Naturally Occurring Spinal Hyperostosis in Dogs as a Model for Human Spinal Disorders

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Abstract

Both spondylosis and diffuse idiopathic skeletal hyperostosis (DISH) are prevalent in humans and are considered distinct entities. Nowadays, the term spondylosis is in the biomedical literature mostly used when concurrently 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. Spondylosis and DISH occur in dogs spontaneously and can co-occur in one animal. Specifically, Boxers may serve as translational disease models for the elucidation of the gene(s) involved in the (etio)pathogenesis of spondylosis and DISH or serve as a test population for newly developed treatment options.

Key Words: Animal model; canine; diffuse idiopathic skeletal hyperostosis; DISH; dog; new bone formation; spine; spondylosis deformans

Introduction

Dogs and humans have been living close together over the last 15,000 to 30,000 years and have been subjected to similar environmental influences, such as nutritional changes (Reif et al. 1992; Reif, Bruns, Lower 1998; Savolainen et al. 2002; Thalmann et al. 2013; Vila et al. 1997). With increasing health and veterinary care for both species, their life span has increased over the last couple of decades (German 2006; National Research Council, Committee on Animal Nutrition, Ad Hoc Committee on Dog and Cat Nutrition 2006). This has resulted in another similarity: both humans and dogs suffer more frequently from similar disorders, such as obesity, endocrinologic syndromes, osteoarthritis (OA), and degenerative spinal diseases (Bostman 1993; Bray and Burbidge 1998; German 2006; Heliovaara 1987; Kiss et al. 2002a; Liue et al. 2005; Muraki et al. 2009; Rijnberk, Kooistra, Mol 2003). As a result, dogs can serve as spontaneous disease animal models for certain of these diseases (An and Masuda 2006; Casal and Haskins 2006; de Bruin et al. 2009; Kooistra et al. 2009).

Several disorders may lead to new bone formation, affecting the spine of both humans and dogs alike. The main disorders associated with spinal hyperostosis are spondylosis deformans (from this point on referred to as spondylosis), diffuse idiopathic skeletal hyperostosis (DISH), OA of the facet joints, and ankylosing spondylitis (an inflammatory disorder found exclusively in humans) (Resnick 1985). In this article, the focus will be briefly on the human and canine spinal anatomy, after which this review will particularly focus on spondylosis and DISH in both humans and dogs. Specific attention will be paid to the question whether dogs may serve as translational animal models for these disorders.

Anatomy

Human Anatomy of the Spine

The human spine consists of 7 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 4 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 and anterior longitudinal ligament (ALL) (Figure 1). The collagen of the annulus fibrosus and the ALL connects with the bone of the vertebra by strong connections, termed Sharpey fibers (Resnick 1985). 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 IVD space, the intermediate spans two or three disc spaces, and the outer superficial layer spans four or five vertebrae (Resnick 1985).

Canine Anatomy of the Spine

The canine spine contains 7 cervical, 13 thoracic, 7 lumbar, 3 (fused) sacral, and, depending on the dog breed, up to 20 caudal vertebrae. As in humans, the IVDs are made up of two cartilaginous endplates, an inner gel-like nucleus pulposus, and annulus fibrosus and are located between all vertebrae except for C1-C2 and the fused sacral vertebrae. The ventral longitudinal ligament and dorsal longitudinal ligament, the analogues of the human ALL and posterior longitudinal ligament, are situated at the ventral and dorsal aspect of the canine spine (Figure 2). On lateral radiographic examination, the individual vertebrae are easily identifiable, but the IVDs are radiolucent and therefore not generally visible.

Figure 1  Median sagittal section of two human lumbar vertebrae and their ligaments (Gray 2000).

Figure 2  Ligaments of the canine vertebral column. 1. Supraspinous ligament; 2. spinous process; 3. interspinous ligament; 4. arch of vertebra; 5. interarcuate ligament; 6. intervertebral foramen; 7. dorsal longitudinal ligament; 8. ventral longitudinal ligament; 9. intervertebral disc (Dyce, Sack, Wensing 2010).
Spondylosis Deformans

Spondylosis Deformans in Humans

Introduction and Etiology

Spondylosis has been defined as a “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 IVD height is normal or only slightly decreased” (Fardon, Milette, Combined Task Forces of the North American Spine Society, American Society of Spine Radiology, and American Society of Neuroradiology 2001). Osteophytes are found in the absence of other degenerative changes (van der Kraan and van den Berg 2007). However, the term spondylosis has also often been used to describe a situation in which osteophytes are found especially in combination with progressive degenerative disc disease, including decreased disc height (Binder 2007; Gibson, Grant, Waddell 1999; Harrop et al. 2007; Lee et al. 2011; Middleton and Fish 2009; Muraki et al. 2009; Shedid and Benzel 2007). For instance, some authors 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), sclerosis, and osteophytes, to grade lumbar spondylosis (Kellgren and Lawrence 1957; Muraki et al. 2009).

The etiology of spondylosis is not well understood. 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 thus to development of osteophytes several millimeters from the disc-vertebral junction (Resnick 1985). The difference in amount and appearance of the new bone formation is used to radiographically differentiate between different disorders. The osteophytes in spondylosis are distinguishable from the syndesmophytes in ankylosing spondylitis and the enthesophytes in spinal DISH. In ankylosing spondylitis, the orientation of the new bone formation is straight from vertebra to vertebra, whereas in case of spondylosis, the orientation is often first anteriorly and later cranio-caudally (Resnick 1985). In spinal DISH, that is, ossification of the ALL, the appearance of the new bone formation is more flowing and by definition affects four or more contiguous vertebrae (Resnick and Niwayama 1976). The difference in amount and appearance of the new bone formation is used to radiographically differentiate between these three distinct disorders. For instance, Haller et al. (1989) investigated human pelves and differentiated between spondylosis and DISH by the pattern and extent of spinal new bone formation. The diagnosis of spondylosis was made when focal osteophytes were found instead of contiguous or flowing new bone formation (Haller et al. 1989).

Prevalence

The prevalence of spondylosis increases with age and is more frequently found in males compared with females (O’Neill et al. 1999; Resnick 1985). In the thoracic region, predominantly the right side of the spine is affected, presumably due to the pulsations of the aorta at the left side. In the lumbar region, both sides of the spine are equally affected (Resnick 1985). In the UK, in a population of 180 people >50 years of age, a prevalence of 84% of spondylosis in men and 74% in women was found (O’Neill et al. 1999). In Japan, in a cohort of 2288 people >60 years of age, a prevalence of 75.8% was found for the presence of spondylosis with and without the presence of loss of disc height (Muraki et al. 2009).

Skeletal Distribution

In humans, spondylosis mainly occurs in the cervical and/or the lumbar region of the spine and less often in the thoracic region (Muraki et al. 2009; Smith and Godersky 1987). 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 (Shedid and Benzel 2007). This is possibly because of 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 (Resnick 1985).

Clinical Symptoms

Neck pain, cervical radiculopathy, and cervical myelopathy are the three main clinical symptoms reported in the presence of cervical spondylosis (Harrop et al. 2007; Shedid and Benzel 2007). Correlations between the amount of lumbar osteophytes and lower back pain have been described (Frymoyer et al. 1984; O’Neill et al. 1999). However, the prevalence of these same degenerative changes among asymptomatic individuals makes the assignment of a clear clinical relevance difficult (Middleton and Fish 2009). In a cohort study of 2288 people >60 years old, no significant association between the presence of lumbar osteophytes and lower back pain was found (Muraki et al. 2009). In combination with loss of disc height, a significant difference in amount of lower back pain was found only in women, whereas a similar significant difference was not found in men (Muraki et al. 2009). Similar frequencies of disc height loss and osteophytes were found in groups without, with moderate, and with severe lower back pain (Frymoyer et al. 1984).

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 (Mazanec and Reddy 2007). In a large meta-analysis published in 1999, a serious lack of scientific evidence supporting surgical management for degenerative lumbar...
Spondylosis Deformans in Dogs

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 (Carnier et al. 2004; Langeland and Lingaas 1995; Levine et al. 2006; Morgan, Hansson, Miyabayashi 1989). The osteophytes vary from small spurs to bony bridges across the disc space, leaving most of the ventral surface of the vertebral body unaffected. As is the case with spondylosis in humans, the etiology of spondylosis in dogs is not well known (Langeland and Lingaas 1995; Read and Smith 1968).

Diagnosis

Similar to spondylosis in humans, canine spondylosis is often diagnosed based on radiographic examination and/or (histo) pathological examination (Carnier et al. 2004; Langeland and Lingaas 1995; Morgan 1967a, 1967b; Morgan, Hansson, Miyabayashi 1989; Morgan, Ljunggren, Read 1967; Read and Smith 1968; Wright 1982a, 1982b) made a distinction between four types of new bone formation based on radiographic examination: type 1 being endplate osteophytes that were described to be the result of spondylosis, and a group of three other types (types 2, 3, and 4) of new bone formation. The spurs of types 2 and 3, compared with type 1, have a broader base of origin at the vertebral body and seem to grow out to be type 4, which consists of a contiguous ventral band of new bone. These types were described to be comparable with what was described as ankylosing hyperostosis (former name for DISH in that time) in biomedical literature (Wright 1982a, 1982b).

Other studies of canine vertebral hyperostosis did not specifically differentiate between spondylosis and DISH, as all bridging ossifications were thought to represent severe spondylosis (Carnier et al. 2004; Langeland and Lingaas 1995; Morgan, Ljunggren, Read 1967; Read and Smith 1968; Wright 1982b). Langeland et al. (1995) and Carnier et al. (2004) subdivided spondylosis in dogs into 3 subclasses according to the degree of osteophyte 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 (Carnier et al. 2004; Langeland and Lingaas 1995). Morgan and Stavenborn (1991) brought forward the possibility that DISH in dogs had possibly earlier been described as a severe variant of spondylosis (Morgan and Stavenborn 1991). Although it may be challenging to radiographically separate DISH from severe spondylosis, the two disorders have been described to differ in radiographic appearance (Morgan and Stavenborn 1991; Woodard et al. 1985).

Prevalence

The prevalence of canine spondylosis increases with age, with a described breed predilection for Boxers. In Norwegian Boxers, a prevalence of 26% (104/402) of spondylosis was found (Langeland and Lingaas 1995). In Italian Boxers, an even higher prevalence (50%) of grade 3 spondylosis was reported (Carnier et al. 2004). The prevalence and the degree, or grade of spondylosis, were described to increase with age (Carnier et al. 2004; Read and Smith 1968). Screening for spondylosis has been performed since 1999 in Boxers. Progress has been made as revealed by an overview of the spondylosis grading during the last 14 years, with an increase of “free” from 35% in 2000 to 65% in 2013 (Table 2) (Hazewinkel, Tellhelm, Leegwater 2013).

Skeletal Distribution

The caudal thoracic, cranial lumbar, and lumbosacral regions were reported to be most frequently affected by spondylosis (Carnier et al. 2004; Morgan, Ljunggren, Read 1967; Read and Smith 1968; Wright 1982a, 1982b). Spondylosis in the cervical spine is described less often (Morgan, Hansson, Miyabayashi 1989; Resnick 1985; Wright 1982a).

Clinical Signs

Stiffness in the back, lameness, changed gait, and pain have been reported as symptoms related to severe canine spondylosis (Carnier et al. 2004). In working dogs, the diminished spinal flexibility is described to limit activity (Morgan, Hansson, Miyabayashi 1989; Vaughan 1990). Osteophyte formations extending dorso-laterally can compress spinal nerve roots at the level of intervertebral foraminae (Morgan, Hansson, Miyabayashi 1989). Spondylosis was also detected on computed tomography (CT) images in 62% of dogs with degenerative lumbosacral stenosis (Suwankong et al. 2008). Although the presence of spondylosis has been suggested to be correlated with Hansen’s type 2 disc protrusion (Levine et al. 2006), spondylosis is also found in combination with healthy IVDs. Generally, spondylosis has been described as not being of great clinical relevance in dogs (Morgan 1967b; Morgan, Hansson, Miyabayashi 1989).
When pain and stiffness are reported, most veterinarians in general practice start out with a conservative treatment consisting of body weight reduction, controlled exercise and/or physiotherapy, and medical treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) (Sharp and Wheeler 2005).

**DISH**

**DISH in Humans**

**Introduction and Etiology**

DISH is a common, systemic disorder of the axial and abaxial skeleton in middle-aged and elderly humans. It results in ossification of soft tissues such as (longitudinal spinal) ligaments and sites of attachment of tendons or muscles and capsules to bone, that is, entheses. Examination of ancient skeletons, such as the remains of Rhamses II (1302–1213 BC in Egypt), of several members of the 16th century Italian D’Medici family, and of ancient clergymen in The Netherlands all resulted in signs of DISH being found (Bjorkengren et al. 1987; Chhem, Schmit, Faure 2004; Giuffra et al. 2010; Rothschild 1987; Verlaan, Oner, Maat 2007).

Although several authors had already mentioned similar anatomic changes, the publication by Forestier and Rotes-Querol in 1950 was the first clinical and radiological study of DISH in which this disorder was comprehensively described (Forestier and Rotes-Querol 1950). Forestier and Rotes-Querol differentiated DISH (which they named senile ankylosing hyperostosis at that time) from ankylosing spondylitis and spinal OA by means of differences in clinical, pathological, and radiological features (Forestier and Rotes-Querol 1950). Over the years, DISH has been given many different names, such as monoliform hyperostosis, spondylitis ossificans ligamentosa, hyperostotic spondylitis, hyperostosis of the spine, ankylosing hyperostosis, Forestier’s disease, generalized juxta-articular ossification of vertebral ligament, and spondylosis hyperostotica (Utsinger 1985), including extra-sapinal manifestations of DISH, Resnick et al. (1975) introduced the term that is currently most often used: diffuse idiopathic skeletal hyperostosis (Resnick, Shaul, Robins 1975).

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 (Li, Jiang, Dai 2007; Mata et al. 1997). DISH is, however, often linked to obesity (Belanger and Rowe 2001; Denko, Boja, Moskowitz 1994; el Miedany, Wassif, el Baddini 2000; Forestier and Rotes-Querol 1950; Kiss et al. 2002a; Mader, Dubenski, Lavi 2005; Mata et al. 1997; Resnick and Niwayama 1976; Utsinger 1985; Vezyroglou, Mitropoulos, Antoniadis 1996). 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 (Sencan et al. 2005). 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 to be associated with DISH are due to DISH or obesity (Mader, Dubenski, Lavi 2005). On the other hand, Vezyroglou et al. (1996) found that differences in metabolic abnormalities persisted even after adjustment was made for the BMI (Vezyroglou, Mitropoulos, Antoniadis 1996). Some authors suggested that hyperglycemia was the most useful laboratory abnormality concurrent with DISH (Utsinger 1985). Others found no significant difference in glucose levels between patients with and without DISH (Denko, Boja, Moskowitz 1994; Mata et al. 1997). The relationship with type 2 DM (or noninsulin-dependent DM) and DISH was often postulated but remains controversial (Kiss et al. 2002a; Li, Jiang, Dai 2007; Sarzi-Puttini and Atzeni 2004). For instance, no differences in the prevalence of DM between 50 patients with DISH and a control group of 50 persons without DISH were found (Daragon et al. 1995). In a study of 133 patients with DM and a control group of 133 persons, no statistically significant difference in glucose levels between the two groups (Sencan et al. 2005). Vezyroglou et al. (1996) found that DM alone was not a risk factor, but in combination with high levels of uric acid and/or hyperleptinemia, patients had a significantly higher incidence of DISH (Vezyroglou, Mitropoulos, Antoniadis 1996). Kiss et al. (2002a) compared a group of patients with spondylosis with a group of DISH patients. They found differences in BMI, the occurrence of DM, and the serum level of uric acid. This higher level of uric acid was not associated with BMI, suggesting that obesity is not the cause for the elevated levels of uric acid in DISH patients (Kiss et al. 2002a). 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 (Sarzi-Puttini and Atzeni 2004). Some authors suggested that hypervascularity could be the localizing factor (el Miedany, Wassif, el Baddini 2000; Sarzi-Puttini and Atzeni 2004). 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 (Mader, Dubenski, Lavi 2005). Denko and Melemud (1994) 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 (Denko, Boja, Moskowitz 1994). It was suggested that hyperinsulinemia may be the factor that links metabolic parameters with the development of hyperostosis (Kiss et al. 2002a; Utsinger 1985). Some authors postulated that heavy work may correlate with the extent of DISH involvement (Pappone et al. 2005). In humans with vitamin A poisoning or long-term treatment with a vitamin A derivative for dermatologic disorders, ligamentous ossification was reported (Gerber, Raab, Sobel 1954; Lawson and McGuire 1987).
Diagnosis

It was not until after the 1970s that the distinction between spondylosis and DISH was made (Kiss et al. 2002a; Mata et al. 1997; Sarzi-Puttini and Atzeni 2004). Between 1960 and 1980, signs nowadays described to DISH were considered to be a type of (severe) spondylosis by certain authors in the biomedical literature (Hajkova, Streda, Skrha 1965; Ott, Schwenkenbecher, Iser 1963; Schmorl and Junghanns 1968; Vernon-Roberts and Pirie 1977).

To differentiate DISH from several other spinal disorders such as spondylosis, osteochondrosis, and ankylosing spondylitis, Resnick and Niwayama (1976) postulated three diagnostic criteria for the diagnosis of DISH in humans (Table 1) (Resnick and Niwayama 1976).

In DISH, a flowing pattern along at least four contiguous vertebral bodies is typically found. In spondylosis deformans, the spinal new bone formation originates from the vertebral body itself instead of the longitudinal ligament (Resnick and Niwayama 1976). According to Haller et al. (1989), 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 (Haller et al. 1989). Whereas in DISH (almost always) preservation of the disc space is present, this is not the case in intervertebral osteochondrosis (Sreedharan and Li 2005). 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. Ankylosing spondylitis usually starts in late adolescence and early adulthood and consists of inflammatory spinal pain and stiffness and decreased range of motion, and after many years it can result 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 (Belanger and Rowe 2001).

To include early stages of DISH, Utsinger (1985) suggested revising the Resnick criteria for epidemiological purposes as follows:

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 enthesial new bone having a well-defined cortical margin.

Based on these revised criteria, DISH was categorized as follows, whereby the difference between categories 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 (particularity if calcaneal spurs occur together with olecranon or patella spurs).

(Utsinger 1985)

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Table 1 Criteria to diagnose DISH according to Resnick and Niwayama (1976)

- 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 2 Spondylosis in Boxer dogs >2 years from 1999 to 2012 (Hazewinkel, Tellhelm, Leegwater 2013). The values in the graph is in %
Recently, a new semiquantitative scoring system for osteophyte progression using CT images was evaluated (Yaniv et al. 2013). Yaniv et al. (2013) describe two patterns of bridging new bone formation that differed in whether the ALL was calcified or not. According to these authors, both patterns were compatible with the diagnosis of DISH. Interestingly, in the presented figures in this paper, the osteophytes that are described not to affect the ALL are comparable with the new bone formation that is diagnosed as spondylosis in dogs by veterinarians.

Prevalence

DISH is mostly seen in the elderly and demonstrates a male predominance (Belanger and Rowe 2001; Kiss et al. 2002a; Sreedharan and Li 2005). The incidence increases with body weight in both genders (Sreedharan and Li 2005; Utsinger 1985). The prevalence in humans varies around the world (Sreedharan and Li 2005). In a hospital population in the United States of people >50 years old, a prevalence of 25% in males and 15% in females was found (Weinfeld et al. 1997). DISH was found to be less common in African blacks, African Americans, Native Americans, and Asians than in American Caucasians (Cassim, Mody, Rubin 1990; Childs 2004; Weinfeld et al. 1997). However, in Pima Indians living in the Gila River reservation in Arizona in the United States, a very high incidence of DISH and type 2 DM was found (Utsinger 1985). 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, this prevalence increased to 7.1% in males and 3.2% in females (Kim et al. 2004). In Israel, a prevalence of 9.8% was found in a cohort of 1020 humans >45 years of age (Mader, Dubenski, Lavi 2005). In The Netherlands, a recent study by Westerveld et al. (2008) of an outpatient population from a clinic for internal medicine showed a prevalence of 22.7% in males and 12.1% in females. 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 incidentally recorded separately. This pre-stage DISH was found in 4.6% of the patients and more frequently in females (Westerveld et al. 2008). Weinfeld et al. (1997) made that same differentiation but called it “likely DISH” (three vertebrae) and “strictly DISH” (four or more vertebrae) (Weinfeld et al. 1997). 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, a prevalence of 27.3% in males and 12.8% in females was found (Kiss et al. 2002b).

Clinical Symptoms

DISH is known to affect the middle aged and elderly and is often asymptomatic. Clinical symptoms resulting from DISH are mainly due to altered biomechanics and may consist of painful stiffness and restriction in range of motion (Belanger and Rowe 2001; Kiss et al. 2002b; Olivieri et al. 2007). Symptoms of thoracic outlet syndrome and heterotopic ossification after hip arthroplasty are also described (Sreedharan and Li 2005). Usually, symptoms are relatively mild, despite

Skeletal Distribution

The portion of the spine that is typically involved in humans is the thoracic region (Sreedharan and Li 2005). Even in patients with cervical or lumbar complaints, the radiographic abnormalities were often found on the thoracic spine (Belanger and Rowe 2001; Sarzi-Puttini and Atzeni 2004; Utsinger 1985). The thoracic enthesophytes in human patients with DISH were usually found at the right side of the spine, presumably because of the pulsatile effect from the aorta on the left side (Verlaan et al. 2011b). Patients with situs inversus totalis and DISH subsequently showed more ossification at the left side of the thoracic spine (Belanger and Rowe 2001). The thoracic abnormalities were most frequently found between the 7th and 10th thoracic vertebrae (Resnick and Niwayama 1976; Utsinger 1985). Mata et al. (1993) showed that the technique of 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 (Mata et al. 1993).

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 (Belanger and Rowe 2001; Utsinger 1985). Compared with the thoracic and lumbar region, the cervical region is less commonly affected but leads to specific symptoms (el Miedany, Wassif, el Baddini 2000; Meyer 1999; Utsinger 1985). Extensive new bone formation of the cervical spine may lead to dysphagia and/or airway obstruction.

Extra-spinal manifestations of DISH are no exception (Haller et al. 1989; Utsinger 1985). It is even suggested that these should be included in the diagnostic criteria (Utsinger 1985). 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 (Belanger and Rowe 2001). Peripheral manifestations of DISH have been characterized by distinctive features: (1) involvement of joints that are often unaffected by primary OA, (2) increased hypertrophic changes compared with primary OA, (3) prominent enthesopathies at various sites adjacent to peripheral joints, and (4) calcifications and ossifications of entheses in sites other than joints (Mader et al. 2009).
the radiological changes that can be quite dramatic because of the extensive calcifications of ligamentous structures (Verlaan, Oner, Maat 2007). Neurological deficits due to spinal cord compression have been described to occasionally occur (Alenghat, Hallett, Kido 1982; Utsinger 1985). Mechanical dysphagia, dyspnea, stridor, hoarseness, sleep apnea, radicular complaints, and difficulty with intubation are complications associated with cervical DISH (Belanger and Rowe 2001; Miyamoto et al. 2009; Sreedharan and Li 2005; Vengust, Mihalic, Turel 2010; Verlaan et al. 2011a). Patients can even die as a result of mechanical respiratory failure, probably because of paralysis of the respiratory muscles (Callahan and Aguilera 1993; Julkunen, Aromaa, Knkt 1981; Mata et al. 1997; Meyer 1999; Paley et al. 1991; Sreedharan and Li 2005; Verlaan et al. 2011a).

Decreased range of spinal motion and reduced flexibility due to DISH can result in spinal fractures even after minor trauma (Belanger and Rowe 2001; Callahan and Aguilera 1993; Sreedharan and Li 2005). Remarkably, the fracture plane found in patients with DISH is most frequently located through the vertebral body, whereas in patients with ankylosing spondylitis, the fracture plane is most often through the disc (Verlaan et al. 2011b; Westerveld, Verlaan, Oner 2009). These fractures in patients with DISH tend to be unrecognized, unappreciated, and associated with treatment delays and permanent neurologic deficits (Belanger and Rowe 2001; Callahan and Aguilera 1993). There are two main reasons why delay in diagnosis often occurs: the patient usually has a baseline level of spinal pain preventing him or her from seeking medical attention in case of an altered pain pattern, and secondly, the treating physician does not suspect a spinal fracture, because the injury may have been considered relatively trivial (Belanger and Rowe 2001).

The efficacy of these therapies is still not well established and more research is necessary (Belanger and Rowe 2001; Troyanovich and Buettner 2003; Utsinger 1985). The treatment of DISH is usually conservative, but occasionally surgical intervention is indicated in case of specific sequelae, such as fractures, dyspnea, or dysphagia (Belanger and Rowe 2001; Sreedharan and Li 2005). Conservative therapy consists of activity modification, physical therapy, weight loss, corset or brace wear, and medical therapy with NSAIDs (Al-Herz et al. 2008; Troyanovich and Buettner 2003; Utsinger 1985). 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 (Utsinger 1985). In the cervical region, if the enthesophytes are impinging on anterior structures, surgical resection is often considered (Belanger and Rowe 2001).

**DISH in Dogs**

**Introduction and Etiology**

Surprisingly few articles are published on DISH in animals. Spinal hyperostosis similar to DISH has been described in dinosaurs, a saber-toothed cat, and old Rhesus monkeys (Bjorkengren et al. 1987; Rothschild 1987; Sokoloff, Snell, Stewart 1968), and several case reports on canine DISH were published (Ciepluch, da Costa, Russell 2013; Kornmayer et al. 2013; Morgan and Stavenborn 1991; Woodard et al. 1985). No etiologic factors of canine DISH have been reported. In humans, type 2 DM is often related to DISH. In dogs, DM is most often the result of autoimmune mechanisms affecting the β-cell function and therefore more comparable with the human type 1 than type 2 DM (Catchpole et al. 2008; Rijnberk, Kooistra, Mol 2003). A genetic predisposition is suggested, because DISH seems to occur in a high percentage in some breeds and not at all in others (Kranenburg et al. 2010, 2011).

**Diagnosis**

(Morgan and Stavenborn 1991; Woodard et al. 1985) The diagnosis of DISH is often based on radiographic examination (Morgan and Stavenborn 1991; Woodard et al. 1985), but
advanced diagnostic imaging using CT (Figures 4 and 5) and MRI are also reported (Ciepluch, da Costa, Russell 2013; Kornmayer et al. 2013; Kranenburg et al. 2011; Ortega et al. 2012). Morgan and Stavenborn (1991) stated that the radiographic and pathologic features of canine DISH closely resembled extensive spondylosis but noticed marked radiographic and morphologic differences. 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 (Morgan and Stavenborn 1991). This is consistent with what Haller et al. (1989) reported in humans (Haller et al. 1989). Morgan and Stavenborn (1991) brought forward the possibility that DISH in dogs had earlier been described as a variant of spondylosis (Morgan and Stavenborn 1991). Preferably all researchers, working in both the veterinary and biomedical fields, should use the same diagnostic criteria. The Resnick-criteria have been used most often in both fields and are suggested to be the gold standard in companion animals as well (Greatting et al. 2011).

Prevalence

A retrospective radiographic study using a grading scheme (Figure 3) reported the prevalence of both DISH and spondylosis in a large group (n = 2041) of purebred dogs (Kranenburg et al. 2010, 2011). 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 specifically high.

Skeletal Distribution

Woodard et al. (1985) described in their case report of a dog with DISH that 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 numerous extra-spatial locations. Some spinal alterations were described to be related to spondylosis; others were more proliferative and were reported to be caused by DISH. Especially the extra-spatial alterations were even more extensive and distinct from alterations seen in primary OA (Woodard et al. 1985).

Morgan and Stavenborn (1991) described a 4-year-old female Great Dane Dog with 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; peri-articular 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 (Morgan and Stavenborn 1991).

Clinical Signs

In the aforementioned two cases of canine DISH, 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

Figure 3 Schematic presentation of a sagittal cross section of canine vertebral bodies with spinal new bone formation showing different grades of spondylosis deformans (grade 1–3) and DISH. V, vertebral body; EP, end plate; flowing (yellow) line, ventral longitudinal ligament (Kranenburg et al. 2011).
resulted in the owners electing for euthanasia (Morgan and Stavenborn 1991; Woodard et al. 1985). Although three of the four cases described by us in an earlier report also had orthopaedic comorbidities, it is likely that the spinal new bone formation itself resulted in spinal pain and stiffness (Kranenburg et al. 2011).

Ortega et al. (2012) showed that vertebral fusion of two or more consecutive IVD spaces was significantly correlated with adjacent segment disease (i.e., IVD degeneration at adjacent levels). Spinal fusion may lead to altered biomechanics at the mobile disc space, including increased mobility and increased intradiscal pressure, which in turn may lead to an accelerated progression of degenerative disc disease. Vertebral fusion, on the other hand, protected the fused segment from IVD degeneration (Ortega et al. 2012).

In a recently reported case of a Weimaraner with DISH, a fracture of the hyperostotic bony bridge and vertebral subluxation of L2-L3 was stabilized with standard vertebral body plating. Two years later, the dog was presented with a fracture of the cranial end-plate and right facet joint distal to the segment (L4-L5) stabilized by a second vertebral plate (Kornmayer et al. 2013). This report indicates that, comparable with humans, dogs with DISH may be predisposed to spinal fractures.

Another recent case report describes a case of canine DISH with both ventral spinal new bone formation and pseudarthroses of several spinal processes. The dog was managed with oral NSAIDs for 2 years until the mobility was severely impaired and the owners elected euthanasia (Ciepluch, da Costa, Russell 2013).

Treatment (Woodard et al. 1985) (Morgan and Stavenborn 1991) 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 causes neurologic deficits or (severe) pain, surgical intervention may be considered. This may include enthesophytectomy and, in the 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 (Binder 2007; Gibson, Grant, Waddell 1999; Harrop et al. 2007; Lee et al. 2011; Middleton and Fish 2009; Muraki et al. 2009; Shedid and Benzol 2007). As a result, in human medicine, the differentiation of spondylosis from full-blown DISH, in which the IVDs are generally not degenerated, is easier. In the veterinary literature, the term spondylosis is primarily used to describe spinal osteophytes without necessary signs of IVD degeneration. This makes the distinction in dogs between spondylosis and specifically early-stage DISH more difficult. In the biomedical literature in the 1960s and 1970s, signs nowadays ascribed to DISH were still considered by some authors to be a type of (severe) spondylosis (Hajkova, Streda, Skrha 1965; Ott, Schwenkenbecher, Iser 1963; Schmorl and Junghanns 1968; Vernon-Roberts and Pirie 1977). Later, the distinction between spondylosis and DISH has been made more frequently, and spondylosis and DISH are currently considered to be distinct disorders in humans (Kiss et al. 2002a; Mata et al. 1997; Sarzi-Puttini and Atzeni 2004). In the veterinary literature, Wright (1982) acknowledged the
occurrence of several different types of spinal bony outgrowths and described the types to be related to different disorders (Wright 1982a, 1982b). Other authors considered these different forms of spinal hyperostosis all to be part of spondylolysis (Carnier et al. 2004; Langeland and Lingaas 1995; Morgan, Ljunggren, Read 1967; Read and Smith 1968; Wright 1982b). It would be advisable to use the same definitions for spondylolysis 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 biomedical fields. Companion animals as disease models complement laboratory animal models but are currently underused as models for human (spinal) diseases. Dogs have been reported to naturally develop spondylosis and DISH and thereby may be useful to study the etiology of both disorders. For instance, little is known about the involvement of specific genes in spondylosis and DISH. Animal models may be used as genetic models to help determine candidate genes for humans. 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 (Lindblad-Toh et al. 2005; Ostrander, Galibert, Patterson 2000; Ostrander and Wayne 2005; Parker and Ostrander 2005). With the present knowledge of the sequenced canine (including Boxer) genome (Lindblad-Toh et al. 2005; Ostrander and Wayne 2005; Parker and Ostrander 2005), 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 (Karlsson and Lindblad-Toh 2008).

An optimal animal model for DISH mimics the human situation as well as possible. Preferably, this includes the involvement of similar etiologic factors as in humans. Although much is still unknown about the etiologic factors involved in human DISH, obesity and type 2 DM are often linked to the occurrence of DISH (Belanger and Rowe 2001; Kiss et al. 2002a; Li, Jiang, Dai 2007). Because some studies question this link (Daragon et al. 1995; Sencan et al. 2005), more research on the involvement of high levels of insulin in the occurrence of DISH is needed. In dogs, obese or not, DM is most often the result of autoimmune mechanisms affecting the β-cell function and is therefore more comparable with the human type 1 DM, in which there is insulin deficiency instead of insulin resistance, as in type 2 DM (Catchpole et al. 2008; Rijnberk, Kooistra, Mol 2003). This may limit the use of dogs as an animal model for DISH when the involvement of type 2 DM, that is, high levels of insulin, is required.

The dog is already frequently used as a model for bone tissue engineering and bone regeneration (Kan and Kessler 2011; Pearce et al. 2007; Viateau and Guillemin 2004). Several similarities and differences in the microstructure, macrostructure, bone composition, bone remodeling, and pathways have been described (Kan and Kessler 2011; Pearce et al. 2007; Viateau and Guillemin 2004). Pearce et al. (2007) state that of the species reported in their review (large animals) describing animal models for implants, the canine model has the most similar bone structure to humans (Pearce et al. 2007). According to the authors’ knowledge, no data have been presented on the specific pathways leading to new bone formation in dogs and/or humans with DISH.

When the focus is specifically on possible treatment options for spondylosis and DISH, dogs may serve as an appropriate test population for preclinical trials of innovative treatments. Clinical outcomes can be determined with the aid of neurological and orthopedic examinations, questionnaires to owners regarding the dog’s functionality, and objective measurements of ground reaction forces using force plate gait analysis (Suwankong et al. 2007; van Klaveren et al. 2005).

Conclusion

Both spondylosis and DISH are prevalent in humans and are considered distinct entities. DISH and spondylosis also occur in dogs, and both may even co-occur in the same dog. In humans, the term spondylosis is mostly used in the biomedical literature when degenerative disc disease is also present, whereas in household dogs, many reports describe spondylosis without IVD degeneration. Therefore, the nomenclature and definitions of both spondylosis and DISH in biomedical and veterinary literature should be more in line to facilitate comparison. Boxers may serve as a translational animal model for the elucidation of the gene(s) involved in the (etiopathogenesis of DISH or serve as a test population for newly developed treatment options.

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References


