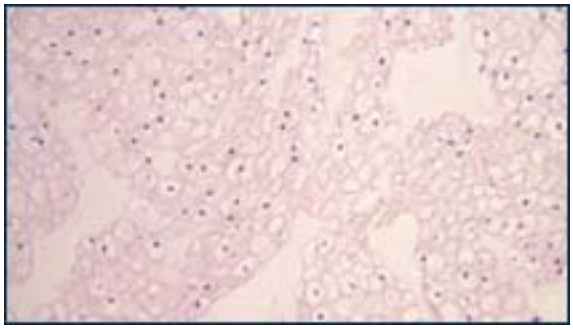
# Intervertebral disc degeneration in dogs.

Niklas Bergknut

Degeneration of the intervertebral disc (IVD) is a common condition in dogs, associated with IVD degenerative diseases such as herniation, lumbosacral stenosis and cervical spondylomyelopathy. This review reports the results of a study aiming to increase the knowledge with regards to the morphological process of degeneration, and the demographics of IVD-related diseases. It also reports and validates the schemes enabling objective grading and monitoring of the degenerative processes [3]. The study presented in this review made use of a new magnetic resonance imaging (MRI) grading scheme for evaluating and monitoring IVD degeneration in dogs, thereby facilitating early diagnosis and, potentially, preemptive treatment for high-risk canine patients. The aforementioned studies also tested the first hypothesis: the morphological process of IVD degeneration in chondrodystrophic (CD; dogs with disproportionally short limbs) and non-chondrodystrophic (NCD) breeds is more similar than previously reported. The only difference is that degeneration starts earlier in life and proceeds more rapidly in CD breeds. The basis for this hypothesis and our findings are described below. A review of pertinent literature [3] led to the conclusion that IVD degeneration cannot consistently be divided into a chondroid and a fibroid form, as previously suggested [11]. The distinction between chondroid degeneration in CD breeds and fibroid degeneration in NCD breeds has been widely accepted by the veterinary community, and is largely based on the studies of Hansen in the 1950ies [11] [12] [49]. He found that CD and NCD breeds differ significantly in the age of onset and speed with which the degenerative changes progress, but considered two essentially different degenerative processes. However, from recent literature and own findings it would appear that the fundamental steps in the degenerative cascade are similar in the two types of dog breed. Degeneration in both types is characterized initially by the degradation and loss of proteoglycans, a change from collagen type II to type I, and a gradual loss of notochordal cells, which are replaced by a less dense population of chondrocyte-like cells (Figure 1).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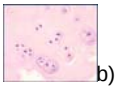
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Figure 1. Midsagittal histological sections of a) a healthy and b) a severely degenerated IVD stained with picosirius red and alcian blue.

These matrix and cellular changes are similar in the two types of breeds, but occur earlier and faster in CD breeds [2] [3] [7] [8] [9] [27] [34]. As Hansen also pointed out, we found that most of the IVDs of CD breeds started to degenerate simultaneously and earlier in life (<1 year of age) than in NCD breeds. In NCD breeds often only one IVD was degenerated, with the other ones remaining healthy. Healthy IVDs, full with notochordal cells, were found in young dogs of both CD and NCD breeds, but only in older NCD breeds (>6-years of age) and not in older CD breeds [3]. Morphologically, all stages of the degenerative process, from Thompson grade I to grade V (Figure 2), can be identified in the IVDs of dogs of both CD and NCD breeds. But again, degeneration occurs earlier in life and more rapidly in CD breeds [22] [24]. The same is true for the degenerative changes seen on MRI graded according to Pfirrmann [18] [23].

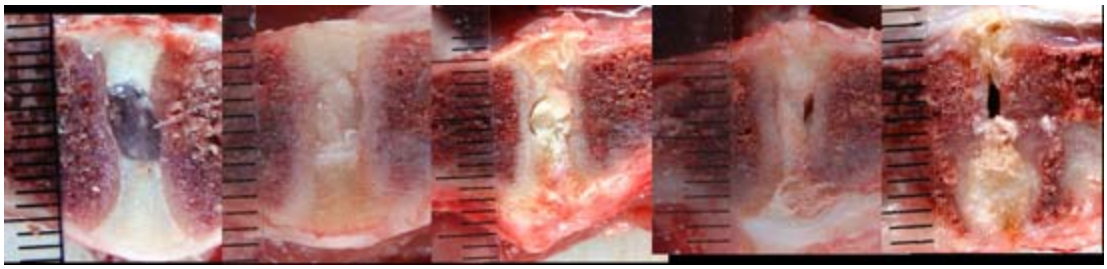


Figure 2. Midsagittal photographs of canine intervertebral discs depicting different Thompson grades. From left to right increasing degree of degeneration: Thompson grade I, II, III, IV and V.

The erroneous assumption that two different pathological processes are active in canine IVD degeneration came about because Hansen referred to the cells he found in the nucleus pulposus (NP) of older NCD-breed dogs as fibrocyte-like and hence called the process fibroid degeneration. To illustrate these fibrocyte-like cells, he presented a histological image of the NP from a 10-year-old Airedale terrier [11]. However, on closer examination, these cells rather resemble what now would be identified as dying notochordal cells [32] [58]. Although his conclusion was erroneous, the distinction Hansen made between degenerating IVDs in CD and NCD breeds was logical, because they show significant differences, not only in the onset of degeneration, but also in the pathological end stage. In CD breeds, the end stage can involve extrusion of degenerated and calcified NP tissue into the spinal canal, where it compresses the neural structures, giving rise to clinical signs (Hansen type I herniation). In NCD breeds, the end stage usually results in bulging of the disc or even protrusion of the degenerated and dorsally bulging annulus fibrosus (AF; Hansen type II herniation), which also causes clinical signs due to compression of neural structures. Hansen already noted in his thesis that the distinction between type I herniation in CD breeds and type II herniation in NCD breeds was not consistent, as type II herniation is occasionally seen in CD breeds and type I herniation in NCD breeds. However, recent evidence indicates that the pathological processes underlying IVD degeneration in CD and NCD breeds are similar [3], though etiologically different, with principally a genetic cause in CD breeds and a multifactorial origin of trauma and “wear and tear” most common in NCD breeds. The distinction between IVD degeneration in CD and NCD breeds should therefore be based on the etiology of degeneration rather than on the pathological process itself.

There is a second important difference between the processes of IVD degeneration in CD and NCD breeds: the common occurrence of mineral deposits in the degenerating IVDs of CD breeds, which are rare in NCD breeds [11] [48] [56] [57] (Figure 3). It is likely that these mineral deposits affect the process of degeneration. Instead of a gradually collapsing IVD due to dehydration and concurrent loss of NP volume, the NP cavity in CD breeds is often filled with mineral deposits, thereby maintaining IVD height and preventing inward collapse of the AF with subsequent disorganization and degeneration, which is often seen in NCD breeds. The AF of the IVDs with a mineralized NP will ultimately also degenerate, but often not until the NP is severely degenerated [11].

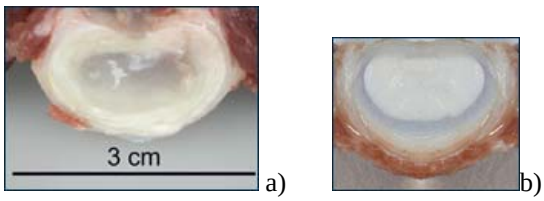



Figure 3. Transverse section through a) a healthy intervertebral disc of a non-chondrodystrophic dog with a gelatinous nucleus pulposus (NP), and b) a degenerated intervertebral disc of a chondrodystrophic dog with a completely calcified NP.

This mineralization may also be the cause of the different types of herniation seen in the pathological end stage of IVD degeneration in both types of dog breed. In the degenerated IVD of

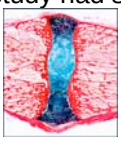
NCD-breed dogs there is less NP material left to extrude into the spinal canal, whereas the degenerated NP of CD-breed dogs is often full of mineralized matrix that can readily be extruded into the spinal canal. However, it remains unclear whether the herniation of mineralized NP tissue occurs secondary to the progressive degeneration of the AF, which finally ruptures, or whether herniation is principally due to altered biomechanical loading of the spinal segment because of the calcified NP. Most likely, Hansen type I herniation is a combination of both, but this remains to be proven. Hansen stated that the calcifications are of a dystrophic origin rather than part of endochondral ossification[11]. This view is supported by more recent studies in humans and sheep [33] [46] [48] [50]. Deposition of different calcium salts has been described in human IVD [33] [50]. It has been suggested that the mineral deposits found in CD breeds consist of hydroxyapatite [48], as is also described in a hereditary form of dystrophic calcification seen in merino sheep and humans [46] [48]. However, it still remains to be proven that the calcifications seen in young CD-breed dogs are indeed composed of hydroxyapatite.

Regarding the demographic characteristics, new findings have confirmed results of previous studies in smaller and geographically more limited study populations [10] [11] [16] [19] [31] [42]. In accordance with most of them, we found that IVD degenerative disease in general (i) has a conservative life-time prevalence of about 3.5% in dogs younger than 12 years; (ii) is most common in CD breeds, especially in Dachshunds, and (iii) is 1.5 times more common in male than female dogs. With regard to the breed predilection for the anatomical site, CD breeds and especially Dachshunds were most commonly affected by thoracolumbar IVD herniation. Large-breed NCD dogs, especially German shepherds, were most commonly affected by degenerative lumbosacral stenosis (DLSS). Cervical IVD degenerative diseases were equally distributed over CD and NCD breeds, with Dobermans and Dachshunds being at highest risk. The novel findings of our study [3] were the high case fatality rates (ratio of deaths to incidence rate of IVD-related diseases), of 1:3 in the overall population, 1:5 in the CD breeds, and more variable in the NCD breeds, with an overall rate of 1:2 in the high-risk NCD breeds. To our knowledge, this is the first large-scale epidemiological study of IVD degenerative diseases to include low-risk breeds. Some breeds, mainly hunting dogs, have a low reported incidence of IVD degenerative disease. The fact that the condition is overrepresented in some breeds and rare in others suggests that there is a genetic component involved; this applies not only to CD breeds but also to some NCD breeds, such as DLSS in the German shepherd and cervical spondylomyelopathy (CSM) in the Doberman. As degeneration in these breeds mostly affects only a single IVD, the genetic component involved in initiating the degeneration seems to affect the IVDs secondarily, through malformation of the vertebrae or misalignment of the facet joints, as proposed earlier [20] [30]. However, in most other NCD breeds a multifactorial origin is more plausible, which is less influenced by genetics and more by physical factors causing “wear and tear” of the disc. A breed can be considered as a subgroup of the species [51], and breed-associated diseases with incidence rates higher than in other breeds are suspected to have a genetic basis [53]. Genetic similarity within a breed is mainly based on multiple common ancestries, which increases the chances of distributing the risk factors within the subgroup [52]. Using this rationale, there is compelling evidence that early IVD degeneration in CD breeds, DLSS in the German Shepherd Dog and CSM in the Doberman are indeed hereditary disorders.

An interesting incidental finding in our study [3] was that most IVDs of Jack Russell terriers, despite their CD phenotype, had a low Pfirrmann grade, irrespective of the dog’s age, in marked contrast with the other CD breeds. This indicates that genetic factors causing chondrodysplasia in dogs might not necessarily be responsible for IVD degeneration. If chondrodysplasia and IVD degeneration are indeed caused by different genetic factors, they are probably closely linked in most dog breeds. Another finding highlighting the complexity of this association is based on a recent publication, that showed that an expressed fgf4 retrogene is a likely cause of chondrodysplasia [17]. This retrogene is not expressed in the Beagle, one of the CD breeds at highest risk of developing IVD degenerative disease, which indicates that different genetic factors could be involved in chondrodysplasia and associated IVD degeneration. The gene(s) involved in the etiology of these abnormalities can possibly be identified using association analysis, by

comparing the frequency of marker alleles in an appropriate cohort (with respect to breed, gender and age) of cases and controls. Detailed knowledge of the genes involved will increase our understanding of the pathogenesis of the diseases and may lead to novel therapies. The latter may include specific interventions in cellular processes to prevent, delay, or stop the sequence of events leading to IVD degeneration.

IVD degeneration is not synonymous with IVD disease (Figure 4). While IVDs that give rise to clinical signs inevitably show degeneration, degenerated IVDs are commonly reported incidental findings [11] [13] [23] [24] [30] [43]. This was evident in our study [3], where MRI often revealed only one or two herniated IVDs that gave rise to clinical signs and asymptomatic degenerated IVDs elsewhere in the spinal segment in CD breeds. In NCD breeds, often only the IVD giving rise to clinical signs was found to be degenerated. Indeed, IVDs can be degenerated without giving rise to clinical signs, as many of the 19 dogs (both CD and NCD breeds) included in the study had severely degenerated IVDs but none had a history of IVD disease [3].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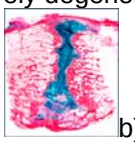
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Figure 4. Transverse histological sections (H&E) of a) a healthy nucleus pulposus richly populated by notochordal cells only, and b) a degenerated nucleus pulposus containing a more sparse cell population of only chondrocyte-like cells clustered in nests.

The MRI grading system originally designed for use in humans can be reliably used to evaluate IVD degeneration in dogs. We based this conclusion on the high inter- and intraobserver reliability and biological validation showing that IVD degeneration was significantly associated with the CD phenotype and with increasing age [3]. For the Pfirrmann grading system to be clinically useful in veterinary practice, however, it must be used in combination with information about disc herniation (if present), such as protrusion or extrusion.

The Thompson scheme is a reliable method for grading canine IVD degeneration with a high inter- and intraobserver agreement [3]. Further, there was substantial agreement between macroscopic grading of intervertebral segments according to Thompson, and grading of low-field MR images according to Pfirrmann, which suggests that the method can be used to accurately identify IVDs in different stages of degeneration. MRI can thus be useful for monitoring progression of IVD degeneration in high-risk breeds and can ultimately lead to identification of IVDs suitable for preemptive treatments. Currently, the only preventive treatment is fenestration [5], which is aimed at preventing herniation by removing most NP tissue. However, fenestration of the IVD changes the biomechanical properties of the spinal segment, which becomes less stable [25] [35] [36] [45] [55]. Also, spinal surgery is associated with considerable morbidity and mortality, so instead of further damaging the IVD by fenestration, a better prophylactic treatment would be to halt the degenerative process or even regenerate the IVD. This may be achieved through the application of growth factors, anti-catabolic agents, or cell-based strategies, which have been investigated in numerous studies over the past decade [6] [37] [38] [39] [40] [41] [47]. Different regenerative treatment strategies are required for different stages of degeneration, which is why an objective and accurate MRI grading scheme for IVD degeneration is needed.

The similarities and differences between the process of IVD degeneration in dogs and humans may be evaluated in order to assess whether the former can be used as an animal model in medical research. Although the dog has frequently been employed in surgical procedures and biomechanical studies of the spine [14] [26] [28] [29] [54] [59] and some studies have discussed the translational aspects between canine and human IVD degeneration [1] [15] [44], few comparative studies have been performed.

When attempting this approach, the specific interspecies differences as well as the differences in IVD degeneration between CD and NCD breeds (early versus late onset, respectively) must be respected. The fact that dogs develop IVD degeneration spontaneously at different ages makes

them suitable as models. CD breeds, which develop degeneration early, are best suited for longitudinal studies, or for preclinical studies of interventional treatments aiming to prevent, delay or halt the course of degeneration. Pathogenesis in NCD breeds, especially the German shepherd, resembles that in humans with lumbosacral IVD degeneration; it develops over a longer period (years) of chronic IVD stress, and of “wear and tear” [16]. These dogs would thus make suitable models for investigating the development of IVD degeneration of the human lumbosacral disc, and as veterinary patients could be used for preclinical studies of new treatments for IVD degenerative diseases. The number of experimental dogs could thereby be reduced, and results could be obtained at considerably lower cost. Also, the pathogenesis of spontaneous IVD degeneration in dogs resembles that in humans probably more closely than induced IVD degeneration in laboratory animals.

It will probably be easier to elucidate the processes of IVD degeneration in dogs than in humans, because of the genetic and phenotypic differences between breeds and the limited genetic variation within breeds. Canine IVD material is also easier to obtain, from different sources, without the use of purpose-bred laboratory dogs. Veterinary patients operated for IVD hernias, post-mortem specimens used with the owner’s consent, research dogs used in unrelated experiments are all available. The fact that dogs walk on four legs has been raised as a factor limiting their use as models of human IVD degeneration, under the assumption that humans have a higher axial loading of the spinal segments due to gravity. However, the axial loading patterns of human and canine IVDs is indeed comparable or even higher in dogs and other quadrupeds [4] [21] [59].

Some differences, however, have been found, such as the absence of growth plates in growing human vertebrae and thicker cartilaginous endplates. Whereas in dogs vertebral growth takes mainly place in the growth plates, in man it is in the junction between the vertebrae and the endplates. This may explain the relatively thicker endplates found in humans (endplate thickness/total IVD height). The importance of these differences with regard to the rate of osmosis needs to be further evaluated, in order to improve the accuracy of extrapolating findings from dogs to humans. Currently not much is known about the rate of nutrient osmosis into the canine IVD. As there is no blood supply providing nutrients to the NP, implanted cells will be dependent chiefly on the osmosis of nutrients through the endplates for their nutritional supply.

Canine spines were used ex-vivo in a study testing a nucleus pulposus prosthesis (NPP) intended for use in humans [3]. A clinically adapted mode of implantation of the NPP into the nuclear cavity of the canine L7-S1 IVD was used. Swelling, fit and restoration of disc height of the prosthesis in situ were monitored by radiography, CT, and MR imaging. The canine spines were found suitable for this type of translational studies, and a NPP might also be a viable treatment option for selected veterinary patients suffering from IVD degenerative disease.

## Key findings

• The traditional division of the processes underlying canine IVD degeneration into chondroid and fibroid degeneration is inaccurate. The fundamental biochemical, histopathological, and morphological changes are similar in CD and NCD breeds. A more appropriate distinction is based on the etiology, as there is principally a genetic cause in CD breeds, whereas a multifactorial etiology including “wear and tear”, is more plausible in most NCD breeds.
• IVD degenerative disease in dogs had a conservative life-time prevalence of 3.5% in dogs younger than 12 years. It was most common in CD breeds, especially in Dachshunds, and 1.5 times more common in male than female dogs. Case fatality rates of IVD degenerative diseases were higher than previously suggested, with rates of 34% in the overall population, around 20% in most CD breeds, and more variable in the NCD breeds with over 50% in the breeds at highest risk.
• The Thompson scheme is a reliable method for macroscopic grading of canine IVD degeneration. Further, the scheme showed substantial agreement with grading of low-field MR images according to Pfirrmann, which suggests that this method can be used to accurately

identify IVD degeneration in dogs.
• Similarities exist between IVD degenerative processes in humans and canines, both in CD and NCD dog breeds. Both could thus serve as translational animal models of spontaneous IVD degeneration for human research, offering diverse possibilities for the use of these two animal models with early onset (CD) versus late onset (NCD) IVD degeneration.
• Veterinary patients suffering from IVD degenerative diseases can be enrolled in preclinical trials, and also be used to study the process of degeneration. Synergistic effects from this approach could lead to new treatment modalities for both dogs and humans, a reduced need for laboratory animals, and lower research costs. In its pathogenesis, spontaneous IVD degeneration in dogs likely resembles the disease process in humans, better than an induced IVD degeneration in laboratory animals.

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# Appendix
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