


**REVIEW**

# Osteoarthritis and intervertebral disc degeneration: Quite different, quite similar

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Intervertebral disc degeneration describes the vicious cycle of the deterioration of intervertebral discs and can eventually result in degenerative disc disease (DDD), which is accompanied by low-back pain, the musculoskeletal disorder with the largest socioeconomic impact world-wide. In more severe stages, intervertebral disc degeneration is accompanied by loss of joint space, subchondral sclerosis, and osteophytes, similar to osteoarthritis (OA) in the articular joint. Inspired by this resemblance, we investigated the analogy between human intervertebral discs and articular joints. Although embryonic origin and anatomy suggest substantial differences between the two types of joint, some features of cell physiology and extracellular matrix in the nucleus pulposus and articular cartilage share numerous parallels. Moreover, there are great similarities in the response to mechanical loading and the matrix-degrading factors involved in the cascade of degeneration in both tissues. This suggests that the local environment of the cell is more important to its behavior than embryonic origin. Nevertheless, OA is widely regarded as a true disease, while intervertebral disc degeneration is often regarded as a radiological finding and DDD is undervalued as a cause of chronic low-back pain by clinicians, patients and society. Emphasizing the similarities rather than the differences between the two diseases may create more awareness in the clinic, improve diagnostics in DDD, and provide cross-fertilization of clinicians and scientists involved in both intervertebral disc degeneration and OA.

**KEYWORDS**

articular joint, degeneration, inflammation, intervertebral disc, mechanical loading, osteoarthritis

## 1 | INTRODUCTION

Low back pain and osteoarthritis (OA) are the two major musculoskeletal causes for disability worldwide.<sup>1–3</sup> Low back pain has several causes and degenerative disc disease (DDD) is one of them.<sup>4–7</sup> The pain, dysfunction, and stiffness characterizing patients with DDD and OA can cause significant loss in work participation and lead to high socio-economic costs.<sup>8,9</sup> The diseases are caused by degeneration of the intervertebral disc and articular joint, following a vicious circle towards joint deterioration.<sup>10,11</sup> While this process of degeneration in the articular joint carries the same name as its disease (ie, OA), the degenerative process in intervertebral discs is commonly known as intervertebral disc degeneration.<sup>12–14</sup> On

plain X-rays both intervertebral disc degeneration and OA are accompanied by a loss of joint space, formation of osteophytes, subchondral cysts and sclerosis.<sup>15,16</sup> No definitive treatment options are available to halt or reverse intervertebral disc degeneration and OA, but early symptoms of DDD and OA can be relieved with physiotherapy and pain medication, and with spinal fusion and joint arthroplasty in end-stage DDD and OA, respectively. Inspired by these similarities, we investigated the analogy between both conditions.

In the 19th century, Luschka was the first to suggest that the intervertebral disc is similar to an articular joint, comparing the cartilaginous endplates of the intervertebral disc to articular cartilage (AC).<sup>17–19</sup> Since then, several studies have focused on clinical aspects in DDD and OA,

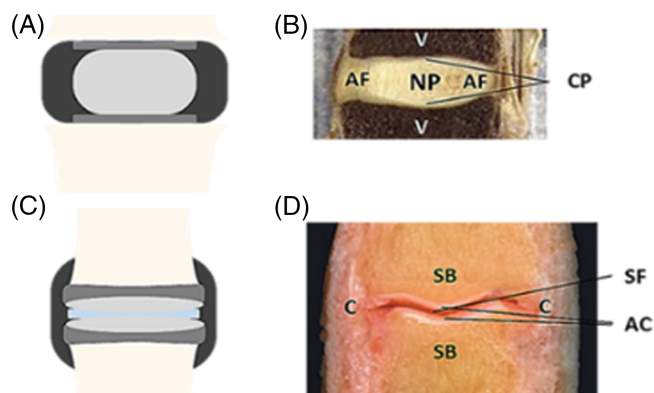
and pathomechanisms and regenerative strategies in intervertebral disc degeneration and OA, but this was often in parallel and not in a comparative way.<sup>13,20,21</sup> Most research on intervertebral disc degeneration has concentrated on only one aspect of degeneration (in particular the nucleus pulposus [NP]),<sup>22-24</sup> while OA is generally regarded as a whole organ disease,<sup>25</sup> rather than just degeneration of the AC. Still, most studies consider the differences between intervertebral disc degeneration and OA rather than the similarities between the two conditions.

In this review, we provide a broad comparison on the human intervertebral disc and articular joint. We investigate similarities and differences in anatomy, embryonic development, cellular behavior and tissue composition. Consecutively, we compare the degeneration of intervertebral discs and articular joints in humans, followed by a clinical perspective on both diseases. Since the NP and AC are believed to be the most affected part of the degenerated intervertebral disc and articular joint, respectively, we focus on the NP and AC.<sup>26,27</sup>

## 2 | THE HEALTHY INTERVERTEBRAL DISC AND ARTICULAR JOINT

### 2.1 | Anatomy and embryonic development

The intervertebral disc is a unique structure in the human body. The intervertebral discs are amphiarthrosic joints and consist of: (a) the NP, (b) the cartilaginous endplates that cover the subchondral bone of the adjacent vertebrae, and (c) the annulus fibrosus (AF),<sup>28</sup> but the functional spinal unit also involves the facet joints and vertebrae (Figure 1A). The articular joints are diarthrosic joints and consist of: (a) the synovial fluid, (b) hyaline cartilage covering the subchondral bone of the adjacent bones, and (c) the capsule (Figure 1B), and its functional unit also involves tendons, ligaments and the bone of the

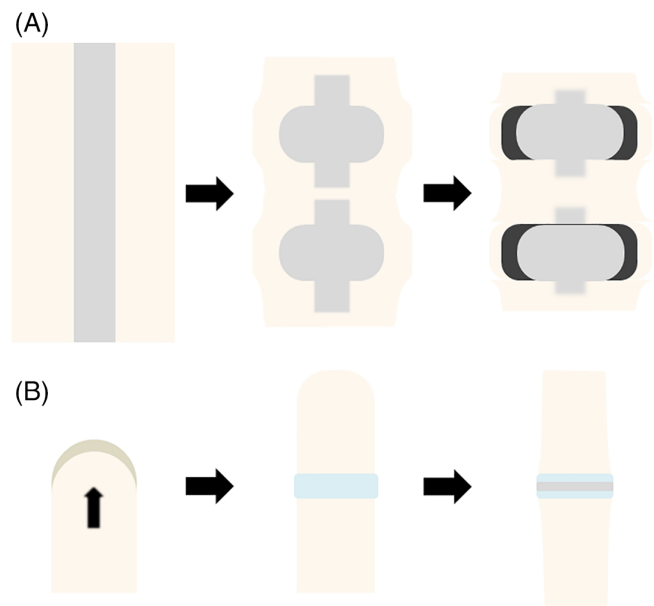


**FIGURE 1** A and B, Anatomy of the human intervertebral disc and articular joint.<sup>29,30</sup> A, The intervertebral disc consists of a nucleus pulposus (light gray), surrounded by an annulus fibrosus (black), and is between two cartilaginous endplates (dark gray) that adhere to the adjacent vertebrae (beige). B, An image of a sagittal section of an intervertebral disc. NP: nucleus pulposus; AF: annulus fibrosus; CP: cartilaginous endplates; V: vertebrae. C, The articular joint consists of articular cartilage (light gray), that lies over the subchondral bone (dark gray) of the adjacent joints, and is divided by synovial fluid (light blue). The capsule (black) surrounds the articular joint. D, An image of a sagittal section of an articular joint. AC: articular cartilage; C: capsule; SB: subchondral bone; SF: synovial fluid

adjacent bones. While the structural elements of all mammalian intervertebral discs are essentially the same, articular joints may contain additional structures specific to the concerning joint (eg, bursae, tendons, menisci).<sup>31</sup>

During early human embryonic development, starting in week 5, the intervertebral discs are formed by two structures: the notochord and sclerotome (Figure 2A). The sclerotome, forming the vertebrae and the outer AF, surrounds the expanding notochord, which will partition into the nuclei pulposi. A transition zone of notochord and sclerotome characterizes the inner AF. The NP and AF are unique structures in humans and other mammals,<sup>32-34</sup> but as other vertebrates like birds and reptiles develop articular joints between vertebrae instead of intervertebral discs, more similarity is suggested than one may expect from looking at anatomy and embryology alone.<sup>28,34</sup> For a more extensive description of the anatomy and embryonic development of human intervertebral discs we refer to.<sup>32,33,35-37</sup>

The formation of arms and legs occurs slightly later in human embryonic development, in week 6 (Figure 2B). Limbs derive from the limb bud, a structure of mesenchyme covered with ectoderm. The limb bud starts to grow gradually outwards forming limbs over time.<sup>38,39</sup> The formation of articular joints occurs later in embryonic development (ie, in week 8) and becomes morphologically visible with the presence of the interzone, which is a region at the location of the future joint where the mesenchymal cells transform into an interspace in between two outer layers adjacent to the epiphyseal end of the



**FIGURE 2** A and B, Embryonic development of the human intervertebral disc and articular joint. A, Starting in week 5, the intervertebral discs are formed by the notochord and sclerotome. The sclerotome (on the outside) forms the outer annulus and surrounds the notochord (inside), which will eventually partition into the nuclei pulposi. A transition zone between notochord and sclerotome characterizes the inner annulus fibrosus. B, In week 6, the limb bud is formed by mesoderm covered by ectoderm and starts to grow outwards in order to form arms and legs. The formation of articular joints occurs later in embryonic development (ie, in week 8), and is characterized by the interzone (light blue), which is a group of mesenchymal cells that form an interspace

future bones.<sup>40</sup> By contrast, intervertebral discs are formed in a process of sequential segmentation. For a more extensive description of the anatomy and embryonic development of articular joints we refer to.<sup>38,39,41–43</sup>

## 2.2 | Extracellular matrix and biomechanical properties

The intervertebral disc and articular joint absorb and distribute the loads that are imposed by muscle force and gravity on the vertebrae and adjacent bones, respectively. To counterbalance the loads, an intradiscal pressure is found in the NP and an intra-articular pressure in the AC.<sup>44,45</sup> These pressures are attributed to the high concentration of negatively charged proteoglycans—predominantly aggrecan—in the extracellular matrix (ECM) of the NP and AC.<sup>44–48</sup> Proteoglycans attract water which generates a hydrostatic pressure within the tissue. This hydrostatic pressure is essential for the NP and AC to provide a healthy mechanobiological stimulus to the cells, and dynamic loading is necessary for transport of nutrients and waste products.<sup>49,50</sup>

Besides proteoglycans, the ECM of the NP and AC contains collagen, mainly collagen type II.<sup>51</sup> The ratio of aggrecan to collagen is more than five times higher in the NP than in AC,<sup>35,52,53</sup> and it is this high ratio of aggrecan that creates a high intradiscal pressure in the intervertebral disc (ie, 0.43–0.50 MPa in relaxed standing<sup>54</sup>), whereas the pressure inside AC is much lower (ie,  $\pm$  300 kPa in 30% compression<sup>45,55</sup>). Toward the outer regions of the intervertebral disc, the AF becomes a more fibrous structure of mainly collagen type I,<sup>51,56</sup> which is able to resist tensile stresses caused by the intradiscal pressure. The articular joint capsule is also a dense fibrous connective tissue and surrounds the articular joint with a variety in thickness, depending on the applied loads.<sup>56</sup>

The collagen type I fibers in the AF are organized in oblique lamellae which limits movement of the spinal segment.<sup>57</sup> This way, the intervertebral disc provides stability and essentially forms an elastic hinge providing flexibility over a small range of motion by deformation of the tissue, but is not able to articulate. In contrast, articular joints provide low-friction articulation, only limited by ligaments that stabilize the articular joints.<sup>58</sup> Thus, articular joints have a much larger range of motion.

## 2.3 | Cells

At birth, the human NP has a high density of notochordal cells,<sup>59</sup> which are large in diameter, contain intracellular vacuoles and appear in clusters.<sup>60</sup> However, they are slowly replaced by chondrocyte-like cells after birth.<sup>61,62</sup> There is some evidence that the cells maintain some of their notochordal characteristics, as human degenerated intervertebral disc cells express brachyury, which is a well-established notochordal marker.<sup>63</sup> Other cell-specific markers found in NP cells are cytokeratin-19, FOX-F1, CA12 and PAX-1. The chondrocyte-like cells are much smaller in diameter and lack intracellular vacuoles.<sup>60</sup> A lack of innervation and vascularization makes that these cells live in a harsh environment, with a relatively low pH (ie, 7.1).<sup>64,65</sup> Only the outer annulus and endplates have minimal blood supply, which culminates in a suboptimal repair mechanism of the intervertebral disc itself.

The articular joints are surrounded by the joint capsule. The capsule has two parts, an inner synovial membrane, consisting of the intima,

which has only one cell layer, and the well-vascularized subintima surrounding the intima.<sup>66,67</sup> The outer, more fibrous membrane of the joint capsule and subchondral bone in the articular joint has minimal blood supply,<sup>68</sup> which is similar to the intervertebral disc. Yet there is an exchange of solutes between the synovial fluid and joint capsule which is incomparable to the intervertebral disc, as there is no distinct exchange between the NP and AF. However, the environment of the chondrocytes, the only cell type present in AC, is also hostile with minimal repair capacity, as blood vessels are absent in the AC.<sup>69</sup> The chondrocytes are differentiated from the embryonal mesenchyme, which is derived from the mesoderm, and their gene expression profile contains SOX9, COMP, FGFB, MAPK, WNT, and JNK.<sup>70</sup> They are round cells, like NP cells, but their cell density is much higher compared to the NP and their distribution differs over the several distinct layers in AC.<sup>60</sup> In adult AC, the chondrocytes are surrounded by the pericellular matrix and they lack cell-cell interactions. Just like the chondrocyte-like cells in the NP, their proliferative activity is very low, but they are still important in maintaining the homeostasis and production of ECM.<sup>71</sup>

For a more detailed description of the cell-types in the intervertebral disc and articular joint, we refer to more extensive reviews on this subject.<sup>60,69,70,72,73</sup> However, considering the resemblance in some features of cell behavior after birth (eg, produce the same type of ECM proteins), the local environment of the cell (ie, ECM and mechanobiological cues) may have more influence on its behavior than its embryonic origin.<sup>35</sup>

In summary, there are differences in anatomy and embryology between the healthy intervertebral disc and articular joint in humans, but there are also marked similarities. The NP and AC correspond especially in the production of predominantly proteoglycans and collagen type II, resulting in an ECM with a high hydrostatic pressure, which is able to endure compressive loads. Furthermore, both structures are mostly avascular, limiting their own regenerative capacities (see Table 1). These similarities between the two healthy tissues provide a good base from which the process of degeneration in the human intervertebral disc and articular joint can be further understood.<sup>10,11</sup>

## 3 | DEGENERATION IN THE HUMAN INTERVERTEBRAL DISC AND ARTICULAR JOINT

The balance between anabolic and catabolic processes is tenuous in the intervertebral disc and articular joint. When the balance is tipped, there is an inequality between the synthesis and degradation of the ECM due to catabolic cell behavior (<sup>58,74–77</sup>). Within the intervertebral disc and articular joint, this mainly affects the NP and AC. Several systemic inflammatory factors have been described to tip this balance toward degeneration in both diseases, such as diabetes, obesity, smoking, and low-grade systemic infection.<sup>78–89</sup> Mechanical overloading is another established factor that induces local inflammation in NP and AC,<sup>90,91</sup> especially in the AC of knee and ankle,<sup>86,92</sup> since the lesions are often localized to weight-bearing cartilage or to sites of trauma.<sup>93,94</sup>

Catabolic cell behavior is characterized by an increase in the expression of cytokines and matrix-degrading enzymes, and a downregulation of their inhibitors.<sup>95–100</sup> The cytokines that have been well-

**TABLE 1** Comparison of the healthy intervertebral disc and articular joint

	Intervertebral disc		Articular joint (eg, the knee)	
Anatomy <sup>28,32,33,35-37,41-43</sup>	Nucleus pulposus		Synovial fluid	
	Cartilaginous endplates covering subchondral bone endplates		Hyaline cartilage covering subchondral bone adjacent bones	
	Annulus fibrosus		Capsule	
	Amphiarthrosic joint		Diarthrosic joint	
Embryonic development <sup>32,33,35-39</sup>	Starts in week 5 in humans		Starts in week 6 in humans	
	Notochord	Forms the nuclei pulposi Disappears in vertebrae	Mesenchyme and ectoderm	Limb bud
	Sclerotome	Consists of mesenchymal cells Forms the vertebrae and outer annulus fibrosus		
	Transition zone of notochord and sclerotome in the inner annulus fibrosus			
	Secondary to somites that form through sequential segmentation		Limb bud forms by appositional growth	
	Extracellular matrix <sup>35,44,46-48,51,55-58</sup>	Proteoglycans (mainly aggrecan) in the nucleus pulposus (15%)		Proteoglycans (mainly aggrecan) in the cartilage (10-15%)
Elastine in the annulus fibrosus		Elastine in the capsule		
Collagen (20%)		Mainly type II in the nucleus pulposus Mainly type I in the annulus fibrosus	Collagen (10-20%)	Mainly type II in the cartilage Mainly type I in the capsule
Biomechanics <sup>35,44,46,55,58</sup>	Hydrostatic pressure in the nucleus pulposus; strain and shear in the annulus fibrosus		Hydrostatic pressure in the synovial fluid and cartilage; longitudinal strain and shear in the capsule	
	Normal joint loads transferred to endplates and vertebrae		Normal joint loads transferred to underlying subchondral bone	
	Elastic deformation of disc		Articulating surfaces	
	Stability by annulus fibrosus, posterior elements, and spinal ligaments		Stability by ligaments and tendons	
	Stability by muscular force		Stability by muscular forces	
Cells <sup>59,61,62,64,69</sup>	Notochordal cells		Chondrocytes	
	Chondrocyte-like cells			

documented to have a detrimental effect in intervertebral disc degeneration and OA are tumor necrosis factor alpha (TNF $\alpha$ ) and interleukin-1 $\beta$  (IL-1 $\beta$ ).<sup>101-105</sup> These cytokines generate local inflammation in the NP and AC by an upregulation of enzymes that degrade the ECM: matrix metalloproteinases (MMPs) and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS).<sup>106-112</sup> Simultaneously, a downregulation of their inhibitors (eg, tissue inhibitor of metalloproteinase 1-3, TIMP 1-3) occurs,<sup>100,113,114</sup> all together pushing the ECM in a vicious cycle of degradation.<sup>10</sup> Several MMPs have been related to degeneration in the NP, including MMP 1-3, MMP 7-10, and MMP 12-14.<sup>108,113,115,116</sup> These factors show remarkable similarity to those found in AC, including MMP 1-3 and 7-14,<sup>93,117-119</sup> although their expression levels may differ from those in the NP (see Table 2). Additionally, the ECM in the NP and AC is also cleaved by ADAMTSs 4 and 5.<sup>125-127</sup>

### 3.1 | Effects of ECM degradation

The degradation of the ECM results in a decrease in the production of proteoglycans in the cartilaginous matrices.<sup>120</sup> Consequently, less fluid is attracted, leading to a decrease in hydrostatic pressure.<sup>121</sup> This causes reduced joint space and an increase in tissue deformation (ie,

shear stresses). Shear stress is a mechanical cue for the cells to shift from collagen type II to collagen type I production, resulting in a more fibrous tissue.<sup>26,122,123</sup> This fibrous tissue has an inferior capacity to resist compressive loads, as there is a loss of the typical poro- and viscoelastic biomechanical properties.<sup>48,121,124</sup> The disruption of ECM not only results in loss of joint space, but also causes subchondral sclerosis and the formation of osteophytes, which is a reaction of the bone to the changing mechanical environment.<sup>4,16,129</sup>

### 3.2 | Genetic aspects

Besides shared environmental factors, intervertebral disc degeneration and OA also share genetic aspects. For example, Bijkerk et al found a strong genetic effect for intervertebral disc degeneration and hand OA,<sup>132</sup> and Loughlin describes several genetic polymorphisms that are attributed to both intervertebral disc degeneration and OA.<sup>133</sup> They demonstrate that GDF5 polymorphism rs143383 is a risk factor for both intervertebral disc degeneration and knee OA, just as the repeat polymorphism of the asporin gene (ASPN).<sup>134</sup> Moreover, polymorphisms of vitamin D receptor (ie, FokI and TaqI) are not only attributed to OA, but also to reduced signal intensity on MRI in lumbar intervertebral discs, suggesting an association with intervertebral disc degeneration.<sup>135,136</sup> Based on

**TABLE 2** Comparison of degeneration in the intervertebral disc and articular joint

	Intervertebral disc			Articular joint (eg, the knee)		
Extracellular matrix <sup>26,76,77,120-123</sup>	Degradation of the proteoglycans: Less fluid attracted to nucleus pulposus			Degradation of the proteoglycans: Less fluid attracted to the articular cartilage		
	Decrease in intradiscal pressure			Decrease in intra-articular pressure		
	Shift to collagen type I: Nucleus pulposus becomes more fibrous			Shift to collagen type I: Articular cartilage becomes more fibrous		
Biomechanics <sup>48,121,124</sup>	Reduced disc height			Reduced joint space		
	Increase in shear stresses			Increase in shear stresses		
	Less resistive to compressive loads			Less resistive to compressive loads		
Cells <sup>95-100</sup>	Inflammatory mediators: Production of catabolic factors			Inflammatory mediators: Production of catabolic factors		
	Catabolism by the chondrocyte-like cells: Degradation of ECM			Catabolism by the chondrocytes: Degradation of ECM		
Caused by <sup>58,74,75,78-94</sup>	Local inflammation	Systemic inflammation by	Diabetes Obesity Smoking	Local inflammation	Systemic inflammation by	Diabetes Obesity Smoking
		Mechanical overloading			Mechanical overloading	
Inflammatory factors <sup>93,100-109,125-127</sup>	TNF- $\alpha$ and IL-1 $\beta$ MMP 1-3, MMP 7-10, and MMP 12-14 ADAMTSs 4 and 5 TIMP 1-3			TNF- $\alpha$ and IL-1 $\beta$ MMP 1-3 and 7-14 ADAMTSs 4 and 5 TIMP 1-3		
Clinical symptoms <sup>12-14,128</sup>	Pain Dysfunction Morning stiffness			Pain Dysfunction Morning stiffness		
Radiological findings <sup>4,15,129,130</sup>	Formation of cysts and osteophytes Loss of joint space Subchondral sclerosis			Formation of cysts and osteophytes Loss of joint space Subchondral sclerosis		
Adjacent structures involved <sup>25,74,81,131</sup>	Vertebrae Facet joints Modic changes Nerve roots, ligaments and muscles			Bone of tibia and femur Meniscal tears Synovitis Nerve roots, ligaments and muscles		

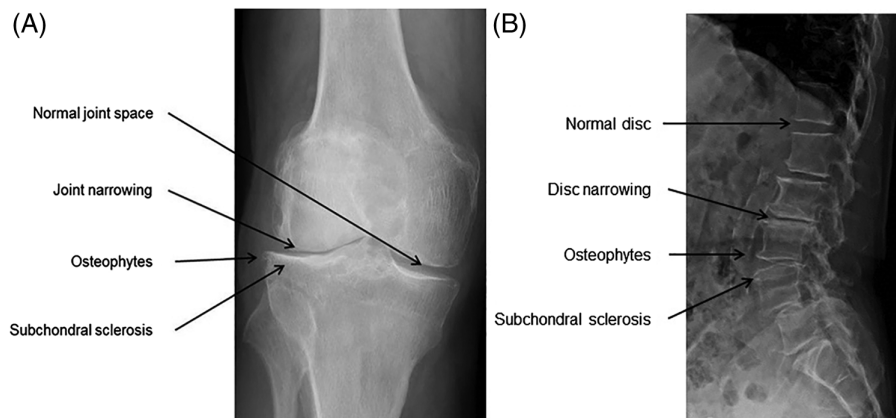
these studies, it is likely that intervertebral disc degeneration is more prevalent in patients with OA and vice versa, which further supports the resemblance between both conditions.

#### 4 | CLINICAL PERSPECTIVE ON INTERVERTEBRAL DISC DEGENERATION AND OA

Intervertebral disc degeneration is not just a disease of the cartilaginous structures, but affects the whole intervertebral disc and adjacent structures, like the vertebrae, nerve roots, ligaments, muscles and spinal facets, and there is an association with Modic changes (ie, changes in signal intensity of endplates and subchondral bone on MRI in patients with spinal degenerative diseases).<sup>74,131,137</sup> The same applies for articular joints: OA not only affects the AC, but involves the whole joint as it is accompanied by bony changes, meniscal tears, synovitis, and muscle weakness.<sup>25,81</sup> Imaging confirms that the whole joint is affected, as both conditions share the same characteristic radiological findings throughout the entire joint: loss of joint space, subchondral sclerosis, and the formation of cysts and osteophytes<sup>4,16,129</sup> (Figure 3A,B).

The degree of degeneration on X-rays, however, in both intervertebral disc degeneration and OA weakly correlates to clinical symptoms.<sup>13,138-140</sup> Clinical symptoms are similar in both DDD and OA: pain, dysfunction and morning stiffness. For OA, these symptoms are the three most important clinical criteria based on the diagnostic guidelines of the American College of Rheumatology (ACR), the most commonly used classification system for OA.<sup>128</sup> These guidelines, combined with patient history, physical examination and X-ray radiographs, make OA easy to diagnose for clinicians. After diagnosis and treatment following a clinical algorithm based on evidence-based medicine and expert opinion, patients return to work rather soon.<sup>141</sup> OA is even that well-known, that the same term is used for both the process of degeneration and the accompanying disease by not only clinicians and scientists, but also by patients and in society.

In contrast to OA, DDD is often disregarded as a risk factor for function loss and disability associated with low-back pain,<sup>142</sup> as widely used classification criteria do not exist for DDD. As such, it is difficult for clinicians to find a specific diagnosis when a patient presents itself with low back pain.<sup>143</sup> For example, the Dutch society for general practitioners has a guideline for "Non-traumatic knee problems" (ie, NHG guidelines), which mainly focuses on knee OA as a cause of



**FIGURE 3** A and B, Radiological examples in the degenerated articular joint and intervertebral disc. Both OA (A) and DD (B) are radiologically characterized by loss of joint space, the formation of osteophytes and subchondral sclerosis

these problems. The guideline for “Non-specific low back pain,” however, mentions DDD only briefly as a possible cause, but is overshadowed by other—relatively rare—conditions, like malignancies, fractures, and spondylarthrosis. This lack of wide recognition and consecutive diagnosis means that there is little opportunity to develop effective evidence-based treatment plans.

#### 4.1 | Treatment

In both DDD and OA, no treatment is available that regenerates the original tissue. Current treatments focus on symptomatic relieve, such as the reduction of overloading and inflammation by physiotherapy and anti-inflammatory drugs in early stage OA.<sup>144,145</sup> Currently, physiotherapy and anti-inflammatory drugs are only a postponement of surgical treatment in OA and most patients eventually undergo arthroplasty.<sup>146,147</sup> Most patients regain their mobility soon after surgery and remain free of pain and disability for some 10 years.<sup>148</sup> Arthroplasty in DD is less typical, but artificial intervertebral discs are starting to show promising results, although spinal fusion is still more common.<sup>149–151</sup>

Several regenerative therapies have been proposed for both diseases, such as hydrogels, stem cell therapy or injectable medications,<sup>20,125,152</sup> but so far none has gained general acceptance. Finding a cure to restore the cartilaginous structures is quite a challenge, but in knee OA there are some advancements in regenerative therapies (eg, by joint unloading), which demonstrate that cartilage does have some intrinsic healing capacity.<sup>153–157</sup> In DDD, however, no regenerative therapies are present, neither clinically nor preclinically.

## 5 | SUMMARY

In this review, we showed that the cartilaginous structures of both the human intervertebral disc and articular joint contain predominantly proteoglycans and collagen type II, resulting in a tissue that is able to create hydrostatic pressure, endure compressive loads and provide flexibility. Their roads to degeneration also show striking parallels: local inflammation takes place as a result of mechanical overloading or low grade systemic inflammation, and is characterized by increased levels of inflammatory cytokines, mainly IL-1 $\beta$  and TNF- $\alpha$ . These cause an upregulation of equivalent factors that decompose

the ECM (eg, MMPs 1-3, 7-10, and 12-14; and ADAMTSs 4 and 5) and a downregulation of their inhibitors (eg, TIMP 1-3), which are similar in both tissues. These results in a vicious cycle of tissue damage and inflammation, causing cell death of the NP cells and chondrocytes, increased in shear stress and decreased levels of proteoglycans and collagen type II. When the healthy intervertebral disc and articular joint degenerate, this is accompanied by identical radiological findings such as loss of joint space, subchondral sclerosis, and the formation of osteophytes, which cause pain and stiffness.

We also found some differences, mainly in anatomy, embryonic development, cells and partly in their biomechanical properties. Therefore, it would be inappropriate to claim that intervertebral disc and articular joint and their degenerative conditions are identical. Nevertheless, some important parts of cellular behavior and ECM in the human adult NP and AC show striking resemblance despite their completely different origin, which suggests that the local mechanobiological environment of the cell after birth has greater influence on its behavior than its embryonic origin.

The biggest difference between both conditions, however, lies in its awareness among health care professionals, patients and society. OA is a well-accepted health problem in society.<sup>158</sup> The condition is no longer regarded as a “wear-and-tear” disease or patho-anatomical finding,<sup>159,160</sup> but as a common disease that disables the patient. Clinicians are easily accessible and patients follow a clear, clinical algorithm of diagnosis and treatment, despite the fact that the relation between clinical symptoms in knee OA and radiographic images is also doubtful.<sup>140</sup> Still, clinicians often find it easier to relate pain to radiographic changes in a single joint than in the lower back. The reason may be that the relation between imaging and pain in articular joints is thought to be much stronger and that the clear clinical algorithms with knee, hip or ankle pain are specifically designed for diagnosing or excluding OA. The clear, clinical algorithm that elderly patients with joint pain follow in OA despite this weak correlation between symptoms and radiographic images, is in contrast to the unawareness, and thus, undervaluation of DDD as a cause of low-back pain. The lack of a specific diagnosis for low-back pain patients causes patients to feel stigmatized.<sup>161,162</sup> Most of the times, they end up consulting a paramedic or psychologist, because no diagnosis is found, nor is there a

straight-forward clinical algorithm to follow for medical professionals in primary care.

If the similarities between DDD and OA would be widely acknowledged, the imbalance between both conditions can be reduced. This may enhance the clinician-patient communication and reduce the negative stigma on low-back pain. The knowledge on both conditions could also be enlarged and finding regenerative therapeutics may be accelerated, as it facilitates cross-fertilization of clinicians and scientists involved in both intervertebral disc degeneration and OA.

In conclusion, the human intervertebral disc and articular joint are not identical, but their composition and process of degeneration are remarkably similar. Intervertebral disc degeneration and OA both follow a vicious cycle of degeneration, eventually resulting in destruction of the intervertebral disc and articular joint, respectively. However, there is a large imbalance between both conditions in knowledge and awareness among patients, clinicians, researchers and society. Acknowledging the similarities between the relatively unknown DDD to its more famous counterpart OA may reduce this imbalance, destigmatize patients by affiliating them with a well-recognized disease, and lower the threshold for patients to visit a clinician.

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The authors have no conflicts of interest to report.

## Author contributions

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