musculoskeletal pain in dogs with hypothyroidism seems to be more prevalent than previously has been reported in the literature. Musculoskeletal pain is described in the form of lameness, stiffness, reduced range of motion and arthralgia during manipulation and palpation in clinical examination, which corresponds to symptoms described in humans. In one of two dogs that presented with lameness at time of hypothyroid diagnosis, there was no record of lameness after hormone therapy. The statistic analyze could not exclude the chances of the hormone therapy being effective on treating lameness. There might be a true effect which could not be captured due to a small study group.

There are limitations in the retrospective study model, e.g., the lack of information about the locomotor apparatus in some of the clinical records. It would be interesting to perform a prospective or longitudinal study of the development of musculoskeletal signs in hypothyroid dogs and cats. It would also be interesting to use a standardized and objective method in examination of the locomotor apparatus, and in determining musculoskeletal pain to ensure that the clinical examination and evaluation is being made in a similar way in all patients, and for excluding other reasons for musculoskeletal pain.

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# Populärvetenskaplig sammanfattning

Den här studien har undersökt förekomsten av smärta i muskler och leder hos hundar och katter med underfunktion i sköldkörteln (hypotyreos) genom att studera journaler från patienter vid Universitetsdjursjukhuset i Uppsala. Smärta i muskler och leder är vanligt förekommande vid sköldkörtelproblem hos människa, och syftet med studien var att se hur utbrett problemet kan vara hos hundar. I studien har smärtförekomst i muskler och leder bestämts genom att leta efter information om förekomst av hälta eller smärta innan diagnosen hypotyreos ställts, eller om tecken på smärta eller hälta funnits vid diagnostillfället.

Det finns flera tänkbara orsaker till smärtuppkomst vid sjukdomen hypotyreos. Det finns studier som visat att muskelnedbrytande enzymer förekommer i mycket hög grad hos patienter med hypotyreos, vilket kan orsaka värk i muskler. Sköldkörtelhormonerna styr också nervaktivitet, bland annat genom att reglera jonkanaler. Vid hypotyreos sänks nervaktiviteten och kan till följd av detta ge en minskad aktivitet till muskeln som nerven styr, och på sikt leda till att muskeln förtvinar. Även detta kan yttra sig i en muskulär smärta. Tyreoida hormoner styr även bildandet av hyaluronrika mukopolysackarider, en struktur som är viktig för bland annat spänstighet i hud och leder. Denna kemiska substans drar till sig vattenmolekyler, och vid hypotyreos ökar produktionen, vilket således leder till en ansamling av vattenmolekyler. Detta kan leda till en så kallad myxomatös ödembildning i underhud, men även i leder där ökad mängd vätska skulle kunna orsaka obehag.

Studien inkluderar 107 journaler från hundar med hypotyreos. Totalt 42 hundar visade smärta eller hade en sjukdomshistorik som inkluderade smärtartade sjukdomstecken i form av hälta, stelhet, smärtsam reaktion vid undersökning av leder och muskler. 27 hundar uppvisade tecken på smärta vid tidpunkten då diagnosen hypotyreos ställdes. 12 av 42 hundar var noterat bättre i sin smärta efter behandling med sköldkörtelhormon, och i gruppen som uppvisade hälta vid diagnostillfället blev 11 av 27 bättre. Genom statistisk analys kunde inget säkert samband ställas att hormonbehandlingen varit effektiv mot smärta i rörelseapparaten hos dessa hundar. Den totala studiegruppen var dock liten i sammanhanget och det kan finnas en sann effekt som inte kunnat fångas upp på grund av detta.

9 katter ingick i studien. Hos katterna kunde inga slutsatser dras gällande sambandet mellan smärta i leder och muskler och sjukdomen hypotyreos. Studieunderlaget var för litet, och uppföljningen var otillräcklig i journalerna. Hypotyreos är generellt en ovanlig diagnos hos katter, och är oftast sekundärt till annan sjukdom t.ex. cancer eller jodbehandling mot överaktivitet i sköldkörteln s.k. hypertyreos.

Innebörden av den här studien kan uppmärksamma att hundar med exempelvis hälta eller andra diffusa tecken på smärta i muskler och leder utan självklar grundorsak kan vara föremål för utredning av sköldkörtelns funktion.

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