Intervertebral disc degeneration in the dog. Part 1: Anatomy and physiology of the intervertebral disc and characteristics of intervertebral disc degeneration

ARTICLE in THE VETERINARY JOURNAL · NOVEMBER 2012
Impact Factor: 1.76 · DOI: 10.1016/j.tvjl.2012.10.024 · Source: PubMed

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Introduction

The canine spine consists of 7 cervical, 13 thoracic, 7 lumbar, 3 (fused) sacral, and a variable number of coccycgeal vertebrae (Hansen, 1952; Dyce et al., 2010). The vertebral bodies of C2-S1 and all coccygeal vertebrae are interconnected by an intervertebral disc (IVD) (Dyce et al., 2010). The IVD is composed of a central nucleus pulposus (NP), an outer annulus fibrosus (AF), the transition zone (TZ), and cartilaginous endplates (EPs) (Fig. 1).

Degeneration of the IVD is a common phenomenon in dogs and can lead to disease (Brisson, 2010; da Costa et al., 2006; Meij and Bergknut, 2010). IVD degeneration is known to predispose dogs to Hansen type I cervical and thoracolumbar disc herniation (Hansen, 1952) and Hansen type II disc herniation diseases, such as degenerative lumbosacral stenosis (DSS) (Meij and Bergknut, 2010) and cervical spondylomyelopathy (CSM) (da Costa et al., 2006). However, IVD degeneration is also a common incidental finding in dogs without clinical signs of disease (Hansen, 1952; da Costa et al., 2006; De Decker et al., 2010).

The first case report of IVD degenerative disease in a dog was published in 1881 and involved a Dachshund with sudden onset of hind limb paralysis (Janson, 1881, cited by Hansen, 1952); the mass that compressed the spinal cord was described as a ‘chondroma located only to the epidural space’. Shortly afterwards, in 1896, a more comprehensive study was published on ‘enchondrosis intervertebralis’ (Dexler, 1896, cited by Hansen, 1952), a reactive inflammation in the epidural space, but it would take another 40 years before that disease was correctly described in the veterinary literature as the herniation of NP material into the spinal canal, causing compression of the spinal cord (Tillmanns, 1939).

Pioneering studies of IVD degeneration in dogs were performed during the 1950s by the Swedish veterinarians Hansen and Olsson, in particular the study that led to the thesis by Hans-Jörgen Hansen in 1952 (Fig. 2) (Hansen, 1951, 1952, 1959; Olsson, 1951; Olsson and Hansen, 1952). Since their studies, numerous publications have described the clinical aspects of IVD degenerative diseases, but few have revisited the fundamental aspects of IVD degeneration (Braund et al., 1975, 1976; Ghosh et al., 1975, 1976a,b, 1977a,b; Cole et al., 1985, 1986; Gillett et al., 1988; Royal et al., 2009; Johnson et al., 2010). The aim of this two-part review was to summarize current literature on canine IVD degeneration. In this first part, the anatomy, physiology, histopathology, and biochemical and biomechanical characteristics of the healthy and degenerated IVD are discussed. In Part 2, the aspects of IVD degeneration in chondrodystrophic and non-chondrodystrophic dog breeds are discussed in detail.
Embryology of the canine spine and intervertebral disc (IVD)

Three somatic germ layers are formed early in mammalian embryogenesis: an outer ectodermal layer, a middle mesodermal layer, and an inner endodermal layer (Vejlsted, 2010). A longitudinal column of mesoderm, the notochord, establishes the cranial/caudal and posterior/anterior axes of the developing embryo (Fig. 3) (Vejlsted, 2010). Ectoderm directly posterior to the notochord gives rise to the neural plate, which is composed of so-called neuroectoderm. The neural tube and neural crest cells (positioned dorsolateral to the neural tube) are formed from the neuroectoderm and give rise to the central nervous system and peripheral nervous system, respectively (Vejlsted, 2010).

During the development of the neural tube, mesoderm adjacent to the developing neural tube forms a thickened column of cells, the paraxial mesoderm. The paraxial mesoderm ultimately develops into discrete blocks, the somites, which form the axial skeleton, the associated musculature, and the overlying dermis. Each somite is divided into: (1) a dermatome, which gives rise to dermis; (2) a myotome, which gives rise to epaxial musculature; and (3) a sclerotome, which gives rise to vertebral structures (Vejlsted, 2010). Sclerotomal cells form a continuous tube of mesenchymal cells, the perichondral tube, which completely surrounds the notochord. An alternating series of dense and less dense accumulations of cells form along the perichondral tube, a process called resegmentation (Sinowatz, 2010). While the bodies of the vertebrae develop from the less dense accumulations, the dense accumulations form the AF and TZ of the IVD, intervertebral ligaments, vertebral arches, and vertebral processes, of which the latter two eventually fuse with their corresponding vertebral body (Sinowatz, 2010). The formation of the vertebral bodies results in segmentation of the notochord, which persists as separate portions in each intervertebral space. These separate portions of notochord expand, forming the NP of the individual IVDs (Sinowatz, 2010; McCann et al., 2011).

The healthy canine intervertebral disc

Anatomy and physiology of the intervertebral disc

The healthy IVD is composed of four distinct components, namely, the NP, AF, EP and TZ. The NP is a mucoid, translucent, bean-shaped structure, mainly composed of water, located slightly...
eccentrically in the IVD (Hukins, 1988; Johnson et al., 2010). The NP is surrounded by the AF, a dense network of multiple, organized, concentric fibrous lamellae. The ventral part of the AF is two to three times thicker than the dorsal part (Hansen, 1952). Near the centre of the IVD, the AF becomes more cartilaginous and less fibrous (Hansen, 1952; Hukins, 1988). This transition from a fibrous to a more cartilaginous/mucoid structure, the TZ or the innermost AF, forms the interconnection between the NP and AF (Butler, 1988). The cranial and caudal borders of the IVD are formed by the cartilaginous EPs (Hukins, 1988). The fibres of the inner AF are strongly connected with the EPs, whereas the fibres of the outer AF form connections with the bony vertebral body epiphyses (Sharpey’s fibres) (Hansen, 1952; Inoue, 1981; Hukins, 1988).

The outer layers of the AF have a limited blood supply, but there is no direct blood supply to the inner layers of the AF or to the NP. However, terminal branches of the vertebral epiphyseal arteries give rise to a densely woven vascular network adjacent to the cartilaginous EPs (Crock and Goldwasser, 1984). Innervation of the IVD tissue is sparse: nerve endings have only been found in the outer lamellae of the AF, and not in the inner AF, TZ, and NP (Hansen, 1952; Forsythe and Ghoshal, 1984; Willenegger et al., 2005). This is in contrast with the dorsal longitudinal ligament, which is densely innervated (Hansen, 1952; Forsythe and Ghoshal, 1984).

The EPs play an essential role in supplying the IVD with nutrients. Small molecules (such as oxygen and glucose) reach the cells of the NP, TZ, and AF through diffusion and osmosis from the capillary buds through the semipermeable EPs (Holm et al., 1981; Holm et al., 1982; Urban et al., 2004). Additional nutrients and oxygen are supplied via the outer, vascularized parts of the AF (Holm et al., 1982; Maroudas, 1988). Larger molecules, such as albumin and enzymes, are transported by bulk fluid flow (‘pumping mechanism’) created by the physiological loading of the IVD and changes in posture (Holm et al., 1981, 1982; Maroudas, 1988; Urban et al., 2004).

Histology of the healthy intervertebral disc

In the healthy IVD, the main cell of the NP is the notochordal cell (Fig. 4C) (Hansen, 1952; Braund et al., 1975; Butler, 1988; Cappello et al., 2006). These large cells are characterized by cytoplasmic vesicles, the content and function of which are still debated (Hansen, 1952; Hunter et al., 2003, 2004), but there are indications that these vesicles are unique organelles, which have an osmoregulatory function, and that they are involved in the swelling and stretching of the embryonic notochord and in the regulation of osmotic stresses in the NP (Hunter et al., 2007). The notochordal cell has relatively few mitochondria and is therefore thought to rely mainly on anaerobic metabolism (Hunter et al., 2003). Notochordal cells are found in clusters (Hunter et al., 2003, 2004) and produce an amorphous basophilic matrix rich in proteoglycans and collagen type II (Hansen, 1952; Butler, 1988; Hunter et al., 2003; Cappello et al., 2006).

The TZ contains chondrocyte-like cells embedded in a loose, acellular fibrocartilaginous matrix network (Hansen, 1952; Braund et al., 1975; Ghosh et al., 1975) and is distinct from the matrix surrounding the notochordal cells (Butler, 1988). Microscopically, the lamellae of the AF can be seen as separate fibrocartilaginous layers composed of eosinophilic fibrous bundles arranged in parallel (Figs. 4B and 5) (Hansen, 1952; Braund et al., 1975; Butler, 1988). The cell population changes from fibrocyte-like cells in the outer layers of the AF to a mixed population of fibrocytes and chondrocyte-like cells in the inner layers (Hansen, 1952; Braund et al., 1975; Ghosh et al., 1975).
et al., 1975; Butler, 1988; Bergknut et al., 2012a). The canine EP (Fig. 4D) consists of cranio-caudally oriented layers of matrix and chondrocyte-like cells (Inoue, 1981), on average 5 (3–8) cell layers thick and comprises 6% (3–11%) of the total width (intervertebral distance) of the canine IVD (Bergknut et al., 2012b).

Biochemical structure of the healthy intervertebral disc

The healthy NP is composed of a complex network of negatively charged proteoglycans interwoven in a mesh of collagen fibres (mainly collagen type II) (Ghosh et al., 1976a; Cole et al., 1985). The proteoglycan molecules consist of a protein backbone with negatively charged glycosaminoglycan (GAG) side chains. The most common side chains are chondroitin sulfate and keratin sulfate, which are covalently bound to the central core protein (Ghosh et al., 1976a, 1977a,b; Cole et al., 1985, 1986). These negatively charged GAGs repel each other, giving the proteoglycans the appearance of a bottle-brush. The most common proteoglycan in the healthy IVD is aggrecan (Cole et al., 1986). The proteoglycans are in turn aggregated with hyaluronic acid, and these negatively charged large complexes create a strong osmotic gradient, attracting water into the NP. As a result, over 80% of the healthy NP is composed of water (Holm and Nachemson, 1983), creating a high intradiscal pressure (Ghosh et al., 1977a,b; Cole et al., 1985).

Fig. 4. (A) Mid-sagittal histological section (H&E) of a healthy, immature canine intervertebral disc, still with active growth plates in the vertebral bodies (*). (B) Annulus fibrosus (AF), showing the lamellar layers with fibrocyte-like cells (arrowhead) and chondrocyte-like cells (arrow). (C) Nucleus pulposus (NP), showing clustered notochordal cells. (D) Cartilaginous endplate (EP), showing chondrocyte-like cells in a hyaline-type matrix. The border between endplate (left) and subchondral bone (SCB) (right) is indicated with arrowheads.

Fig. 5. An electron microscopy image of the annulus fibrosus from a healthy canine, lumbar intervertebral disc. The overview to the left shows the well-organized lamellar layers. To the right, a higher resolution image showing the individual collagen bundles. Photos courtesy of Andrea Friedmann.
The biomechanical function of the healthy intervertebral disc

The biomechanical function of the IVD is to transmit compressive forces between vertebral bodies and to provide mobility as well as stability to the spinal segment (White and Panjabi, 1978; Adams and Hutton, 1988). Like in humans, the horizontally-positioned spine in dogs is loaded along its longitudinal axis, which is the result of contraction of the trunk muscles and the tension on structures such as the ligaments (Zimmerman et al., 1992; Smit, 2002). Since relatively few biomechanical studies investigating the canine IVD have been performed, we will also discuss studies in humans.

During motion, the canine IVD can be subjected to several motions/loading conditions, namely axial compression, shear, tension, bending, and torsion (White and Panjabi, 1978; Smitt, 2002). The NP, AF, TZ, and EPs work as a functional unit to resist these loads, with each component having a different specialized function (Hukins, 1988; Roughley, 2004; Setton and Chen, 2006). The NP is a highly hydrated structure that exerts swelling pressure inside the IVD. The EPs and AF function to contain the NP during loading. During axial compression, the majority of the compressive load is absorbed by the NP and the inner TZ. The surrounding AF protects the NP against shearing induced by the applied load and its own internal swelling pressure, thereby maintaining the disc circumference in spite of a decrease in disc height. The alternating arrangement of the annular lamellae, combined with the oblique orientation of the lamellar fibres, enables the AF to cope with tensile forces generated during loading (Adams and Hutton, 1988).

The IVD is rarely subjected to pure tensile loads, as the trunk muscles constantly act to keep the IVD compressed. The mechanism by which the IVD permits bending is essentially the same for flexion, lateral flexion, and extension. During flexion, the hydrostatic pressure in the NP increases, and the obliquely running fibres of the AF change their orientation. For example, in the transition from neutral position to dorsosflexion, the compressive stress within the NP increases on the dorsal side of the disc, the fibres of the ventral AF extend, whereas those in the dorsal AF become compressed, resulting in bulging of the dorsal AF. The capacity of the IVD to resist bending is directly related to the volume of the NP: if the nuclear volume is increased (by saline injection), the resistance to bending increases (Adams and Hutton, 1988). In comparison to bending motion, IVDSs are stiffer in axial rotation/torsion (Adams and Hukins, 1988).

Vertebral motion has been shown to cause an outflow of fluid from the IVD, especially from the NP (Adams et al., 1996). Any outflow of fluid is reversed when the spine is unloaded. The diurnal cycle of load-induced fluid expression and regain seems to have important consequences for transport of large solutes and nutrients, because factors affecting diffusion, such as disc height (diffusion distance), are sensitive to hydration (Urban et al., 2004). This is further illustrated by the finding that spinal motion over a longer period of time increases the aerobic metabolism of IVD cells, thereby decreasing the production of lactate (Holm and Nachemson, 1983). However, the effects of the diurnal cycle on the nutrition of the canine IVD are still largely unknown.

The degenerating canine intervertebral disc

The characteristics of degeneration of the IVD discussed below are applicable for chondrodystrophic (CD) and non-chondrodystrophic (NCD) dog breeds. Specific differences regarding the characteristics of IVD degeneration between CD and NCD dog breeds are discussed in Part 2 of this review (Smolders et al., 2012a).

Degeneration of the IVD is a complex, multifactorial process that is characterized by changes in the composition of the cells and extracellular matrix of the NP, TZ, AF, and EPs. The pathophysiology of IVD degeneration in dogs has been largely unexplored. However, IVD degeneration in dogs is very similar to human IVD degeneration (Bergknut et al., 2012b), and therefore the fundamental, pathophysiological processes involved in human IVD degeneration will be briefly discussed.

IVD degeneration is described as an aberrant, cell-mediated response to progressive structural failure of the IVD and is associated with genetic predisposition, chronic physiomechanical overload and trauma, inadequate metabolite and nutrient transport to and from the cells with the IVD matrix, cell senescence and death, altered levels of enzyme activity, changes in matrix macromolecules, and changes in water content (Fig. 6) (Buckwalter, 1995; Adams and Roughley, 2006). In the process of IVD degeneration, the GAG content decreases with a concurrent increase in collagen content. As a result, the matrix of the IVD becomes more rigid and loses its hydrostatic properties to function as a hydraulic cushion, rendering the IVD matrix suboptimal to fulfill its biomechanical function. Structural failure of the matrix results in a changed biomechanical environment of the IVD cells within the matrix. In addition, because of the changes of the IVD matrix, diffusion of nutrients and the bulk fluid flow in and out of the disc became impaired, further deteriorating the health of the IVD cells and synthesis of healthy matrix.

The avascular and low cellular nature of the IVD and the inferior biomechanical environment eventually impair the ability of IVD cells to adequately repair the matrix. The weakened IVD is vulnerable to damage by levels of stress that are considered physiological for the healthy IVD. Consequently, a vicious cycle of continued damage and inadequate repair and regeneration is triggered, resulting in degeneration rather than healing (Fig. 6). Structural failure of the IVD manifests itself in characteristic macroscopic changes. As a result of dehydration of the IVD (especially the NP), the disc height (distance between two EPs) may decrease, and due to the decreased functionality of the NP, the AF, and EPs are loaded non-physiologically, eventually resulting in annular tears and EP fractures, respectively (further discussed below). Structural failure of the IVD as a whole may also result in bulging or herniation of the IVD.

The changes seen in early IVD degeneration closely resemble those of physiological ageing of the disc. Although the definition proposed by Adams and Roughley (2006) may partially distinguish truly degenerative changes from age-related ones, it cannot be applied to the onset and early stages of IVD degeneration. Therefore, we use the term ‘IVD degeneration’ to describe deterioration of the quality of the IVD matrix as a result of pathological and age-related changes and the associated structural changes of the disc, as described below.

Macroscopic aspects of intervertebral disc degeneration

Thompson et al. (1990) described what is now accepted as the gold standard for reproducible and objective grading of the macroscopic changes associated with IVD degeneration in humans, and this grading scheme has been validated for use in dogs (Bergknut et al., 2011). According to this scheme (Fig. 7; Table 1), the gradual process of IVD degeneration can be divided into five stages, ranging from a completely healthy IVD (grade I) to a severely degenerated IVD (grade V). This grading scheme does not include herniation and prolapse of the IVD, which are considered consequences of the degenerative process (Hansen, 1952).

Degeneration commonly starts in the mucoid NP, which changes colour from shining translucent grey to dull, non-translucent white–grey or yellowish green–brown. These changes are accompanied by cleft formation and ultimately collapse of the NP. As the NP degenerates, the lamellar structure of the AF buckles inwards and becomes disorganized. The TZ widens and becomes irregular, making it difficult to distinguish the AF from the NP (Hansen, 1952; Braund et al., 1975; Ghosh et al., 1975; Cappello et al., 2006). The cartilaginous EP thickens, becomes irregular and may fracture. New bone may be formed at the peripheral margins of the vertebral bodies, resulting in osteophytes and ventral spondylolisthesis (Thompson et al., 1990). Continued degeneration will lead to highly irregular and sometimes breached EPs and subchondral bone. As degeneration proceeds, the IVD space becomes smaller or may disappear completely in extreme cases, with bulging of the degenerated AF or even rupturing of the AF and herniation of the NP.

Histopathology of intervertebral disc degeneration

The histopathological changes that occur during IVD degeneration in dogs were first described by Hansen (1952), but few studies of these changes have been published since (Braud et al., 1975; Ghosh et al., 1975; Hunter et al., 2004; Royal et al., 2009; Johnson...
The early stage of degeneration is characterized by cellular changes within the NP. The large notochordal cell clusters are lost, resulting in smaller notochordal cell clusters or single notochordal cells (Fig. 9C). Concurrently, single or clusters of chondrocyte-like cells, surrounded by extracellular matrix, appear in the NP, dividing it into lobules, resulting in the gradual expansion of the TZ into the NP (Fig. 9D) (Hansen, 1952; Bergknut et al., 2012a). In essence, notochordal cells are replaced by chondrocyte-like cells and their associated extracellular matrix, which resembles hyaline cartilage and consists largely of disorganized collagen fibres. This process is referred to as chondrification (Hansen, 1952; Braund et al., 1975; Ghosh et al., 1975; Hunter et al., 2004; Cappello et al., 2006). While chondrocyte-like cells may migrate from the TZ into the NP, recent evidence suggests that it is more likely that they are of a differentiated notochordal cell lineage (Choi et al., 2008; Risbud et al., 2010; McCann et al., 2011). Degeneration of the extracellular matrix of the NP can be observed as clefts and cracks, which are a result of the altered biochemical properties of the matrix.

Histologically, degeneration of the AF is characterized by the disorganization of the lamellar fibres and the ingrowth of chondrocyte-like cells from the TZ (Fig. 9B) (Hansen, 1952; Bergknut et al., 2012a). Cross-links between the annular fibres, which prevent lamellar movement in the AF, are more numerous in degenerated IVDs (Puustjarvi et al., 1993). The inability of normal AF movement combined with NP degeneration and loss of IVD height may result in rupture or bulging of the AF, resulting in IVD herniation (Hansen, 1952; Smolders et al., 2012a,b,c).

The EPs become thicker in the early stages of degeneration, and in later stages become increasingly irregular and may breach at several places (Fig. 9E). The breaches usually occur in the central parts of the EPs and can give rise to a 'Schmorl’s node', which is herniation of the NP into the vertebral body (Schmorl, 1926).

Biochemical changes involved in intervertebral disc degeneration

IVD degeneration is associated with a decrease in proteoglycan contents and in the degradation of GAG molecules of the NP, with the long chondroitin sulfate side chains being replaced by shorter keratin sulfate side chains (Ghosh et al., 1976a, 1977a,b; Cole et al., 1985, 1986). The relative content of collagen also increases, first in the NP and subsequently in the AF (Fig. 8) (Ghosh et al., 1976a, 1977a,b). Little is known about the biochemical changes involved in degeneration of the canine EPs. Degeneration of the human EP is accompanied by a decrease in the water, collagen type II, and proteoglycan content (Antoniou et al., 1996) and ultimately in mineralization (Oda et al., 1988), leading to obstruction of capillary buds and obstruction of the physiological transport of solutes to and from the IVD (Oda et al., 1988; Roberts et al., 1997).

MMPs are involved in remodelling and degeneration of the human disc and MMP-1 and -2 are responsible for the breakdown of collagen types I and II, respectively. A correlation has been found between an increase in MMP-2 and the severity of IVD degeneration in dogs (Bergknut et al., 2012b). ADAMTS-4 causes the breakdown of aggrecan in human IVD degeneration (Mosyak et al., 2008). The most important MMP inhibitors in the IVD are protease inhibitors, called tissue inhibitors of metalloproteinase (TIMPs). Inflammatory mediators that exacerbate the degenerative process, such as tumour necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6, have been identified in degenerated IVDs (Podichetty, 2007).

Biomechanical effects of intervertebral disc degeneration

The inability of the IVD to fulfil its physiological function interferes with the normal action of the vertebral column, thereby influencing other components of the functional spinal unit, such as ligaments, facet joints, and vertebral bodies (Adams and Roughley, 2006). Therefore, deficits in the biomechanical quality and integrity of the IVD caused by degeneration can lead to structural failure of the functional spinal unit and ultimately to spinal cord compression.

The reduced proteoglycan content of the NP leads to dehydration and to a consequent loss of NP size and intradiscal pressure. Consequently, the AF takes over the compressive load-bearing function that is usually performed by the hydrated NP (McNally and Adams, 1992; Adams et al., 1996a). As a result, the AF increases in size (McNally and Adams, 1992; Johnson et al., 2010) and becomes stiffer and weaker, leading to structural failure, which prevents the AF from resisting tensile forces. The degenerative changes ultimately cause the IVD to bulge outwards when it is subjected to physiological loading (Adams and Roughley, 2006). In addition, structural failure of the AF can result in annular defects or tears (Adams and Roughley, 2006), through which degenerated NP material can extrude (Hansen, 1952; Adams and Roughley, 2006). Since the dorsal AF is 2–3 times thinner than the ventral AF, structural failure and IVD herniation usually occur on the dorsal side.

Removal of the NP through an annular window in canine cadaveric spines, a procedure which resembles IVD herniation, causes...
spinal instability, indicating that AF and NP integrity are essential to the functionality of the spine (Schulz et al., 1996; Macy et al., 1999; Hill et al., 2000; Smith et al., 2004; Smolders et al., 2012a,b,c). Conversely, annular damage (fissures) may occur independently of NP degeneration and is likely to result in increased stress on the NP (Adams and Roughley, 2006). In addition to structural failure of the NP and AF with subsequent disc displacement, degeneration of the NP and AF results in an uneven distribution of load on the EP, making it more susceptible to damage. Degeneration of the IVD can therefore result in cracks in the EP with extrusion of the degenerated NP (Grant et al., 2002).

As a component of the functional spinal unit, degeneration of the IVD affects not only the disc, but also other spinal components, such as ligaments, facet joints, and vertebral bodies (Adams and Roughley, 2006). Decreased IVD function alters and increases facet joint loading (Kahmann et al., 1990), which can lead to secondary osteoarthritic changes. The altered loading pattern can also affect the adjacent vertebrae, leading to remodelling, sclerosis, and spondylosis of the vertebral bodies (Keller et al., 1989).

With increasing degeneration (Thompson grades I to IV), the stabilizing function of the IVD in relation to rotational biomechanics (i.e., flexion/extension, lateral bending, axial rotation) is lost, accompanied by an increase in the mobility of the affected spinal segment. However, in the final stages (Thompson grade V) of IVD degeneration, laxity decreases and the spine ‘restabilizes’ as a result of the formation of osteophytes/spondylosis and collapse of the IVD space (Fujiwara et al., 2000; Smolders et al., 2012c).

Conclusions

The physiological function of the IVD, an essential structure of the spine, is largely dependent on the quality of its extracellular matrix and therefore of the ability of its constituent cells to synthesise, remodel, and maintain a biochemically healthy matrix. Degeneration of the IVD involves significant cellular changes, with a shift from the native notochordal cell population to a suboptimal chondrocyte-like cell population. At the same time, the quality of the matrix deteriorates as a result of the changes in cellular composition and of the aberrant homeostasis of the matrix and matrix-regulating enzymes. This cascade of events ultimately leads to structural failure of the AF, NP and EP. Since the individual components of the IVD function synergistically, deterioration of one component leads to degeneration of the other, resulting in a degenerative cascade that can lead to bulging or herniation of the IVD.

Conflict of interest statement

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

Acknowledgments

The authors would like to thank the Multimedia Department of the Faculty of Veterinary Medicine, Utrecht University for their technical assistance.

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