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Chapter 6

Spine Osteoarthritis

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Additional information is available at the end of the chapter

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1. Introduction

Osteoarthritis (OA) is a widespread disease and is considered the most common form of arthritis. The current OA prevalence is estimated at 15% of the population [1], but this rate is predicted to double by 2020 [2] and this increase is related with some lifestyle diseases like obesity [2]. OA affects the joints of the hand and the lower extremities such as knee and hip. OA of the spine occurs in approximately 40–85% of the adult population, but it is often omitted in prevalence studies. The rate disparities are due to the differences on the definition of the disease and to the variability between demographic groups studied [3]. Generally, the costs for OA care are high, as well as the economic implications for prolonged work disability [4, 5]. Symptomatically, it is considered that 80% of Americans suffer an episode of low back pain (LBP) in their lifetime [6, 7], thus care costs for LBP are estimated to be more than 100 billion dollars per year in the US [8], with a loss of 149 million workdays per year [9, 10].

OA of the lumbar spine is related with the degeneration of the intervertebral disc (ID) and bone formation, which is called spondylosis [11]. There has been a lack consensus on whether or not the combination of decreased disc space and osteophyte formation is a characteristic of OA or is a separate phenomenon. Clinically, the association between OA of the hand, knee and facet joint has been described, but no relationship was found between disc degeneration (DD) and OA of the hip, knee, or hand, or between the formation of osteophytes and OA of the hip and hand [12].

OA is defined as a disease resulting in structural and functional failure of synovial joints, which usually is characterized by progressive articular cartilage damage, involvement of the synovium and subchondral bone hypertrophy. OA affects the spinal zygapophyseal joints and is closely related to degenerative disc disease (DDD) despite the pathophysiological differen-

ces between the two disorders [13]. This degenerative cycle has mechanical impact with significant and progressive changes in the functional anatomy and mechanobiology, manifesting pain syndromes, destabilization, and impaired quality of life.

2. Anatomy and mechanics of the spinal joints

2.1. Normal facet joints

The vertebral joints are complex structures made up of posterior and anterior elements. The posterolateral spine consists of facet joints that are considered true synovial joint. One ID and two facet joints comprises a "three-joint complex." This complex binds two adjacent vertebrae, and the superior articular process of the inferior vertebra joins with the inferior articular processes of the overlying vertebra (Figure 1). The joint surfaces in the cervical and thoracic spinal regions are convex and concave, and the lumbar region of the facet joints shows a devastated form [14]. The orientation of the articular surfaces has a basic biomechanical role. The articular surfaces of the cervical and thoracic spinal segments are arranged horizontally [14, 15], favoring the axial rotation and lateral flexion [16, 17]. Comparatively, lower thoracic and lumbar spinal regions tend to adopt a more vertical orientation [18] that limits lateral flexion and rotation, protecting the IDs and spinal cord. Generally, the inclination angles of cervical facet joints in the sagittal plane ranges from 20° to 78° and in the axial plane from 70° to 96°, while the angle between the thoracic facet joints range from 55° to 80° and 85° to 120°, and the lumbar region range from 82° to 86° and 15° to 70° in both planes, respectively [14, 18].

Typically, facet synovial joints have a hyaline cartilage cover, subchondral bone, synovium, and a ligament system that envelops the entire joint [19, 20]. The cartilage layer is thinner at the edges of the joint surface and gradually thicker in the central portion thereof [21]. The composition of the articular cartilage does not differ from that observed in other diarthrodial surfaces, a cellular component, chondrocytes, and an abundant extracellular matrix (EM) composed of water, fibrillar proteins, glycosaminoglycans, and proteoglycans. The mechanical properties, such as load distribution and low-friction movement are dependent on the articular cartilage integrity [22, 23].

The subchondral bone has been considered as a morphological unit that provides a link between the articular cartilage and cancellous bone, which plays a key role in mitigate the impact of axial forces during dynamic joint load [24, 25]. It has been reported that the subchondral bone thickness is greater in asymptomatic males and increases with each successive lower spinal level, suggesting its association with the increased load [25].

Additionally, synovium and the ligament system facilitate movement with minimal friction and provide mechanical resistance, while synovial fluid lubricates and nourishes the joint surfaces [26]. The meniscoides or intraarticular synovial folds also protect the articular cartilage during movement [27], compensate the irregularities of the joint surface and increase the contact surface with the facets [28]. The meniscoides are formed by fatty, fibrous connective tissues and a lining of synovium [29, 28].

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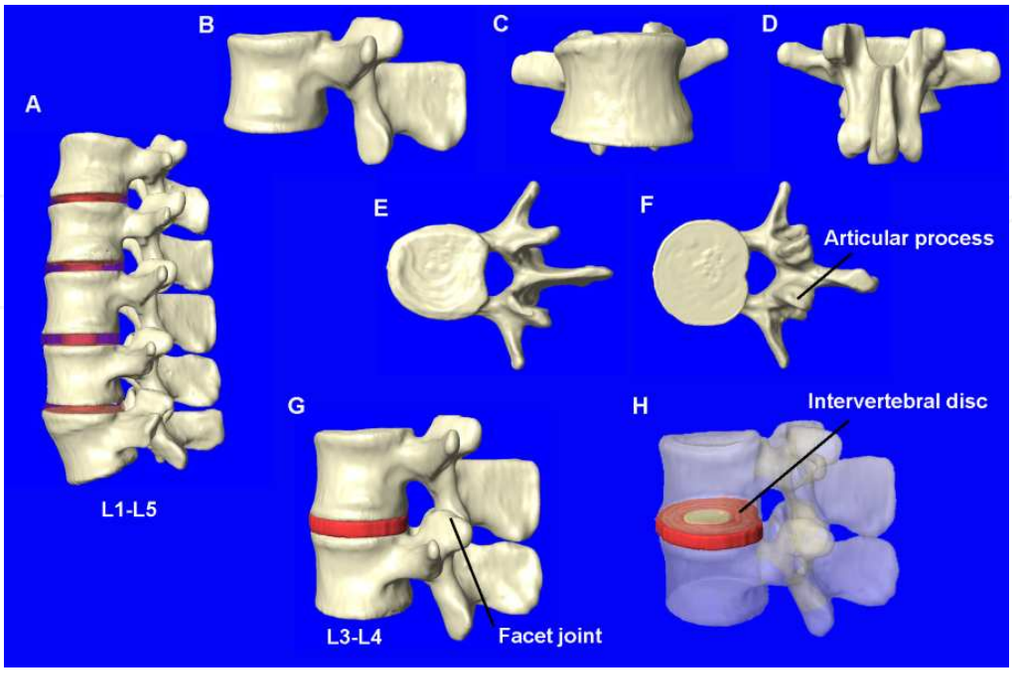

Figure 1. Normal anatomy of the facet joint and ID. A. Sagittal view of segments L1–L5; B. Sagittal view (L3); C–D. Coronal views (L3); E–F. Axial view (L3); G. Lumbar disc-facet unit (L3–L4); H. ID (L3–L4).

Moreover, the capsule comprises ligament fibroblasts, dense collagen fibers, elastic fibers, and proteoglycans [30, 31], and one of its main functions is to allow movement without provide mechanical resistance.

2.2. Normal intervertebral disc

In the anterior spine, the vertebral bodies are attached through the IDs. These structures provide support for load and flexibility during mechanical exposure; they also facilitate the movements of flexion, extension, and rotation. The typical composition of the ID consists of a central nucleus pulposus, which is contained in an outer annulus fibrous at the periphery, and the inferior and superior cartilage endplates [32].

Annulus fibers are agreed in concentric lamellae and consist predominantly of type I collagen [33]. In the early stages of life, these lamellae are arranged regularly, these are divide and interdigitate, and during aging they form an intricate and complex network in response to the load. Adult lumbar discs may contain up to 25 lamellae, thus lead to an increase in thickness toward the center portion thereof [34]. Annulus cells are small, elongated, disposed parallel to lamellae, and synthesize types I and II collagen [35], elastin [36], proteoglycans [37], and types III, IV, and VI collagens in various proportions [38, 39, 40, 41]. Other proteins with leucine-rich repeat, such as fibromodulin, decorin, and lumican, regulate the assembly of collagen fibers; similarly, the cartilage oligomeric matrix protein (COMP) is involved in regulation of the assembly of fibrillar proteins. Furthermore, chondroadherin, other protein

with leucine-rich repeat without carbohydrate substituents and without the N-terminal binds to collagen participates in the maintenance of chondrocyte phenotype [41].

The center of the ID is the nucleus pulposus, which becomes gelatinous and more fibrous with aging. The nucleus pulposus is surrounded by a fibrous capsule and consists of round or oval chondrocyte-like cell with abundant cytoplasm and prominent cytoskeleton. These cells are called "physaliphorus" cells, which present large vacuoles. In this region, these cells are responsible in the synthesis of type II collagen [35]. The nucleus pulposus is rich in proteoglycan aggrecan, which consists of approximately chondroitin sulfate chains hundred, and each polysaccharide chain has about hundred negatively charged groups. Furthermore, the keratan sulfate chains are disposed in clusters located in a different area to that of chondroitin sulfate chains. Moreover, hundred molecules bind aggrecan and hyaluronate, as well as fibulin and tenascin proteins [41, 42]. These negatively charged macromolecular structures promote osmotic water retention.

The interface between the disc and the vertebral body consists of a thin layer of hyaline cartilage called endplate. This is extended across most of the vertebral body except at the outer rim, where the fibers of annulus fibrosus are inserted. In adults, this tissue is avascular, so the metabolites diffuse through it to the cells of the endplate and the center of the disc. During adulthood, the endplate thickness is reduced to approximately 0.6 mm [43]. Biochemically, the endplate contains type X collagen, which is involved in calcification processes [44].

It is well known that the main source of energy disc cells is derived from glycolysis [45]. Due to the low oxygen tension, protein synthesis and macromolecules, such as sulfated glycosaminoglycans is inhibited. Stimuli such as growth factors also come from the extracellular fluid [46], while the ATP production in disc cells depends on the local pH and nutrient availability. Most studies have reported that an acidic pH level significantly reduces the glycolytic metabolism and the rate of oxygen consumption, with concomitant decrease in ATP production [47, 48]. However, the effect of oxygen concentration in disc cells remains controversial, as some studies have described a positive effect [45, 46]. Protein synthesis is also a process affected by local oxygen and pH levels, which significant decrease if the low oxygen tension to less than 5% [46]. Similarly, extracellular pH affects protein synthesis, so an abrupt decrease in acidic environments [48]. Contrary to this event, the activity of matrix metalloproteinases is generally not inhibited at low pH, which may enhance the rate of matrix breakdown [49].

Dependent glucose supply (primary energy source), disc cells can die within 24 hours if glucose concentrations fall below 0.2 mM. Under these conditions, the intracellular glucose transport is also significantly reduced [50]. In this respect, it has been reported that the rate of cell death of the disc increases in acidic conditions (pH 6.0) despite of an adequate glucose intake [51, 52].

The avascular nature of the adult human ID is well known, with minimal penetration of capillaries and nerve endings in the outer regions of the annulus. This capillary network comes from the vertebral arteries which across the subchondral bone forming the loops of the interface between cartilage endplate and the bone [53, 54]. Thus, vascularity is protected by the cartilage endplate and promotes selective transport of molecules through the disc [55, 56].

Nutrients diffuse from capillary vascularity of the disc, through cartilage endplate, EM until the cells [57, 58, 59]. This solute movement is associated with load patterns to which it is usually subjected the disc. Apparently, the mechanical load on the disc is inversely proportional to nutrient transport. For example, during the redistribution of the load, the disc thickness is decreased, favoring the transport of nutrients from the cartilage endplate; however, if the proportion of fluid in the tissue matrix is decreased, diffusion is reduced, and this could affect the metabolic levels [60, 61]. This charge-nutrients ratio in the ID is still under investigation. Diffusion gradient, which is dependent on passive transport, leads to differences in the metabolic activity of the disc cells. Generally, the center of the disc contains lower concentrations of glucose and oxygen, and higher concentrations of lactic acid [45].

2.3. Mechanobiology

The mechanical load on the ID can cause multiple physical changes and mechanobiological effects. Volumetric changes, fluid flows, pressure changes, electrokinetic activity, and changes in cell shape are events that occur secondarily to tension, compression, or shear. Previous studies in vitro and in vivo on animal models have shown that the static compressive load or strain (0.2 to 0.4 MPa) [62] can induce anabolic cellular responses in the disc, with increased gene expression and synthesis of EM components such as proteoglycans and types I and II collagens [63].

Comparatively, during dynamic compression at low frequency (0.01 Hz, 1 MPa) in cells of rodent disc, induce an increase in the gene expression of macromolecules such as aggrecan and types I and II collagens. At higher frequencies of load an increase in expression of mRNA of proteases like MMP-3, MMP-13, ADAMTS-4 (a disintegrin and metalloproteinase with thrombospondin motifs) has been observed [64, 65]. Additionally, disc cell death occurred after exposure to high magnitudes (> 0.4 MPa) and low frequency (0.01 Hz) of dynamic load.

In response to moderate hydrostatic pressure (<3.0 MPa), the cells cultured or tissue explants of disc may increase the synthesis collagen, proteoglycans, and tissue inhibitor of metalloproteinase 1 (TIMP1), which applies to cells of the nucleus pulposus and annulus inner regions [66, 67, 68]. The inhibition of protein synthesis, the increase in the nitric oxide and the synthesis of MMP-3 have been shown in disc cells in extreme downward or high pressures [69].

Similarly, the metabolic activity of the disc cells has been influenced by changes in osmotic pressure. In vitro tests have shown high rates of proteoglycan synthesis at in situ extracellular osmolarity (~430 mOsm); however, when this concentration is increased or decreased, protein synthesis declines [70]. Another manifestation of compressive deformation of disc cells is the reorganization of the cytoskeleton, including the increase of early polymerization of vimentin [63]. Also depolymerization of actin filament calcium-dependent and the volume change on disc cells grown in hyper or hypo-osmotic media has also been shown [71, 72].

Moreover, disc cells exposed to stress in vitro undergo changes in the membrane potential associated with apoptosis. These cells increase nitric oxide production and decrease the proteoglycans synthesis [73, 74].

3. Epidemiology

3.1. Facet arthrosis

LBP is considered epidemic, and its prevalence varies in developed countries from 60% to 90% of patients undergoing orthopedic consultation [75, 76]. The cost of care for these patients varies from $100 to $200 billion annually [8]. One of the main causes of LBP is facet arthrosis. Since 1930, it has been called as facet syndrome [77, 78]; many studies on cadavers have described the presentation of facet arthrosis around the third decade of life [79, 80]. According to epidemiological studies based on imaging, the cervical facet OA has been reported in 19% of adults between 45 and 64 years of age and in 57% of adults over 65 years [81]. On severe lumbar facet OA diagnosed by computed tomography (CT) images, prevalence rates are estimated to be 36% in adults under 45 years of age, 67% in adults between 45 and 64 years, and 89% in individuals over 65 years [82]. Thus, it can be concluded that the prevalence of facet OA and its progression are dependent on age [81, 83].

The literature reports higher prevalence and degree of arthrosis at L4–L5 facet joints [79, 84, 85]. This was more prevalent at L4–L5 (from 45.1% to 79%), followed by L5–S1 (from 38.2% to 59%), and finally L3–L4 (from 30.6% to 72%) [79, 84]. These reports support the fact that the degenerative lumbar stenosis is related to the more mobile segments (L3–L4, L4–L5) of the lumbar spine [86, 87]. On the frequency of occurrence on the right or left side, an equal distribution has been reported [88].

With respect to gender, higher prevalence has been reported in males, and apparently, there is no significant difference in relation to race [79, 80]. However, in image studies using CT scans and planar radiography, women have been shown to have a higher prevalence of lumbar facet OA than men [12].

Moreover, the body mass index (BMI) has been found to be associated with an increased prevalence of cervical facet OA [83] and, even more, of the lumbar region [12, 82]. In this respect, the risk of lumbar facet OA is almost three times higher in overweight individuals (BMI 25–30 kg/m^2) and five times more associated with obesity (BMI 30–35 kg/m^2), in comparison with the normal-weight reference group (BMI ≤ 25 kg/m^2) [12].

Another risk factor for facet OA is the anatomy of the spine; for example, the changes in the orientation of the articular facet and facet joint asymmetry or "tropism" [89, 90, 91, 92] and simultaneously the disc-height narrowing represents the risk of contracting the disease [82]. Similarly, other factors such as the poor quality of the extensor muscles have been associated with facet OA of L4–L5 [93].

3.2. Disc degeneration

Although there is no standard definition of disc degeneration (DD), it is considered the product of the degradation and remodeling of the ID and adjacent vertebrae, with adaptive changes and/or consequential damage induced by physical load. Radiographic studies, particularly

magnetic resonance imaging (MRI), have allowed qualitative assessment of disc degeneration (DD). Particular emphasis has been given on disc space narrowing, the disc-vertebra remodeling with formation of osteophytes and disc bulge peripherals, changes or loss of signal intensity with development of annular tears, herniations, Schmorl nodes, and endplate sclerosis [94, 95]. In this regard, the prevalence of disc-bulging has been described from 10% to over 80% in asymptomatic patients, and the prevalence of annular tears varies from 6% to 56% [3].

Age has been widely related to disc degeneration (DD). Degenerative changes have been described since childhood and young adulthood, such as the presence of annular tears between 3 and 10 years old [96, 97, 98]. Moreover, the water content of the nucleus pulposus shown by the disc signal intensity has been reported from 35 years of age [99].

It has also been proposed that mechanical load and nutritional states could contribute to the early development of DD, and it has found more severe in men than in women [100]. The association of heavy physical load and DD is still controversial and inconsistent. Similarly, relation to smoking has not been found [99].

Studies on the genetic influence in monozygotic male twins have shown a substantial familial influence on disc degenerative changes such as lumbar disc-height narrowing, bulging or herniation, and disc desiccation [99, 101, 102]. It seems likely that the DD is a multifactorial genetic condition, oligogenic. Some of the human gene forms reported as TaqI and FokI of the vitamin-D receptor gene have been associated with low intensity of magnetic resonance signal of thoracic and lumbar discs [103]. Two genotypes of MMP-3 gene have been related with degenerative disc changes in the elderly, and type IX collagen, alpha 2 (COL9A2), and 3 (COL9A3) gene forms have been linked with symptomatic disc pathology [104]. Nevertheless, research in this is still lacking.

4. Pathophysiology

4.1. Mechanical response and degeneration

DD is the manifestation of damage set caused by heavy physical load, posture or improper movement, and vibration. Therefore, it is extremely important to know the mechanical consequences of spinal motion segments under conditions of cyclic load, load magnitude, and frequency [105]. The investigations on degenerative mechanisms have been greatly supported in numerical models of the disc in animals, such as a finite element model [106]. One of the main advantages of the finite element model is the ability to parametrically manipulate one input factor and evaluate the resulting effects. These models have improved gradually, with the inclusion of poroelastic material properties of the motion segment facilitating the evaluation of physiological parameters related to cyclic load [107].

The application of the models in the evaluation of DD include analysis of disc geometry and mechanical properties of the nucleus, changes in permeability, porosity, and water content.

The decreased content of fluid that occurs in degenerative processes is known to affect not only the nucleus pulposus but also the annulus matrix resulting in disc stiffness [106, 108, 109]. Poroelastic finite models have allowed evaluation of the effect on the strain-dependent permeability and osmotic potential in cyclic compression and expansion [110, 111]. These studies have shown time-dependent deformation of a lumbar motion segment subjected to multiple creep-compression-expansion loads. Another study that used an asymmetric disc-body-disc poroelastic finite element model has shown that sustained compression maintains tensile stresses in the outer portion of the annulus but not in the middle and inner regions [108]. This correlates with the progressive disruption of the annulus fibrosus observed in vivo as well as the increase in apoptosis and the consequent decrease of cellularity. Similarly, other authors have demonstrated changes in the density and distribution of electric charges in healthy versus degenerated discs, which induced stress, water loss, and nutritional implications [59, 112].

A poroelastic finite element model determines the interaction of fluid with the proteoglycans in the nucleus. Using this model, it has been shown that normal discs are much more deformable that discs degenerate in response to cyclic load. The loss of healthy disc height in load cycle at a maximum load of 2000 N varied between 2.5 mm and 4.5 mm as opposed to between 1.0 mm and 1.8 mm in the degenerated disc [107, 113]. Similarly, stiffness of the disc was shown to be inversely proportional to the load cycles, while under higher compression loads (3000 N), loss of healthy disc height was demonstrated in 48% in comparison with 40% in degenerated discs [108].

Additionally, the poroelastic finite element model can predict the evolution of disc failure. A previous study showed that disc failure is propagated when the elastic modulus is decreased and the rate of disc failure associated with increase load was greater than that due to the decrease in elastic modulus [107].

4.2. Intervertebral disc aging and degeneration

DD is a process related to physiological conditions, such as aging in most asymptomatic individuals, and is associated with pathological processes involving pain and disability. The definition of DD has not been fully established; two possibilities have emerged: one in which degenerative disc changes correspond to premature aging, and the other in which there is similarity between DD: and age changes but at an accelerated rate [114, 115]. It is possible that changes in the spine associated with aging are genetically predetermined and/or are associated with exposure to heavy mechanical forces throughout life. Independent of the trigger mechanism, degenerative changes begin with biochemical alterations, followed by structural changes of the spinal functional units [116].

The notochordal cells constitute the primordium of the nucleus during the development of the ID and generally decrease in number rapidly after birth [117, 118]. Gradually, cellularity of the nucleus pulposus is replaced by chondrocyte-like cells, which may originate and migrate from the cartilaginous endplate and inner annulus [119]. Apparently, the Fas-mediated apoptosis

plays an important role in this process [120]. The notochordal cells synthesize more proteoglycans than chondrocytes and might be responsible in maintaining the fluid gelatinous nucleus pulposus [121]. Due to the reduction of these cells, the nucleus pulposus becomes more solid cartilage, which also decreases the signal intensity on MRI. On cell density, some studies have suggested an increase in the proportion of cells in the inner annulus fibrosus and the nucleus pulposus [122, 123].

The normal ID maintains a balance between synthesis and degradation of EM components, but it is well known that the age-related early degenerative changes are loss of aggrecan, collagen, and water in the nucleus pulposus. In addition, the release of molecules, including proinflammatory cytokines such as interleukin 1 (IL-1) and tumor necrosis factor-α (TNF-α) [124, 125], increases the synthesis of metalloproteinases [126] contributes also to this degenerative process. However, it is noteworthy that annulus cells in the early stages of DD synthesize a larger amount of proteoglycans and collagen, probably in response to a repair process [127]. The progress of degeneration involves the reduction of production of most of the molecules of the EM, except for biglycan and fibronectin [127].

Generally, degenerative disc changes are of multifactorial origin. One of the most important determinants is the nutritional deficit secondary to decreased blood supply to the endplate. Apparently, this process could start early in the second decade of life [97]. Vascularization and innervation of the disc are also associated with aging and degeneration. Similarly, inflammatory cells and macrophages have been identified in degenerated discs and have been found responsible in the synthesis of cytokines and proteases by endogenous cells and by the vascular cells of the invading vessels [128]. The painful sensation that accompanies DD associated with aging is due to the presence of nociceptive nerve fibers in the annulus and inner nucleus [129].

Additionally, macroscopic changes can be observed, as well as concentric fissures and radial tears in the annulus from the third and fourth decades of life [130]. These modifications are due to increased synthesis of metalloproteinases that occurs as a result of the advance of age [130].

Besides, cell viability is also affected in aging due to thinning and calcification of the endplates, which impair the nutritional contribution of the disc [131]. Also, other factors like stress induced by overload or nonphysiological static compression and cyclic stretching are involved in cell death and DD [65, 74, 108, 132, 133, 134]. Furthermore, there are reports of cell proliferation in human degenerative discs especially in areas where cell clusters are integrated [135].

4.3. Facet articular OA and aging

The degenerative processes associated with age or other factors may also affect the facet joint indirectly. These changes are usually associated with variations in the load surfaces of the joint [136]. This can manifest macroscopically with osteophytes and bone overgrowth with stenosis of the foramen, lateral and central spinal canal [85, 88, 90, 137, 138, 139]. Previous studies reported that the subchondral cortex shows no significant morphological variation in different spinal levels as a result of aging, suggesting that it may be due to a slower rate of remodeling.

Moreover, the fraction of bone volume and trabecular thickness decrease is more frequent in women than in men during aging [140].

It is generally accepted that degenerative facet changes are preceded by DD [137, 141]. We already mentioned that the consequences of DD include segmental instability and increase in facet load, which could induce joint subluxation and damage the cartilage surface. The changes in the cartilage are characterized by progressive erosion and subchondral bone sclerosis. Degenerative changes of facet articular are identical to OA seen in other synovial articulations. In addition to facet hypertrophy, apophyseal misalignment and osteophyte formation may narrow the spinal canal. Also, involvement of the triple articulation can influence degenerative spondylolisthesis and scoliosis [116].

Bone also undergoes sclerosis with consequent redistribution of loads, which may progress and induce bone remodeling and subsequent rotatory deformities of the posterior elements [142].

5. Spinal pain

5.1. Lumbar facet syndrome and cervical facet pain

The facet joints are often associated with neck pain and LBP. The mechanical painful stimuli have been detected in sensory fibers, nociceptive endings, sensory afferent nerve endings, and types III/A and IV/C fibers located in the joint capsule, ligaments, periosteum, and subchondral bone [143, 144].

Neurophysiological studies have shown the involvement of small-diameter sensory neurons of the capsule, facet sensory neurons during inflammation and the effect of substance P in lumbar facet pain [145, 146, 147]. Furthermore, it has been demonstrated that substance P is also contained in nerve endings of subchondral bone in patients with facet OA [148].

The prevalence of cervical facet pain has been reported in about 55% of patients with chronic nonspecific pain [149]. Previous studies have suggested that the cervical facet pain signals are derived from the capsule, where the immunoreactivity of substance P and calcitonin gene-related peptides has been demonstrated [150]. Several mechanisms have been proposed in facet joint injury including facet-joint impingement, synovial pinching, and strain injury to the capsule [151, 152, 153, 154, 155]. In this regard, it was deduced that noxious and trigger nociceptive discharges from the capsule are transmitted to the central nervous system for pain sensation [155]. This response was seen not only as a result of the injury but also secondary to high-magnitude mechanical stimuli such as tension, compression, and rotation. This persistent discharge was related to nerve or capsular injury with the consequent release of inflammatory mediators, which could stimulate signaling pathways of pain in the spinal cord by central sensitization [156, 157].

5.2. Disc pain

Degenerative spinal disease is the condition most frequently associated with chronic LBP, particularly in older adults. As a definition, degenerative spinal disease includes DDD and degenerative facet disease or facet OA [158]. A study for the purpose analyze and compare the radiographic severity of DDD and facet degeneration of the lumbosacral spine in adult subjects with and without chronic LBP showed no association between them. This was despite the fact that the highest radiographic severity scores were associated with the presence of pain [159]. Usually, DD may result in radicular pain secondary to stenosis and nerve-root or cauda equina irritation, and discogenic pain derived from disc lesion [160].

Animal studies of healthy IDs have demonstrated the presence of mechanoreceptors in the outer portion of the annulus fibrosus. These nerve fibers correspond to small myelinated (group-III or A-delta fibers) and unmyelinated (group-IV or C fibers) fibers [161, 162, 163]. These fibers are classified into those containing neuropeptides, which express substance P and calcitonin gene-related peptides [164], and nociceptors fibers related to inflammatory pain. These fibers are also dependent on nerve growth factor and have high affinity with the tyrosine kinase A (TrkA) receptor [165]. Discal nerve fibers generally exhibit afferent axons, and cell bodies are located in the dorsal root ganglia [166].

6. System grading in DD and facet joint degeneration

Currently, MRI is considered as the gold standard in imaging of the spine; however, the diagnosis of facet OA remains a challenge for clinicians. For this purpose, different methods have been used such as the planar X-ray, CT and MRI scans, dynamic bending films, and planar radionuclide bone scanning [167].

Usually, the degree of DD is determined by macroscopic observation on MRI. Comparatively, facet OA may not be evaluated with precision by MRI as with CT scans [168, 169]. Commonly, conventional radiography (X-ray films) is used in the evaluation of arthritic changes of the spine, although CT shows joints with better resolution [170, 171]. It has been reported that CT can show the axial plane of the facet joint and the osteoarthritic changes with precision [171]. However, MRI provides axial and sagittal images of the facet, which are useful in assessing degenerative spinal joint disease [168]. Several studies have reported accuracy in the evaluation of the facet OA with MRI at the rate of between 93% and 95% [85, 172]. So far, it has been accepted that MRI is a useful method in the assessment of OA of the lumbar facet joints.

Different scoring systems have been described in evaluating the disc and facet degeneration. A previous study recommends intraobserver and interobserver reliability tests in the evaluation of lumbar degenerative changes [173]. One of these systems used lateral radiographic projections and was easy to apply [174]. However, one that used MRI showed high feasibility [175]. Comparatively, other systems cannot be applied to patients and have been used to evaluate DD in vitro based on detailed morphological studies [97, 176]. In cervical DD, a system based on lateral radiographs and easy to implement was the only one recommended [177].

Regarding grading systems for lumbar facet joint degeneration, recommendations were based solely on CT [170] or CT and MRI systems [178]. Differentially in cervical facet joint degeneration, a system based on lateral radiographs was recommended [177].

Lumbar DD is classified into five grades according to macroscopic characteristics such as fibrosis, mucinous degeneration, erosion of cartilage endplate, and osteophyte formation on sagittal sections [176]. Histologically, lumbar DD on sagittal paraffin sections contains parameters such as cell proliferation, mucinous degeneration, cell death, tear and cleft formation, and disc granular changes. Additional features include disorganization and cracks of cartilage, microfractures, bone neoformation, and endplate sclerosis [97].

Radiographically, a method for assessing the presence and severity of lumbar DD is based on joint space narrowing, anterior and posterior osteophyte formation, and subchondral sclerosis [174]. However, the best accepted grading system is based on the characteristics of the degenerative lumbar disc on MRI, such as the distinction of nucleus and annulus, the signal intensity, and height of ID [175]. Moreover, grading of lumbar facet joint degeneration appreciates the joint space narrowing, sclerosis, hypertrophy, and osteophyte formation on oblique conventional radiographs and CT scans [170] or CT and MRI scans [178].

Categorization of cervical DD is based on plain radiography and includes parameters such as osteophytosis, disc space narrowing, and sclerosis of vertebral plates [177]. Furthermore, grading of cervical facet joint degeneration on lateral radiographs determines the presence of osteophytes on the articular margins of facets of apophyseal joints and sclerosis [177].

Additionally, radionuclide bone scintigraphy with single photon emission CT (SPECT) has been used to detect microcalcification due to increased osteoblastic activity [179, 180]. More recently, it was reported that the hybrid SPECT/CT imaging identifies potential chronic spinal pain generators in 92% of cervical spine scans and 86% of lumbar spine scans [181].

Figures 2 and 3 show the MRI results of patients with cervical and lumbar OA.

7. Inflammatory cytokines and degenerative lumbar spinal disease

It is known that OA is associated with facet joint pain. The generation mechanisms of pain could be due to mechanical stress and joint instability or misalignment that often accompany DD and aging. In this regard, the presence of inflammatory mediators such as prostaglandins in facet joints of patients with lumbar spinal degenerative disorders were found [182]. These findings suggest that chemical factors besides mechanical factors arising from the facet joint could be related to pain in OA [183, 184, 185].

Another study demonstrated increase in the concentration of IL-6 in the synovium and cartilage of the facet joint by CLEIA method (Chemiluminescent Enzyme Immunoassay). The tissues analyzed in this study were obtained from patients with disc herniation and lumbar spinal stenosis [186]. The role of IL-6 in the spinal joint disease is controversial; it can facilitate the inflammation together with IL-1β and TNF-α in the early stages of the immune reaction,

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or may be involved in autoimmune states producing antibodies or act as an anti-inflammatory cytokine. According to these assertions, the authors proposed that IL-6 induces continuous local inflammation caused by mechanical stress on the facet joint [186]. Similarly, a significant increase was detected in IL-1β in patients with lumbar spinal canal stenosis than the lumbar herniated disc, which correlated with higher scores on scales of leg pain [187]. More recently, the overexpression of MMP-1 induced by IL-1β was revealed, suggesting an important role in the inflammation associated with lumbar facet joint degeneration [188].

Also were reported inflammatory chemical mediators such as prostaglandins and leukotrienes in facet cartilage and subchondral bone obtained from patients with degenerative lumbar spinal disorders. Here, it was suggested that these chemical mediators may be involved in inflammation and pain generation at the local lumbar facet joints [182].

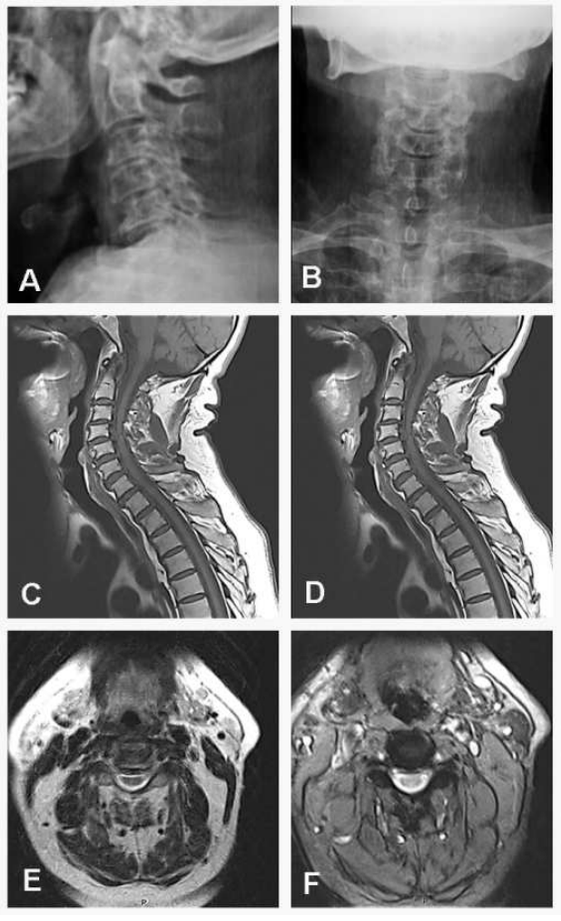

Figure 2. A. Lateral cervical spine radiograph with decreased general bone density; correction of the cervical lordosis; vertebral platforms sclerosis; decrease in intervertebral spaces at C3–C4, C4–C5, and C5–C6; syndesmophytes; reduction in diameter of intervertebral foramina at C2–C3, C3–C4, and C4–C5; decreased facet interface at C2–C3, C3–C4, and C4–C5; and spondylolisthesis at C4–C5. B. Anterior-posterior cervical spine radiograph with loss facet interface at C2–C3, C3–C4, and C4–C5; decreased vertebral space at C2–C3, C3–C4, and C4–C5. C. Sagittal MRI of cervical spine at stage T1 with vertebral platforms sclerosis, osteophyte formation, decreased height of IDs, and disc extrusion mainly in the intervertebral spaces at C4 and at C3–C4–C5. D. Sagittal MRI in T2 phase with decrease caliber medullary canal by the presence of posterior osteophytes, hypertrophy of posterior longitudinal ligament, and ID extrusion. E–F. MRI axial slices in T2 phase with reduced caliber of the cervical canal and compression of the spinal cord.

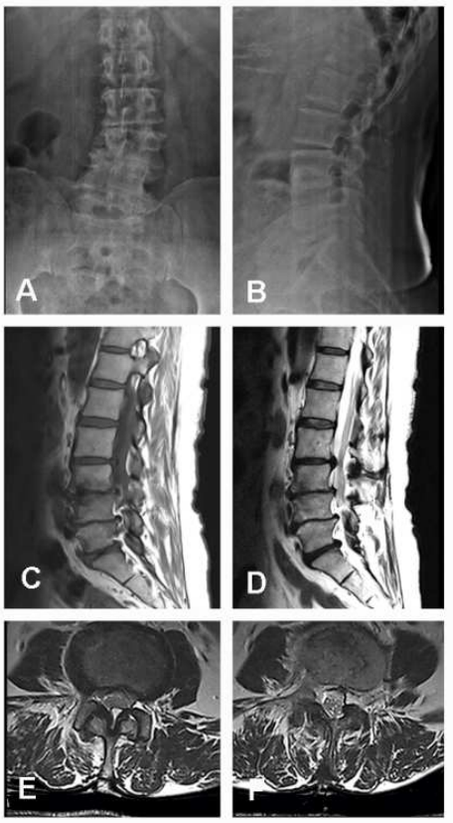

Figure 3. A. Antero-posterior radiograph with left lumbar scoliosis, plastic deformation of the last three lumbar vertebrae, vertebral platforms sclerosis, osteophytes, and decreased height of intervertebral spaces. B. Lateral radiograph of lumbar spine with spinal platform sclerosis, osteophytes, and reduced height of the L3–L4, L4–L5, and L5–S1 IDs. C. Sagittal MRI of lumbar spine in T1 phase with sclerosis of the vertebral platforms, Modic changes, osteophytes, decreased height of IDs, and disc protrusion at L3–L4, L4–L5, and L5–S1 with narrow lumbar canal. D. Sagittal MRI of lumbar spine in T2 phase with vertebral platform sclerosis; osteophytes; decreased height of IDs; disc protrusion at L3–L4, L4–L5, and L5–S1 with lumbar canal narrowing; decreased spaces at L3–L4 and L4–L5; and bulging of IDs at L2–L3 and L5–S1. E–F. MRI axial slices of lumbar spine facet degenerative changes and hypertrophy of the ligamentum flavum and lumbar stenosis at different levels.

8. Angiogenesis, calcification, and programmed cell death in DD

As described above, degenerative changes of the ID involve processes such as neovascularization, calcification, and cell death. Angiogenesis has been described in degenerated and herniated discs [189]. A degenerative disc is defined as a disc protruding into the spinal canal or neural foramens resulting in compression of the nerve roots [189]. The herniated nucleus pulposus develops fibrotic and angiogenic reactions [190, 191]. This process involves factors such as TGF-β, TNF-α, VEGF, MMP-1, and MMP-3 [191, 192].

Similarly, the intradiscal calcification has been significantly correlated with DD [193]. Disc calcification occurs in the annulus, fibrocartilaginous plate, and nucleus pulposus that appears as amorphous deposits of calcium salts [194] asymptomatic in most cases. The frequency of degenerative disc calcification varies from 3.1% to 65% as assessed by microscopy and MRI

[195, 196, 197]. Another study reported that microscopic calcification was significantly higher in degenerative discs than in those obtained from normal cadavers (54.4% vs. 6.7%), and it is also higher in Modic type III than in type I (95.0% and 13.0%, respectively). The same study also refers angiogenesis in degenerative discs (41.0%) and in calcified discs (59.2%) [198].

The etiology of disc calcification remains uncertain. Two possible mechanisms of calcification disc have been proposed: one in which inflammatory cytokines such as VEGF and MMPs released into the degenerative disc promote expression of osteopontin, induce differentiation of osteoprogenitor cells, and allow calcification; and the other through indirect mechanisms in which these molecular mediators promote angiogenesis, and this, in turn, stimulates macrophage infiltration, the formation of new osteoprogenitor cells, and finally the progressive calcification [198].

As we have mentioned in this review, in addition to mechanical and genetic factors, apoptotic cell death is another event type that contributes to the development of disc degeneration (DD) [74, 132, 134, 199, 200, 201, 202, 203]. Apoptosis in degenerative discs is described as that occurring through activation of the mitochondrial [74], death receptor [204], and the endoplasmic reticulum pathway [205, 206].

The static axial compressive load [74, 108, 134], the static bending compressive load [133], the dynamic axial compressive load [65, 207], and the imbalance of dynamic and/or static forces of the spine [199] have been considered in programmed cell death (PCD) on degenerative disc. Load effects increase lactate concentration, decline oxygen tension, decrease nutrient level, reduces tissue permeability and secondarily the water content [208, 209]. Biomechanical stimuli such as serum deprivation [210], nitric oxide [201], lipid peroxidation [132], hypoxia-inducible factor-1α [211], and even normal oxygen concentrations [212] have also been involved in the induction and increase of PCD.

The death of disc cells has been reported to be significant as age increases [97]. Elsewhere in the body, it is well established that apoptotic cells are removed by phagocytosis; however, macrophages or phagocytes are not cells that are normally present on the disc. In vitro studies have shown that nucleus pulposus cells are able to perform, as well as competent phagocytes and stimulate phagocytosis [213].

9. Conclusion

Spinal OA is a condition characterized by failure in motion segments, usually as a result of exposure to heavy physical load and aging. By definition, this disease induces degenerative changes in the facet joints and the IDs. One of the predominant symptoms of spinal OA is neck pain and LBP syndrome, which involves prolonged disability and high care costs. However there is controversy whether the prevalence, severity, and imaging findings are related to the pain sensation. The fields of molecular biology and mechanobiology of the degenerative process also require research to understand the pathophysiological mechanisms that lead to it and, thus, be able to contribute in the development of regenerative medicine and technological innovation with the improvement of prototypes for design of orthopedic components.

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