Spinal hyperostosis in humans and companion animals

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Introduction

For over 15,000 years, companion animals and their masters have been subjected to similar environmental influences including nutritional and toxic substances [98, 99, 104, 124]. During recent decades, both humans and their pets have enjoyed an extended life span and have simultaneously grown more obese [6, 57, 89]. By getting older and increasingly obese, humans and pets suffer more frequently from similar disorders, including endocrinological syndromes, osteoarthritis (OA) and degenerative spinal diseases [4, 5, 6, 28, 39, 40, 61, 67, 76, 88, 102]. For specific human diseases, companion animals, including pet patients, can serve as spontaneous disease animal model [8, 36, 42, 48, 68] .

Several disorders may lead to new bone formation affecting the vertebral column of both humans and companion animals alike. In dogs for instance, this new bone formation may be visualized by radiographic examination (Figure 1 and 2) or macroscopically on a skeleton post mortem (Figure 3a, 3b, 3c). Spondylosis deformans (from this point on referred to as spondylosis), diffuse idiopathic skeletal hyperostosis (DISH), osteoarthritis (OA) of the facet joints, and ankylosing spondylitis (an inflammatory disorder found exclusively in humans) are the most important disorders associated with spinal hyperostosis [100]. After a brief introduction of the human and companion animal spinal anatomy this introduction will particularly focus on DISH and spondylosis in both humans and companion animals. Specific attention will be paid on whether companion animals may serve as translational models for these disorders.

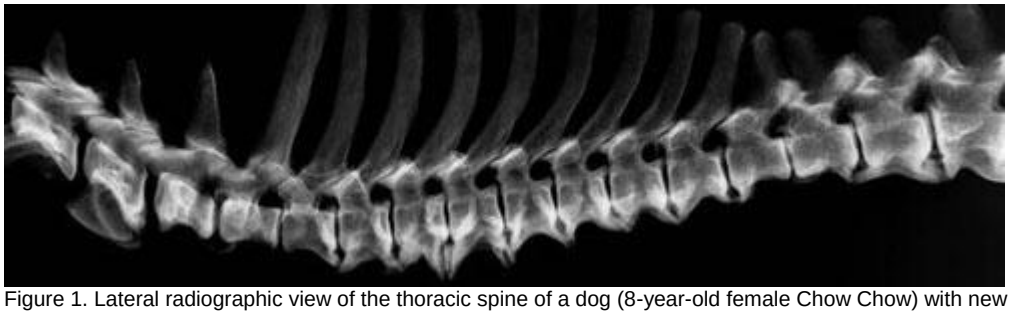

Figure 1. Lateral radiographic view of the thoracic spine of a dog (8-year-old female Chow Chow) with new bone formation visible from T2-T13.

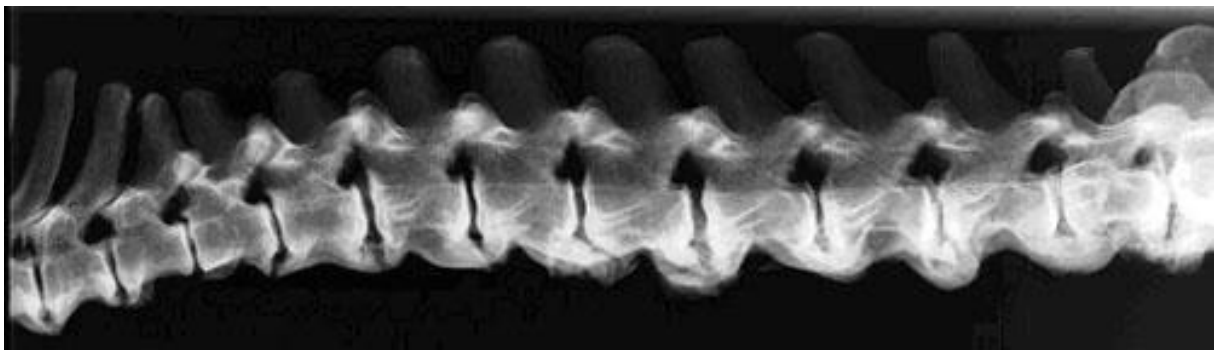

Figure 2. Lateral view of a radiograph of the lumbar canine spine with new bone formation from T9-S1 (same dog as in figure 1).

Figure 3a. Lateral view of a canine skeletal spine with new bone formation resembling diffuse idiopathic hyperostosis (same dog as in figure 1).

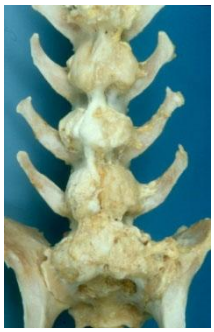


Figure 3b, 3c. Ventral views of the lumbar region of the new bone formation. Note the flowing pattern of the ventral ossifications (skeletal specimen of private bone collection, Dr. B.P. Meij, Utrecht University, The Netherlands)

Anatomy

Human anatomy of the spine

The human spine consists of seven cervical, twelve thoracic, five lumbar, five sacral and four fused coccygeal vertebrae. Between the second cervical spinal segment and the first sacral vertebral, a total of 23 intervertebral discs (IVDs) are situated. Except between the first two cervical vertebrae and between the fused vertebrae, IVDs are situated between all other adjacent vertebrae. All IVDs consist of two cartilaginous endplates, an inner gel-like nucleus pulposus and a fibrous ring called annulus fibrosus. The IVD is dorsally and ventrally enclosed by the posterior longitudinal ligament (PLL) and anterior longitudinal ligament (ALL). The collagen of the annulus fibrosus and the ALL connects with the bone of the vertebra by strong connections, termed Sharpey fibers [100]. The ALL is relatively narrow in the cervical spine and expands in width in the thoracic spine and especially the lumbar area. The ALL consists of three layers. The deepest layer connects one intervertebral disc space, the intermediate spans two or three disc spaces and the outer superficial layer spans four or five vertebrae [100].

Companion animal anatomy of the spine

The canine and feline spine contains seven cervical, thirteen thoracic, seven lumbar, three (fused) sacral, and depending on the dog breed up to 20, and cat breed 22 or 23, caudal vertebrae. As in humans, the IVDs, made up by two cartilaginous endplates, an inner gel-like nucleus pulposus and a fibrous ring called annulus fibrosus, and are located between all vertebrae except for C1-C2 and the fused sacral vertebrae. The ventral longitudinal ligament (VLL) and dorsal longitudinal ligament, the analogues of the human ALL and PLL, are situated at the ventral and dorsal aspect of the canine and feline vertebral column. On lateral radiographic examination the individual vertebrae are easily identifiable, but the intervertebral discs are radiolucent.

Spondylosis deformans

Spondylosis deformans in humans

Introduction and etiology

In the biomedical literature spondylosis has been defined as: “degenerative process of the spine involving essentially the annulus fibrosus and characterized by anterior and lateral marginal osteophytes arising from the vertebral body apophyses, while the intervertebral disc height is normal or only slightly decreased” [51]. Osteophytes are found in the absence of (other) degenerative changes [117]. However, spondylosis has also often been used to describe a situation in which osteophytes are found in combination with progressive degenerative disc disease with decreased disc height [37, 55, 60, 73, 84, 88, 107]. Some authors for instance, use the Kellgren/Lawrence grading system, which is designed for OA and describes the amount of loss of joint space (in this case disc height), amount of sclerosis, and amount of osteophytes, to grade lumbar spondylosis [64, 88]. The etiology of spondylosis is not well known. It is proposed that abnormalities in the peripheral annular fibers lead to discontinuity and weakening of the anchorage of the IVD. This subsequently facilitates abnormal anterolateral (or ventral) disc displacement and leads to traction at the site of the Sharpey fibers and development of osteophytes several millimetres from the disco-vertebral junction [88].

Diagnosis

The diagnosis of the new bone formation and differentiation between different disorders is most often based on radiographic examination. The osteophytes in spondylosis are distinguishable different from the syndesmophytes in ankylosing spondylosis and the enthesophytes in spinal DISH. In ankylosing spondylosis, the orientation of the new bone formation is straight from vertebra to vertebra, while in case of spondylosis the orientation is often first ventrally and later cranio-caudally [88]. In spinal DISH, i.e., ossification of the ALL, the new bone formation is more flowing and by definition affects four or more contiguous vertebrae. The difference in amount and appearance of the new bone formation is used to radiographically differentiate between these three distinct disorders. For instance, human pelves were investigated and differentiated between spondylosis and DISH by the pattern and extent of spinal new bone formation [59]. The diagnosis of spondylosis was made when focal osteophytes were found instead of contiguous or flowing new bone formation [59].

Prevalence

The prevalence of spondylosis increases with age and is more frequently found in males compared to females [88, 91]. In the thoracic region predominantly the right side is affected, presumably due to the pulsations of the aorta at the left side. In the lumbar region both sides are affected equally [88]. In the UK, in a population over 50 years of age a prevalence of 84% of spondylosis in men and 74% in women was found [91]. In Japan, in a cohort of 2288 people over 60 years of age a prevalence of 75.8% was found for the presence of spondylosis with and without loss of disc height [88].

Skeletal distribution

In humans, spondylosis mainly occurs in the cervical or the lumbar region of the vertebral column and less often in the thoracic region.[88, 108]. Osteophyte formation is described to be accelerated by motion and could therefore be more frequently found in the more flexible C5-C6 and C6-C7 segments [107]. Possibly this is due to acceleration of the aforementioned weakening of the anchorage of the annulus fibrosus to the vertebral body and traction at the site of the Sharpey fibers [100].

Clinical symptoms

The three main clinical symptoms found in cervical spondylosis are neck pain, cervical radiculopathy and cervical myelopathy [60, 107]. Correlations between the amount of lumbar osteophytes and low back pain have been described [53, 90]. However, the prevalence of these same degenerative changes among asymptomatic individuals make the assignment of a clear clinical relevance difficult [84]. In a cohort study of 2288 people over 60 years old, no significant association between the presence of lumbar osteophytes and low back pain was found [88]. In combination with loss of disc height, only a significantly difference in amount of low back pain was found in women [88]. Similar frequencies of disc height lose and osteophytes were found in groups without, with moderate, and with severe low back pain [53].

Treatment

When spondylosis is present in combination with painful degenerative disc disease, conservative (e.g., pharmacological and/or physical) treatment is often the initial management [82]. The outcome of a large meta-analysis published in 1999 was that there was a serious lack of scientific evidence supporting surgical management for degenerative lumbar spondylosis [55]. In a large survey, many spine surgeons revealed to recommend surgical intervention when the symptoms did not resolve with conservative treatments [55, 73]. Surgical options include anterior and/or posterior fusion or transforaminal lumbar interbody fusion/posterior lumbar interbody fusion (TLIF/PLIF) [55, 69, 73, 127]. These interventions, however, are primarily a treatment for painful degenerative disc disease and not specifically for the new bone formation.

Spondylosis deformans in companion animals

Introduction and etiology

In the veterinary literature, spondylosis is described as a non-inflammatory, degenerative disease of the region peripheral to the endplate associated with new bone formation originating several millimeters from the disco-vertebral junction [3, 12, 16, 20]. The osteophytes vary from small spurs to bony bridges across the disc space, leaving most of the ventral surface of the vertebral body unaffected. Similar to humans, the etiology of spondylosis in companion animals is unknown [12, 23].

Diagnosis

Spondylosis can be diagnosed through radiographic or (histo)pathological examination [3,12, 18, 19, 20, 21, 23]. Using radiographs, a distinction was made between endplate osteophytes (type 1) described to be the result of spondylosis, and a group of three other types (types 2, 3 and 4) of new

bone formation [33] (Figure 4). The spurs of type 2 and 3, compared to type 1, have a broader base of origin at the vertebral body and grow out to be type 4, which consists of a contiguous ventral band of new bone. These types are comparable with those seen in human ankylosing hyperostosis (former name for DISH) [32, 33]. Other studies of canine vertebral hyperostosis did not specifically distinguish between spondylosis and DISH [3, 12, 21, 23, 33]. In these studies, all bridging ossifications were thought to represent severe spondylosis and subdivided spondylosis in dogs into 3 subclasses according to the degree of osteophytes development. In grade 1, the bony spur does not protrude beyond the caudal/cranial edge of the vertebral border; in grade 2, it does protrude beyond the caudal/cranial edge of the vertebral border; and in grade 3, a bony bridge is formed from the corner of one vertebra to the next [3, 12]. It was brought forward that DISH in dogs had possibly been described earlier as a severe variant of spondylosis [22]. Radiographic differentiation between DISH and severe spondylosis might be challenging, but the disorders have been described to differ in radiographic appearance [22, 31].

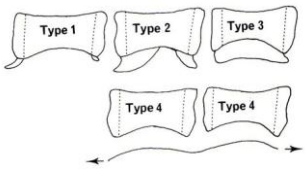

Figure 4. Subdivision of types of osteophytes in the canine spine according to Wright [33].

Prevalence

The prevalence of canine spondylosis increases with age, with a breed predilection for Boxers. In Norwegian Boxers, a prevalence of 26% of spondylosis was found [12], while in Italian Boxers, a prevalence of 50% of grade 3 spondylosis was reported [3]. Both, the prevalence and the degree, or grade of spondylosis, increase with age [3, 23]. Spondylosis has also been reported in cats and in the 1960's prevalence values ranging from 34-68% were reported [1, 23]; in 55 out of 100 cats more than one site of the axial column was affected [70].

Skeletal distribution

The caudal thoracic region, cranial lumbar region and the lumbosacral region were reported to be most often affected by spondylosis [3, 21, 23, 32, 33]; spondylosis in the cervical spine is described less often [20, 32, 100]. In cats, spinal segments T4-T10 are most frequently affected [1, 4, 5, 13, 23, 70]. Extensive new bone formation was found more frequently in the caudal part of the vertebral column [4, 7, 9, 70].

Clinical signs

Signs related to severe canine spondylosis are stiffness in the back, lameness, changed gait and pain [3]. In working dogs the diminished spinal flexibility may limit their activity [20, 118]. Osteophytes extending dorso-laterally can compress spinal nerve roots at the intervertebral foramina [20]. Spondylosis was also detected on computed tomography (CT) images in 62% of dogs with degenerative lumbosacral stenosis (DLS) [113]. Although the presence of spondylosis has been suggested to be correlated with Hansen's type 2 disc protrusion [16], spondylosis is also found in combination with healthy intervertebral discs. Generally, spondylosis is not of great clinical relevance in dogs [18, 86].

In cats, the spondylosis-associated changes of the intervertebral junction, a cartilaginous joint, are dissimilar to those associated with OA of synovial joints [87]. Nevertheless, both OA and spondylosis are considered as part of degenerative joint disease (DJD) and may be an overlooked cause of discomfort and pain in cats [4, 7, 13, 28, 71]. Cats are known to mask signs of skeletal pain and often only adjust their behaviour as a coping mechanism [13, 25]. Here more research is needed, including studies using questionnaires of owner perceived changes of the cat's behaviour [14, 15]. Recently, spondylosis of the caudal spine was found to be related with behavioural changes: decreased willingness to greet the owner, reluctance to being petted, increased aggressiveness and a perceived poorer quality of life as interpreted by the cat's owners [9]. The owners of the cats with spondylosis were unaware of this at the time they filled in the questionnaire and the cats did not have any known orthopaedic comorbidities [9]. It would be interesting to use this feline model in a randomized placebo controlled study to evaluate the efficacy of pharmaceutical and/or nutritional treatment options that are available for spinal hyperostosis in humans and spondylosis in cats.

Treatment

When pain and stiffness are reported, most veterinarians in general practice start out with a

conservative treatment that consists of body weight reduction, controlled exercise or physiotherapy, and medical treatment with non-steroidal anti-inflammatory drugs (NSAIDs) [27].

Diffuse idiopathic skeletal hyperostosis (DISH)

Diffuse idiopathic skeletal hyperostosis (DISH) in humans

Introduction and etiology

Diffuse idiopathic skeletal hyperostosis (DISH) is a common, systemic disorder of the axial and peripheral skeleton in middle aged and elderly humans. It results in ossification of soft tissues such as (longitudinal spinal) ligaments, sites of attachment of tendons or muscles and capsules to bone, i.e., entheses. DISH is not a typical disorder of recent history. Signs of DISH have been found for example in the skeletons of the remains of Rhamses II (1302-1213 BC in Egypt), in several members from the Italian 16th century Di Medici family and in ancient clergymen in the Netherlands [38, 45, 56, 103, 120]. DISH was first comprehensively described in1950 [52]; although others had previously mentioned anatomic changes similar to these descriptions, the publication was the first clinical and radiological study of this disorder. DISH (which was then named senile ankylosing hyperostosis) was differentiated from ankylosing spondylitis and spinal OA by means of differences in clinical, pathological, and radiological features [52]. Over the years DISH has been given many different names, including monoliform hyperostosis, spondylitis ossificans ligamentosa, hyperostotic spondylosis, hyperostosis of the spine, ankylosing hyperostosis, Forestier's disease, generalized juxta-articular ossification of vertebral ligament and spondylosis hyperostotica [115]. The current name was introduced when extra-spinal manifestations of DISH were acknowledged [101].

The etiologic factors involved in DISH are not clear. Various metabolic, endocrinological, genetic and environmental factors have been postulated but none has generally been agreed upon [74, 80]. DISH is often linked to obesity [2, 17, 24, 49, 50, 52, 67, 80, 115, 123]. In a case control study of 131 patients the body mass index (BMI) was significantly higher in the DISH group than in the control group [6]. Clinical consequences of obesity can be hypertension, OA, pulmonary and cardiac failure, type 2 diabetes mellitus (DM) and cardiovascular diseases. It is therefore not known if the cardiovascular risk factors reported are due to DISH or to obesity [17]. On the other hand, the differences in metabolic abnormalities persisted even after adjustment was made for the BMI [123]. Some authors suggested that hyperglycemia was the most useful laboratory abnormality concurrent with DISH [115]. Others found no significant difference in glucose levels between patients with and without DISH [49, 80]. The relationship with type 2 DM (or non-insulin dependent DM) and DISH remains controversial [26, 67, 74]. For instance, no differences in the prevalence of DM between 50 patients with DISH and a control group of 50 persons without DISH was found [47]. In a study of 133 patients with DM and a control group of 133 persons no statistically significant difference in the prevalence of DISH was found [109]. Furthermore DM alone was no risk factor, but in combination with high levels of uric acid and/or hyperlipemia, patients had a significantly higher incidence of DISH [123]. When a group of patients with spondylosis was compared with a group of DISH patients, differences in BMI, the occurrence of DM, and higher serum level of uric acid were reported. The latter was not associated with BMI, suggesting that obesity is not the cause for those elevated levels of uric acid in DISH patients [67].

DISH has been related to abnormal bone cell growth or activity that could reflect the influence of metabolic factors that lead to new bone formation. For example, serum matrix Gla protein could be a marker of osteometabolic syndromes that cause hyperostosis [26]. Some authors suggested that hypervascularity could be the localizing factor [26, 50]. Others suggested that hyperinsulinemia, associated with high BMI, suppressed the production of insulin-like growth factor (IGF) binding protein-1. As a result, it aggravated the growth-promoting effect of IGF, which in turn may induce hyperostosis [17]. It was reported that DISH patients had elevated insulin and growth hormone values. Symptomatic therapy (with NSAIDs) resulted in lower serum GH levels, with values approaching those found in a normal age-matched population, but IGF-1 levels were unchanged [49]. It was suggested that hyperinsulinemia may be the factor that link metabolic parameters with the development of hyperostosis [67, 115]. Some authors postulated that heavy work may correlate with the extent of DISH involvement [96, 106]. In humans with vitamin A poisoning or long-term treatment with a vitamin A derivative for dermatologic disorders, ligamentous ossification was reported [54, 72].

In summary, the (etio)pathogenesis is not clear; many explanations for the etiology and development of hyperostosis of ligaments are hypothetical and lack evidence [2, 67].

Diagnosis

During the 1960's and 1970's, some authors considered signs nowadays described to DISH to be a type of (severe) spondylosis [58, 94, 105, 122]. Later, the distinction between spondylosis and DISH has been made [26, 67, 80]. Three diagnostic criteria for the diagnosis of DISH in humans have been used most frequently: spondylosis, intervertebral osteochondrosis, and ankylosing spondylitis [24]. In typical spondylosis deformans, a flowing pattern along at least four contiguous vertebral bodies, as in DISH, would not be found and the spinal new bone formation originates from the vertebral body itself instead of the longitudinal ligament [24]. DISH should be considered as a distinct entity that differs from spondylosis not only by the contiguous aspect of the ossification, but also by the dominance of ligamentous ossification in the spine and in extra-spinal locations [59]. The preservation of the disc space is not present in intervertebral osteochondrosis while in DISH this is the case [111]. In DISH, the enthesophytes project ventro-caudally from the vertebral bodies with the classic appearance of flowing candle wax, forming a flowing extra-articular ankylosis. This new bone formation can be distinguished from the more cranio-caudally oriented 'bamboo spine-like' outgrowths that form a more intra-articular ankylosis in ankylosing spondylitis. This usually starts in late adolescence and early adulthood and consists of inflammatory spinal pain and stiffness, decreased range of motion and it can result - after many years - in characteristic postural abnormalities such as 'the Bechterew stoop' (marked thoracic kyphosis). The presences of degenerative signs like facet hypertrophy and disc space narrowing usually exclude the diagnosis of DISH [2].

Utsinger [115] suggested revising the Resnick criteria for epidemiological purposes. With these revised criteria it would be possible to include early stages of DISH. He postulated three criteria:

1. Contiguous ossification along the anterolateral aspect of at least four contiguous vertebral bodies, primarily in the thoraco-lumbar spine. Ossification begins as a fine ribbon-like wave of bone but commonly develops into a broad, bumpy, buttress-like band of bone.

2. Contiguous ossification along the anterolateral aspect of at least two contiguous vertebral bodies.

3. Symmetrical and peripheral enthesopathy involving the posterior heel, superior patella or olecranon, with the entheseal new bone having a well-defined cortical margin.

• The presence of flowing calcification and ossification along the ventrolateral aspects of at least four contiguous vertebral bodies with or without localized pointed excrescences at intervening vertebral body-disc junctions.
• The relative preservation of disc height in the involved areas and the absence of extensive radiographic changes of degenerative disc disease (intervertebral osteochondrosis), including vacuum phenomena and vertebral body marginal sclerosis.
• The absence of apophyseal joint bony ankylosis and sacroiliac joint erosion, sclerosis or intra-articular bony fusion.

Table 1. Criteria to diagnose diffuse idiopathic skeletal hyperostosis according to Resnick and Nywayama [26].

According to these revised criteria several categories of DISH were made, the difference between category B and C (i) has not been made clear:

A. Definite DISH: criterion 1

B. Probable DISH: criterion 2, 3

C. Possible DISH: (i) 2 and 3

(ii) 2

(iii) 3 (particularly if calcaneal spurs occur together with olecranon or patella spurs)[70].

Prevalence

DISH is mostly seen in the elderly and demonstrates a male predominance [2, 67, 111]. The incidence increases with body weight in both genders [111, 115]. The prevalence in man varies around the world [111]. In a hospital population in the USA of people over 50 years old, a prevalence of 25% in males

and 15% in females was found [125]. DISH is less common in African blacks, Afro-Americans, Native Americans, and Asians than in American Caucasians [43, 125]. However, in Pima Indians living in the Gila River reservation in Arizona USA, a very high incidence of DISH and type 2 DM was found [115]. In Korea using the Resnick criteria, a prevalence of 5.4% in males and 0.8% in females was found. When looking at two or more bridges these prevalence increased to 7.1% in males and 3.2% in females [65]. In Israel, a prevalence of 9.8% was found in a cohort of 1020 humans over 45 years of age [17]. In The Netherlands, a recent study of an outpatient population from a clinic for internal medicine showed a prevalence of 22.7% in males and 12.1% in females [126]. In this study the authors also looked at ossification of the ALL over three, instead of four, contiguous vertebral bodies. This was considered to be a precursor of full-blown DISH. It was defined as pre-stage DISH and recorded separately. This pre-stage DISH was found in 4.6% of the patients and more frequently in females [30]. That same differentiation was made but was called 'likely DISH' (three vertebrae) and 'strictly DISH' (four or more vertebrae) [125]. In a study of 635 persons in Hungary, a prevalence of 6.1% in males and 1.2% in females was found. When using the modified Resnick criteria, looking at two or more bridges, prevalence of 27.3% in males and 12.8% in females were found [66]. In a cohort of Italian females a prevalence of 15.1 % was reported [96]. Overall, the difference in prevalence found throughout the world suggests a possible genetic or ethnic factors [125].

Skeletal distribution

The portion of the spine that is typically involved in humans is the thoracic region [111]. Even in patients with cervical or lumbar complaints the radiographic abnormalities were often found on the thoracic spine [2, 26, 115]. The thoracic enthesophytes were usually found at the right side of the spine, presumably because of the pulsatile effect from the aorta on the left side [121]. Patients with 'situs inversus totalis' and DISH subsequently showed more ossification at the left side of the thoracic spine [2]. The thoracic abnormalities were most frequently found between the 7th and 10th thoracic vertebrae [24, 115]. Human chest radiographs yields a sensitivity of 77%, specificity of 97%, positive predictive value of 91% and a negative predictive value of 91% for diagnosing DISH in humans [81]. In the lumbar region radiographic changes resemble those in the thoracic spine but without the predilection of the right side. The cranial part of the lumbar region is most often involved and may be as much as 2 cm thick [2, 115]. Compared to the thoracic and lumbar region, the cervical region is less commonly affected but leads to specific symptoms [50, 83, 115]. Extensive new bone formation of the cervical spine (Figure 5) may lead to dysphagia and/or airway obstruction.

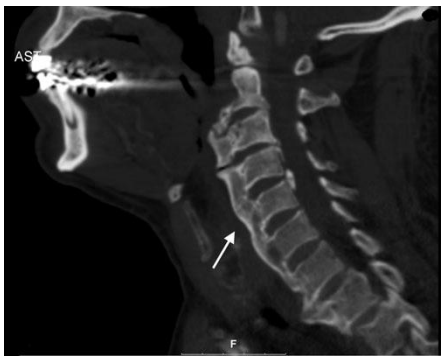

Figure 5. Transverse computed tomography image of 53-year-old woman with cervical DISH. Note extensive new bone formation (arrow) at the anterior side of several vertebrae (Courtesy of Dr. J.J. Verlaan).

Extra-spinal manifestations of DISH are no exception [59, 115]. It is even suggested that these should be included into the diagnostic criteria [115]. Various anatomic locations, such as joints, sites of attachment of ligaments, tendons and capsules to bone can be affected. In humans, every location has its own characteristic findings that are usually bilateral and symmetrical [2]. Peripheral manifestations of DISH have been characterized by distinctive features:

(i) involvement of joints that are often unaffected by primary OA,

(ii) increased hypertrophic changes compared with primary OA,

(iii) prominent enthesopathies at various sites adjacent to peripheral joints, and

(iv) calcifications and ossifications of entheses in sites other than joints [77].

Clinical symptoms

DISH is known to affect the middle aged and elderly and is often asymptomatic. Clinical symptoms resulting form DISH are mainly due to altered biomechanics and may consist of painful stiffness and restriction in range of motion [2, 66, 90]. Symptoms of thoracic outlet syndrome, and heterotopic

ossification after hip arthroplasty are also described [111]. Usually symptoms are relatively mild, despite the radiological changes that can be quite dramatic because of the extensive calcifications of ligamentous structures [120]. Neurological deficits due to spinal cord compression have been described to occur occasionally [34, 115]. Mechanical dysphagia, dyspnea, stridor, hoarseness, sleep apnea, radicular complaints, and difficulty with intubation are complications associated with cervical DISH [2, 29, 84, 111, 119]. Patients can even die as a result of mechanical respiratory failure, probably due to paralysis of the respiratory muscles [29, 41, 62, 83, 95, 111].

Decreased range of spinal motion and reduced flexibility due to DISH can result in spinal fractures even after minor trauma [2, 41, 111]. Remarkably, the fracture plane found in patients with DISH is most frequently located through the vertebral body while in patients with ankylosing spondylitis the fracture plane is most often through the disc [121, 126]. These fractures in patients with DISH tend to be unrecognized, unstable and associated with treatment delays and permanent neurologic deficits [2, 41]. There are two main reasons for the delay in diagnosis: the patient usually has a baseline level of spinal pain preventing him/her to seek medical attention in case of an altered pain pattern, and secondly the treating physician does not suspect a spinal fracture because the injury has been considered trivial [2]. The findings of a fracture on plain radiographs can be subtle, so additional CT-scans and/or MRI may be indicated. Especially great care must be exercised when there is a history of trauma and pain in combination with (extensive) new bone formation [2, 34, 41]. The risk of spinal fractures may even be higher in some advanced cases of DISH in which multiple completely fused segments exist [95]. Increasing age may also be a confounder in the relationship between DISH and the increased incidence of spinal cord injuries [111]. Factors associated with increasing age, such as failing eyesight and decreased mobility, could predispose to a growing risk of falling with subsequent risk for fractures. When DM and DISH occur concomitantly, this might make patients more prone to falls because of complications of DM such as peripheral neuropathy, autonomic neuropathy, retinopathy, cataracts and episodes of hypoglycaemia [111]. A high percentage (51.2%) of hyperextension fractures in patients with DISH was described in a systematic review [126] when compared to the percentage (0.2%) described in a group of 1,445 spine fractures [79]. Considering an increasing prevalence of DISH in western societies, this disorder poses an emerging challenge for physicians working with spinal injuries [126].

Treatment

Treatment of DISH is usually conservative but occasionally surgical intervention is indicated in case of specific sequelae, such as fractures, dyspnea or dysphagia [2]. Conservative therapy consist of activity modification, physical therapy, weight loss, corset or brace wear, and medical therapy with NSAIDs [35, 114, 115]. The efficacy of these therapies is not well established [2, 114]. Pain in the peripheral skeleton may respond to NSAIDs. Pain from spurs can be treated with local injection with lidocaine with or without steroids. When conservative treatment is not successful surgical intervention can be considered [115]. In the cervical region, if the enthesophytes are impinging on anterior structures, surgical resection is often considered [2].

Diffuse idiopathic skeletal hyperostosis (DISH) in companion animals

Introduction and etiology

Surprisingly, few articles have been published on DISH in animals. Spinal hyperostosis similar to DISH has been described in dinosaurs, a saber-toothed cat and old rhesus monkeys [38, 103, 110]. Only two case reports of DISH in dogs have been published (of a 4-year-old Labrador [31], and a 4-year-old female Great Dane [22]), and none in cats. In cats, hypervitaminosis A is known to give rise to extensive new bone formation throughout the spinal column and the large peripheral joints [106]. In humans with vitamin A poisoning or long-term treatment with a vitamin A derivative for dermatologic disorders, ligamentous ossification is also reported [54, 72]. In contrast, in dogs treated with 300,000 IU vitamin A on a daily basis for 2 months increased bone resorption and reduced bone formation in dogs was reported [78].

Diagnosis

In the both canine case reports [22, 31] the diagnosis of DISH was based on radiographic examination. In one case it was stated that the radiographic and pathologic features of canine DISH closely resembled extensive spondylosis, but radiographic and morphologic differences were mentioned. Vertebral osteophytes associated with spondylosis typically center on individual degenerated discs and do not have patterns of flowing bone growth involving contiguous segments or dorsal periarticular changes [22]. This is consistent with what was reported in humans [59]. DISH in

dogs might earlier have been described as a variant of spondylosis [22].

Prevalence

Recently, we reported a retrospective radiographic study on the prevalence of both DISH and spondylosis in a large group (n=2041) of pure-bred dogs [10, 11]. Canine DISH and spondylosis were found alone or in combination, and the prevalence of both disorders increased with age. The prevalence of DISH (40.6%) and of spondylosis (55.1%) in the group of Boxer dogs was particularly high. Since earlier only two cases of canine DISH were reported we included four other cases of DISH to provide more background on the appearance of canine DISH. Radiography, computed tomography (CT), magnetic resonance imaging (MRI), and/or (histo)pathology were described for these four dogs with DISH [10].

Skeletal distribution

In the previously described case report [31], the first skeletal abnormalities were seen on the caudal proximal third of the right femur and appeared to extend caudally to the ischium and cranially to the ilium. The authors stated that the changes in the right hip were combined with spondylosis of L6 and L7. Twenty-six months later, more abnormal calcifications were noted in the spine and in numerous extra-spinal locations. Some spinal alterations were related to spondylosis, others were more proliferative and were reported to be caused by DISH. Especially the extra-spinal alterations were even more extensive and distinct from alterations seen in primary OA [31].

The other report in the Great Dane Dog showed heavy new bone formations throughout the thoracic, lumbar and sacral spine, resulting in fusion of multiple vertebral segments. This dog also demonstrated new bone formation at multiple extraspinal locations: periarticular new bone formation extended the articular surfaces of humeral and femoral heads, and both shoulders, both elbows, both hip joints and the right stifle joint were affected [22].

Clinical signs

In the aforementioned two cases, the dogs showed orthopedic and neurological abnormalities. Extreme stiffness and pain in the axial and appendicular skeleton, presumably due to DISH, were not responsive to treatment and resulted in the owners electing for euthanasia [22, 31]. Although 3 of the 4 cases described by us in a earlier report also had orthopeadic comorbidities it is likely that the spinal new bone formation resulted in spinal pain and stiffness [10].

Treatment

No treatment other than instructions for nursing care was suggested [31]. In the other case report [22] no therapeutics were described. Possibly, as in humans with DISH, NSAIDs may give some pain relief and resolution of clinical signs. When new bone formation impairs the range of motion and/or cause neurologic deficits or (severe) pain, surgical intervention may be considered. This may include enthesophytectomy and in case of radiculopathy due to obstruction of a spinal nerve a foraminotomy may be necessary.

Terminology

In medical practice, the term spondylosis is currently most often used to describe a situation in which degenerative disc disease is found in combination with the presence of osteophytes [37, 55, 60, 73, 84, 88, 107]. As a result, the differentiation of spondylosis from full blown DISH, in which the intervertebral discs are generally not degenerated, is easier. In the veterinary literature spondylosis is primarily used to describe spinal osteophytes without necessary signs of intervertebral disc degeneration. This makes the distinction in dogs between spondylosis and - specifically early stage - DISH more difficult. In the biomedical literature in the1960's and 1970's signs nowadays described to DISH were by some authors still considered to be a type of (severe) spondylosis [93, 105, 122]. Later, the distinction between spondylosis and DISH has been made more frequently and currently spondylosis and DISH are considered to be distinct disorders in humans [26, 67, 80]. In the veterinary literature, the occurrence of several different types of spinal bony outgrowths are acknowledged, and related to different disorders [32, 33]. Other authors considered these different forms of spinal hyperostosis all to be part of spondylosis [3, 12, 21, 23, 33]. It would be advisable to use the same definitions for spondylosis and DISH in both the biomedical and veterinary literature.

Future research on spondylosis and DISH using animal models

The outcome of studies focusing on spinal hyperostosis in companion animals may be beneficial for

researchers working in both the veterinary and the biomedical field. Companion animals as disease model complement laboratory animal models, but are currently underused as models for human (spinal) diseases. Dogs that naturally develop spondylosis and DISH may be useful to study the etiology of both disorders - e.g.- assessing the involvement of specific genes. The canine genome is completely sequenced and dog breeds constitute close gene pools with a high degree of familiar relationships, making pedigree dogs useful to elucidate specific genes involved in diseases [75, 92, 93, 97]. With the present knowledge of the sequenced canine (including Boxer dog) genome [93, 97, 122] future studies could focus on the elucidation of the gene or genes involved in the pathogenesis of DISH using association studies with single nucleotide polymorphisms at high density [63].

An optimal animal model for DISH mimics the human situation as closely as possible, preferably, including similar etiologic factors. Thus obesity and type 2 DM are often linked to the occurrence of DISH [2, 67, 74]; since some studies question this link [109] research on the involvement of high levels of insulin in the occurrence of DISH are warranted. In dogs obese or not, DM is most often the result of autoimmune mechanisms affecting the β-cell function and therefore more comparable to the human type 1 DM, in which there is an insulin deficiency instead of an insulin resistance as in type 2 DM [44, 102]. This may limit the use of dogs as a DISH model when the involvement of type 2 DM, i.e., high levels of insulin, is required. When the focus on treatment options for spondylosis and DISH, however, dogs may serve as an appropriate test population. Clinical outcomes can be determined with the aid of neurological and orthopedic examinations, questionnaires regarding the dog's functionality, and even force plate gait analysis [112, 116]. Veterinarians should be aware of the occurrence and the possible clinical relevance of DISH.

Conclusion

Both spondylosis and DISH are prevalent in humans and are considered distinct entities. Presently, the term spondylosis is in the biomedical literature mostly used when also degenerative disc disease is present. In companion animals, many reports on spondylosis, often without intervertebral disc degeneration, are described. The nomenclature and the definitions of both spondylosis and DISH in biomedical and veterinary literature should be more in line to facilitate comparison. DISH occurs in dogs but has not been described in cats yet. DISH and spondylosis can co-occur in dogs in a single dog. Boxers may serve as translational disease models for the elucidation of the gene(s) involved in the (etio)pathogenesis of DISH or serve as a test population for newly developed treatment options.

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Appendix
Spinal hyperostosis in humans and companion animals: Additional references [34] – [127]

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