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Molecular Background of Low Back Pain

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Abstract: Intervertebral disc degeneration is a major cause of low back pain and disability around the world. The nucleus pulposus (gelatinous core), annulus fibrosus (fibrous outer ring), and cartilage endplates make up the disc. Disc degeneration causes structural, morphological, and functional alterations. Fissures in the annulus fibrosus might contribute to disc herniation. Intervertebral disc prolapse, which is caused by degeneration, is a prevalent cause of low back discomfort. Alterations in the vertebral endplates, evident on MRI as medic alterations, are also linked to disc degeneration and low back pain. Uncontrolled cell growth, cell death, and cell senescence occur during disc degeneration. The provision of nutrients to disc cells is crucial, and disruptions in blood supply can cause degeneration. Mechanical stress and damage can both start the degenerative process-rays are used for initial assessment, and MRI is used for enhanced visualisation of soft tissue. Kinetic MRI in weight-bearing situations can detect problems that static scans cannot. RI Pfirrman grading evaluates disc degeneration. Proteoglycans, which contain covalently linked glycosaminoglycans (GAGs), are essential for disc hydration and function. GAGs are sulphated glycans that are linear and heterogeneous. Low back pain is a widespread and incapacitating complaint that, despite advanced imaging, frequently has an unexplained explanation. MR imaging reveals morphological changes associated with ageing in the absence of symptoms. Molecular alterations, such as proteolytic enzymes and inflammatory cytokines, are important in disc degeneration and modify the MR signal. Understanding these alterations can help with the specific treatment of low back pain.

IndexTerms **– Intervertebral disc degeneration, Low back pain, Nucleus pulposus, Annulus fibrosus, Disc Prolapse**

INTRODUCTION

LOW BACK PAIN (LBP): THE PROBLEM:

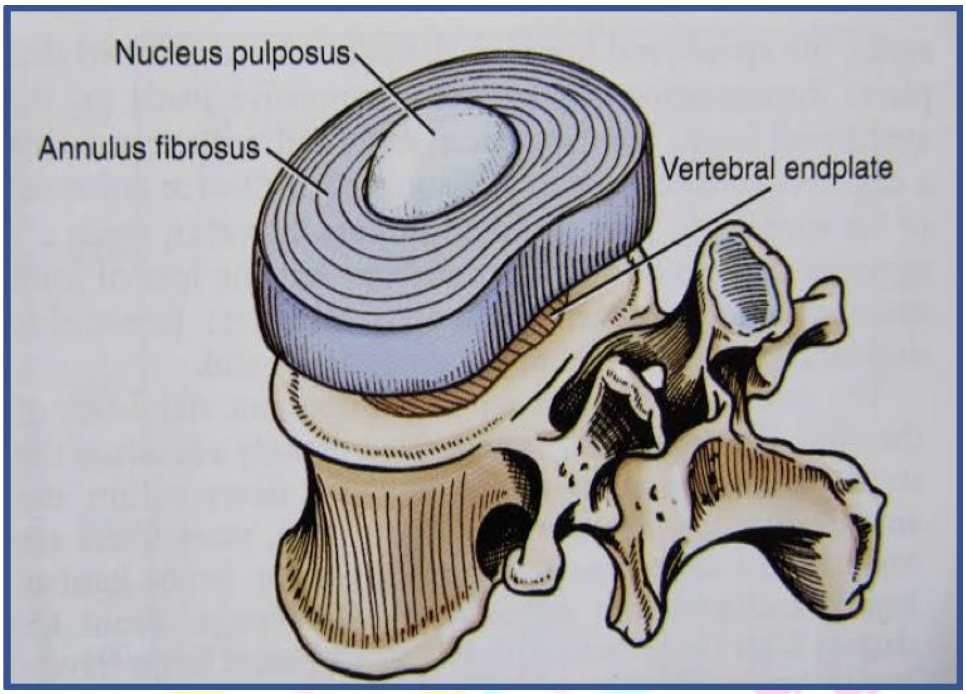
Back pain is a major public health problem all over the world. It causes suffering and distress to patients and their families. Intervertebral disc degeneration has been suggested to be a cause behind the occurrence of low back pain and can be associated with sciatica, disc herniation or prolapse (**1).** It alters disc height and the mechanics of the rest of the spinal column, possibly adversely affecting the behaviour of other spinal structures such as muscles and ligaments. In the long term it can lead to spinal stenosis, a major cause of pain and disability in the elderly; its incidence is rising exponentially with current demographic changes and an increased aged population **(2).**

Annulus of the intervertebral disc often form fissures during the process of disc degeneration, is considered to be painful and increases the risk for developing herniation **(3)**. Prolapsed intervertebral disc is also considered to be a form of disc degeneration and has been suggested to contribute to about 50% of the cases for low back pain **(4)**. Vertebral endplate changes also called as modic changes visible on the MRI are assumed to be associated with degenerative discs and have a significant relationship with low back pain and sciatica (**5)**. It is clear, therefore, that intervertebral disc degeneration and low back pain is a musculoskeletal disorder affecting enormous numbers of population world-wide and is the cause of severe pain and disability.

Intervertebral discs structure and function:

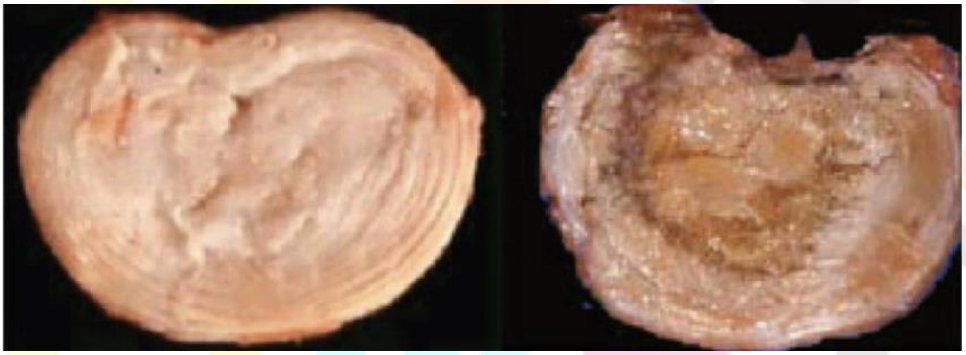
Intervertebral disc are pads of white fibrocartilage that resist spinal compression but permits limited movements. It spreads the load evenly on the vertebral bodies when the spine is flexed or extended **(6).** The intervertebral discs are the chief bonds between the adjacent surfaces of vertebral bodies from C2 to the sacrum. Except at the sites of the unco-vertebral (Neurocentral) joints of Luschka, disc outlines correspond with the adjacent bodies **(6).** Their thickness varies in different regions and within individual discs. In cervical and lumbar regions the discs are thicker anteriorly, contributing to the anterior convexity of the vertebral column. In the thoracic region they are nearly uniform, and the anterior concavity is largely due to the vertebral bodies. The discs are thinnest in the upper thoracic region and thickest in the lumbar region **(7).** They adhere to thin layers of cartilage on the superior and inferior vertebral surfaces, the vertebral end-plates. The latter do not reach the periphery of the vertebral bodies but are encircled by ring apophyses. The end-plates contain both hyaline and fibro cartilage. The fibro cartilaginous component lies nearer to the disc, while the white fibro cartilaginous components of the endplates is present above and below the nucleus pulposus, together with the innermost lamellae of the anulus fibrosus with flattened sphere of collagen which surrounds and encloses the nucleus **(6,7)** .The overall proportion of fibrocartilage in the end-plate increases with age . Intervertebral discs form about a quarter of the length of the postaxial vertebral column: cervical and lumbar regions make a greater contribution than the thoracic and are thus more pliant **(8).**

Morphologically intervertebral discs are complex structures that consist of a thick outer ring of fibrous cartilage termed the annulus fibrosus, which surrounds a more gelatinous core known as the nucleus pulposus; the nucleus pulposus is sandwiched inferiorly and superiorly by cartilage end-plates.



Fig,1- Anatomy of IV Disc

1.3 Annulus fibrosus: It is the peripheral part of the disc which has a narrow outer collagenous zone and a wider inner fibro cartilaginous zone. The fibres of the outer zone forms lamellae, which are convex peripherally when seen in vertical section and are incomplete collars. Each lamellae of the annulus is made up of type 1 collagen fibres with a sparse proteoglycan gel **(7, 8).** The outer annulus contains a relatively dense population of fibroblasts like cells which tend to be elongated and aligned parallel to the layers of lamellae of collagen fibres (**8**). The cells of outer annulus are of mesodermal in origin. The internal vertical concavity of the lamellae confirms to the surface profile of the nucleus pulposus. In all outer part of the annulus, about half the lamellae are incomplete and the proportion increases in posterolateral region **(9).** The fibres of the rest of each lamella are parallel and run obliquely between vertebrae at about 65° to the vertical fibres in successive lamellae and cross each other obliquely in opposite directions, thus limiting rotation. The obliquity of fibres in deeper zones varies in different lamellae. The posterior fibres may sometimes be predominantly vertical, which possibly predisposes them to herniation **(10).**



Fig, 2: The normal and degenerate lumbar intervertebral disc. The figure shows a normal intervertebral disc on the left. The annulus lamellae surrounding the softer nucleus pulposus are clearly visible. In the highly degenerate disc on the right, the nucleus is desiccated and the annulus is disorganized **(10, 16).**

1.4 Nucleus pulposus- It is the central part of the disc and is soft, gelatinous at birth. The nucleus pulposus is better developed in cervical and lumbar regions and lies between the centre of the disc and its posterior surface. It is composed of mucoid material and contains a few notochordal cells and is invaded by cells and collagen fibres from the inner zone of the adjacent annulus fibrosus. The nucleus pulposus contains chondrocytes like cells which are notochordal in origin. These cells may be present singly, in pairs and may frequently form small to large clusters **(6, 9).** Along with the cells the nucleus also contains type 2 collagen fibres which are randomly organized and forms the 20% of its dry weight. The collagen along with sparse elastin fibres normally hold the highly hydrated aggregating proteoglycan gel. These proteoglycans are abundant in the nucleus and the main proteoglycan aggrecan has a core to which 100 sulphated cationic GAG chains are covalently attached **(9, 10).**

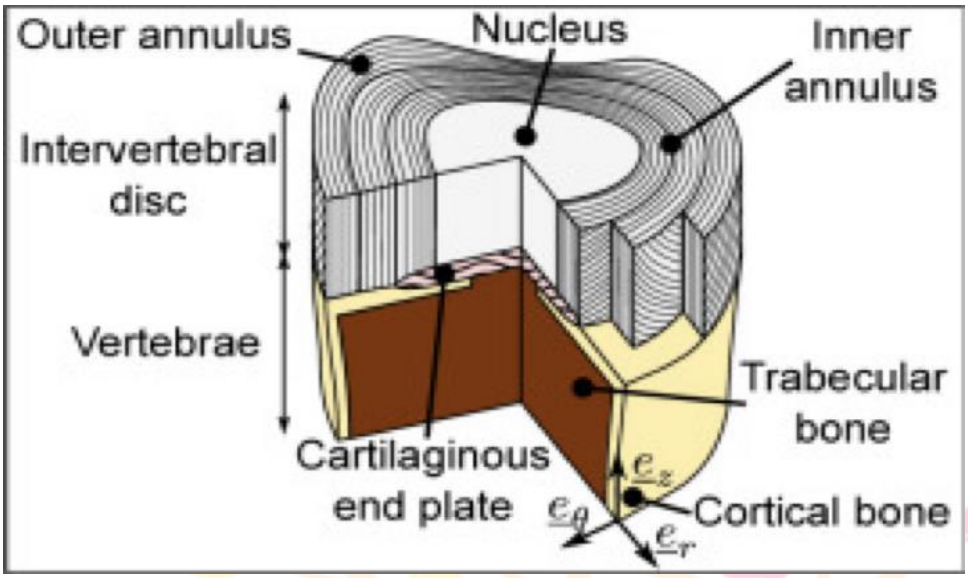
The notochordal cells disappear in the first few years, and the mucoid material is gradually replaced by fibro cartilage, derived mainly from the annulus fibrosus and the plates of hyaline cartilage adjoining the vertebral bodies. It is kept under tension and act as a hydraulic shock absorber (**7).** The nucleus pulposus becomes less differentiated from the remainder of the disc as age progresses, and gradually becomes less hydrated and increasingly fibrous **(6, 10).** The type II collagen of the nucleus becomes more like the type I of the annulus as its fibril diameter increases. The quantity of aggregated proteoglycans in the nucleus decreases, while the keratan sulphate/chondroitin sulphate ratio increases. As increased cross-linking occurs between collagen and the proteoglycans the discs lose their water-binding capacity, become stiffer and more liable to injury **(10).** The annulus gradually loses height as its radial bulge increases, but the nucleus retains height and may increase in convexity as it increasingly indents the end-plate.

End Plate:

A vertebral end plate is the transition region where a vertebral body and IV disc interface with each other. It is made up of two layers-

- Cartilaginous layer that fuses with the disc
- Thin layer of porous bone that attaches to the vertebra

Nutrients of the IV disc pass through vertebral end plate. The cartilaginous layer of end plate also maintains the form and function of the disc. Any damage to the end plate may speed up disc degeneration **(10).**



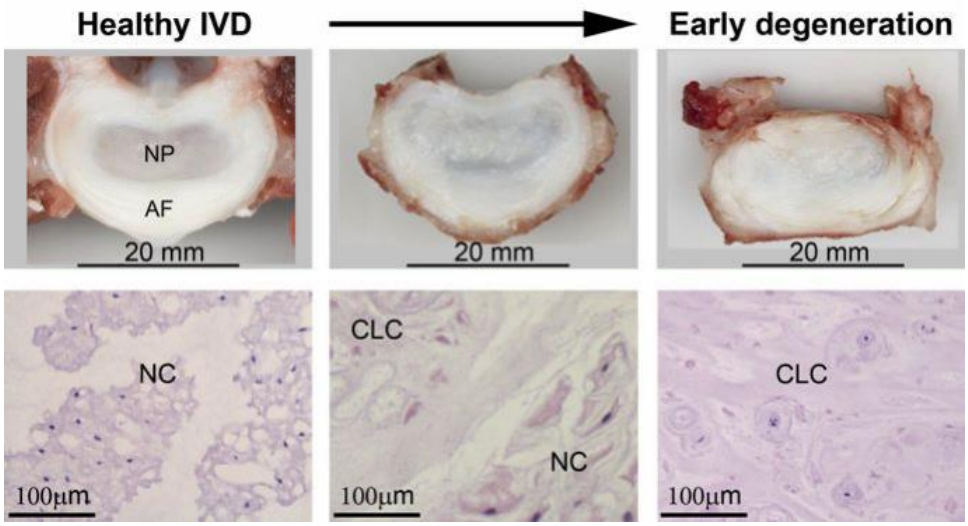
Fig, 3- Parts of IV Disc

Disc Degeneration

Disc degeneration structural, morphological and functional changes: Degeneration of the intervertebral discs, a process characterized by a cascade of cellular, biochemical, structural and functional changes, is strongly implicated as a cause of low back pain. Current treatment strategies for disc degeneration typically address the symptoms of low back pain without treating the underlying cause or restoring mechanical function. A more in-depth understanding of disc degeneration, as well as opportunities for therapeutic intervention, can be obtained by considering aspects of intervertebral disc development **(13).** Early postnatal changes, including altered cellularity, vascular regression and altered extra cellular matrix composition, might set the disc on a slow course towards symptomatic degeneration **(14).**

Disc degeneration and age related changes: During growth and skeletal maturation of disc the boundary between annulus and nucleus becomes less obvious, and with increasing age the nucleus generally becomes less hydrated and gel-like. With increasing age and degeneration the disc changes in morphology, becoming more and more disorganized. Often the annular lamellae become irregular, bifurcating and interdigitating, and the collagen and elastin networks also appear to become more disorganized. There is frequently cleft formation with fissures forming within the disc, particularly in the nucleus **(15).**

Disc degeneration and cellular changes: With advancing degeneration uncontrolled cell proliferation occurs, leading to cluster formation, particularly in the nucleus. With advancing age and degeneration large cluster tend to appear in nucleus pulposus and inner annulus fibrosus region. In cell cluster there may be 3 or more than 3 cells in close proximity to each other with a large lacuna. They have a distinct pericellular matrix rich in proteoglycans, fine fibrillar collagens and non-collagenous molecules **(16).** Cell death also occurs, with the presence of cells with necrotic and apoptotic appearance. These mechanisms are apparently very common; it has been reported that more than 50% of cells in adult discs are necrotic **(14).** The degeneration may also occur due to failure of the nutrient supply to the disc cells. The cells of the disc require nutrients such as glucose and oxygen to remain alive and active. In vitro, the activity of disc cells is very sensitive to extra-cellular oxygen and pH, with matrix synthesis rates falling steeply at acidic pH and at low oxygen concentrations, and the cells do not survive prolonged exposure to low pH or glucose concentrations **(7,16).** A fall in nutrient supply that leads to a lowering of oxygen tension or of pH (arising from raised lactic acid concentrations) could thus affect the ability of disc cells to synthesize and maintain the disc's extra-cellular matrix and could ultimately lead to disc degeneration. The disc is large and avascular and the cells depend on blood vessels at their margins to supply nutrients and remove metabolic waste **(16,8).** The pathway from the blood supply to the nucleus cells is precarious because these cells are supplied virtually entirely by capillaries that originate in the vertebral bodies, penetrating the subchondral plate and terminating just above the cartilaginous end plate. Nutrients must then diffuse from the capillaries through the cartilaginous end-plate and the dense extra-cellular matrix of the nucleus to the cells, which may be as far as 8 mm from the capillary bed. The nutrient supply to the nucleus cells can be disturbed at several points **(7,8).** Factors that affect the blood supply to the vertebral body such as atherosclerosis, sickle cell anaemia. Caisson disease and Gaucher's disease all appear to lead to a significant increase in disc degeneration.



Fig, 4:- Histological changes between healthy and degenerating disc.

Disc degeneration and cell senescence: Disc cells undergoes senescence that plays a direct role in disc ageing and degeneration. There are 2 types of cell senescence replicative and stress induced premature. Both the forms of senescence may make the disc cells function inappropriately in such a way that clusters of metabolically active senescent cells could degrade a large surface area due to increase synthesis of matrix degrading enzyme. These enzymes such as MMP-1, 2, 3 & 9 have been shown to increase with disc degeneration (**16,8**). Elevated level of these enzymes subsequently cleave collagen fibers, glycosylated, and non-glycosylated protein and proteoglycan molecules into smaller fragments and may evoke inflammatory response. Mechanical load and injury abnormal mechanical loads are also thought to provide a pathway to disc degeneration. For many decades it was suggested that a major cause of back problems is injury, often work-related, which causes structural damage **(15).** It is believed that such an injury initiates a pathway that leads to disc degeneration and finally to clinical symptoms and back pain. Animal models have supported this finding. Although intense exercise does not appear to affect discs adversely and discs are reported to respond to some long-term loading regimens by increasing proteoglycan content, experimental overloading or injury to the disc can induce degenerative changes. Further support for the role of abnormal mechanical forces in disc degeneration comes from findings that disc levels adjacent to a fused segment degenerate rapidly (**15,16**).

Radiological evidences, changes and evaluation during disc degeneration:

X-Rays & Disc degeneration: The most commonly used spinal imaging test is X-ray because of its low cost, and a routine X-ray examination is mostly indicated as part of initial investigation. There is no evidence to prove that obtaining X-rays is associated with better patient outcomes or treatment procedures. X-rays are helpful for evaluation of fracture (**13),** bony deformity including, sacroiliitis, disk and vertebral body height, and assessment of bony density and architecture. A drawback of lumbar radiography is exposure of gonads to ionizing radiation, especially with oblique view or multiple exposures (**21**). Another drawback of lower back X-ray in acute back pain are the identification of certain abnormalities, like facet joint abnormality or mild scoliosis, that are only incidental findings and are unrelated to the back symptoms as most of these conditions are seen in persons without back pain. Despite these limitations, radiographs are commonly recommended prior to proceeding with more advanced imaging (MRI/CT).

MRI Investigation & disc degeneration: MRI does not require radiation exposure and provides better visualization of soft tissue and spinal canal, and thus preferred over x-ray. Conventional MRI examinations of the spine usually are performed in supine position, in functional rest, but the lumbar spine instability is often shown by upright standing and hidden in the supine position. However, it provides only non-weight bearing **(21),** static images, whereas spinal disorders, especially cervical and lumbar stenosis, are posture-dependent. Pathological conditions underlying clinical symptoms, often prompted by standing or sitting, are therefore not seen **(14).** This can result in negative findings, even in the presence of symptoms, or an underestimation of pathological specimens. To overcome this limitation, radiographic studies of spinal kinematics have shown that changes occur in the seated and erect posture in relation. Kinetic MRI (k MRI) can image patients in a weight-bearing position (either standing up or sitting) and in flexed and extended positions, thus revealing abnormalities that are missed by traditional MRI studies (**14,19**).

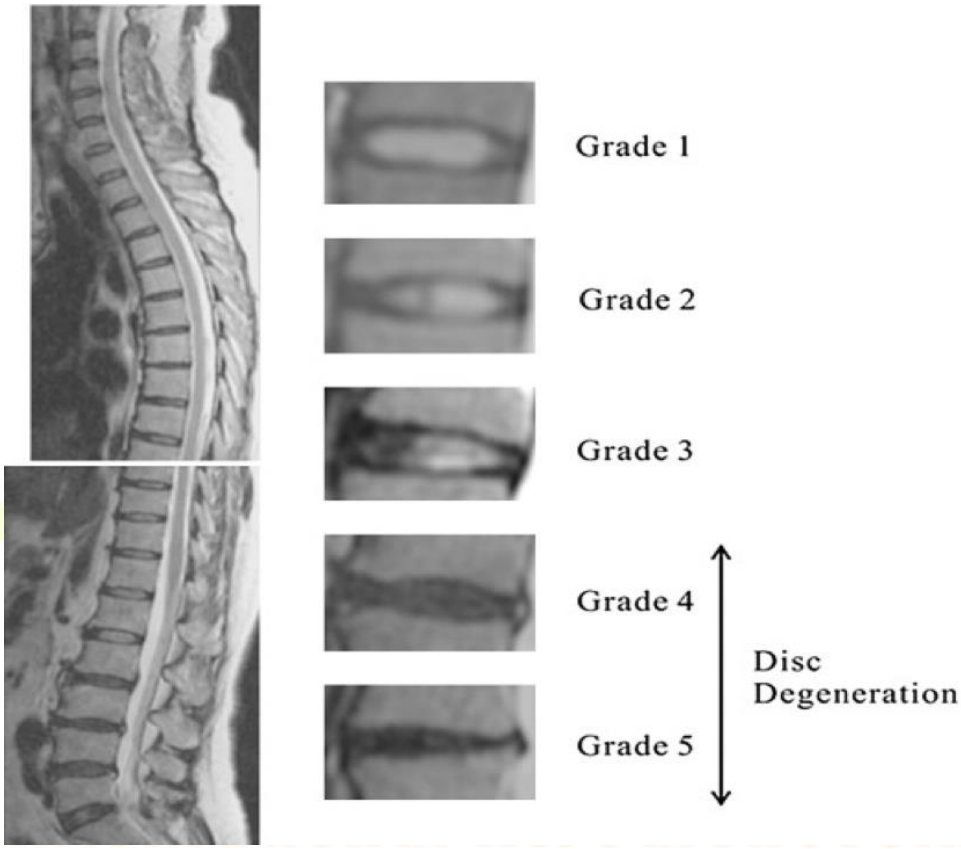
A first attempt to evaluate the spine under the loading condition was done with the axial load technique, which is to simulate physiological loading of the spine in the orthostatic position, both with CT and MRI, by compression devices which administer an axial compression force. Although results were certainly interesting, the technique has not achieved a general consensus. Studies with axial load **(18)** even if they allow better assessment in relation 3.4 to the higher signal to-noise ratio (SNR) afforded by the high-field equipment, do not allow evaluation of the influence that physiological load - represented by the weight of the head and body and by muscle activation – has on the lumbar spine, simulating a load with caudate-cranial direction. Dynamic MRI use open magnet scanners that allowed upright scanning in either seated or standing body position, which allow better performance in terms of assessment of spinal instability and variations of some pathologic conditions from recumbent to upright position (**19**). Imaging of the spine in a weight-bearing position with extension and flexion or placing the spine in the position of pain may also increase the diagnostic accuracy also for spine surgeons.

MR Findings of osteophytes: Osteophytes were visually detected on sagittal radiographs and sagittal conventional T1/T2 spine MRI scans based on their cortical and medullary continuity with the vertebral body and based on their specific shape. On conventional T1/T2-weighted spine MRI scans, osteophytes display accordingly an isointense signal to the vertebra **(15).** On SW-MRI scans, osteophytes were identified based on the following properties: hyperintense on inverse SW-MRI magnitude images with a hyperintense surface on SW-MRI phase images. Sizes of osteophytes were measured on SW-MRI magnitude, T1- and T2-weighted MRI scans **(14).**

MR Findings of disc protrusion: - Schmorl nodes refer to protrusion of the IV disc through the vertebral body endplate and into the adjacent vertebra. The protrusion may contact the marrow of the vertebra, leading to inflammation. These nodes are best seen on the sagittal sequences and usually exhibit the same signal characteristics as the adjacent disc with a thin rim of sclerosis at the margin. Acute herniation can appear more aggressive with surrounding bone marrow oedema and peripheral enhancement (**18**).

Commonly used MRI positions of Spine: - Usually the magnetic fields are 0.25 T, 0.5 T, and 0.6 T. Images are obtained with patient both supine and upright in the flexed, extended, rotated, standing, and bending positions. Cervical and lumbar spine are most commonly studied.

Pfirrmann grading of Disc Degeneration: - It can be graded on MRI T2 spin-echo weighted images using a grading system proposed by Pfirrmann. This classification is not used on routine spine reports, being more important for research purposes **(21**). **Grade I:** disc is homogeneous with bright hyperintense white signal intensity and normal disc height. **Grade II** disc is inhomogeneous, but keeping the hyperintense white signal nucleus and annulus are clearly differentiated, and a gray horizontal band could be present disc height is normal. **Grade III** disc is inhomogeneous with an intermittent gray signal intensity distinction between nucleus and annulus is unclear disc height is normal or slightly decreased (**20, 21). Grade IV** disc is inhomogeneous with a hypointense dark gray signal intensity there is no more distinction between the nucleus and annulus disc height is slightly or moderately decreased. **Grade V** disc is inhomogeneous with a hypointense black signal intensity there is no more difference between the nucleus and annulus the disc space is collapsed **(20)**

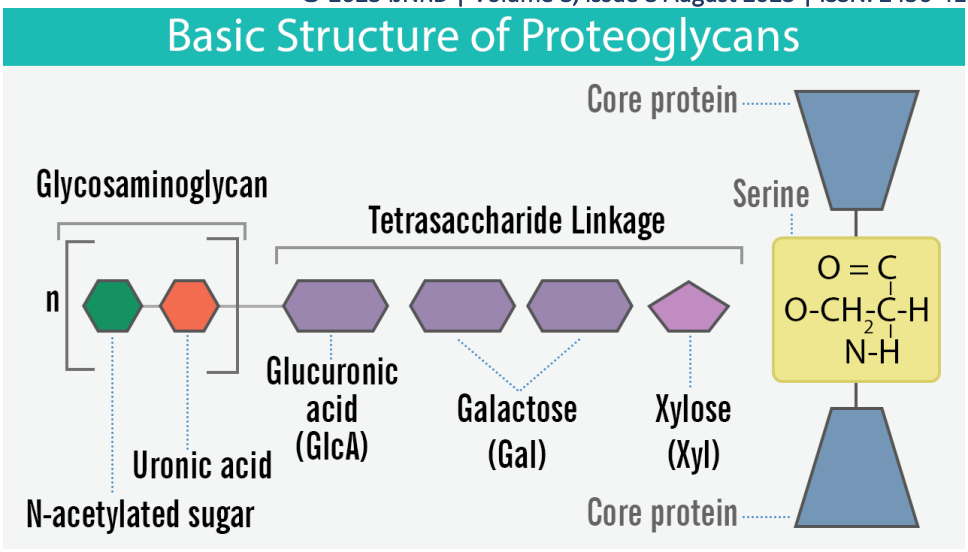


Fig, 5 - Pfirrmann grading of disc degeneration

Molecular Structure of Proteoglycans & glycosaminoglycans (GAG)

Proteoglycans (mucoproteins) are glycosylated proteins which have covalently attached highly anionic GAG. They are found in all connective tissues, extracellular matrix (ECM) and on the surfaces of many cell types. Proteoglycans are remarkable for their diversity (different cores, different numbers of GAGs with various lengths and compositions).

GAGs are linear and heterogeneous sulfated glycans. Although they are structurally complex, the backbones of these polysaccharides are simply made up of repeating disaccharide building blocks composed of alternating uronic acid (UA) and hexosamine units **(30).** The UA units can be either β-D-glucuronic acid (GlcA) or its C5 epimerized version, α-L-iduronic acid (IdoA). The amino sugars can be either glucose (Glc)-based (α-D- or β-D-glucosamine, GlcN) or galactose (Gal)-based, as N-acetyl-β-D-galactosamine (GalNAc). The permaturation of these monosaccharide units within the GAG backbones gives rise to different GAG families, such as the GlcN-containing heparan sulfate (HS) and Hp, and the GalNAc-containing CS and dermatan sulfate (DS). Keratan sulfate (KS) alternates N-acetyl-glucosamine (GlcNAc) with Gal, and does not contain UA; hyaluronan or hyaluronic acid (HA) alternates GlcNAc with GlcA, and does not have a protein core **(31).**

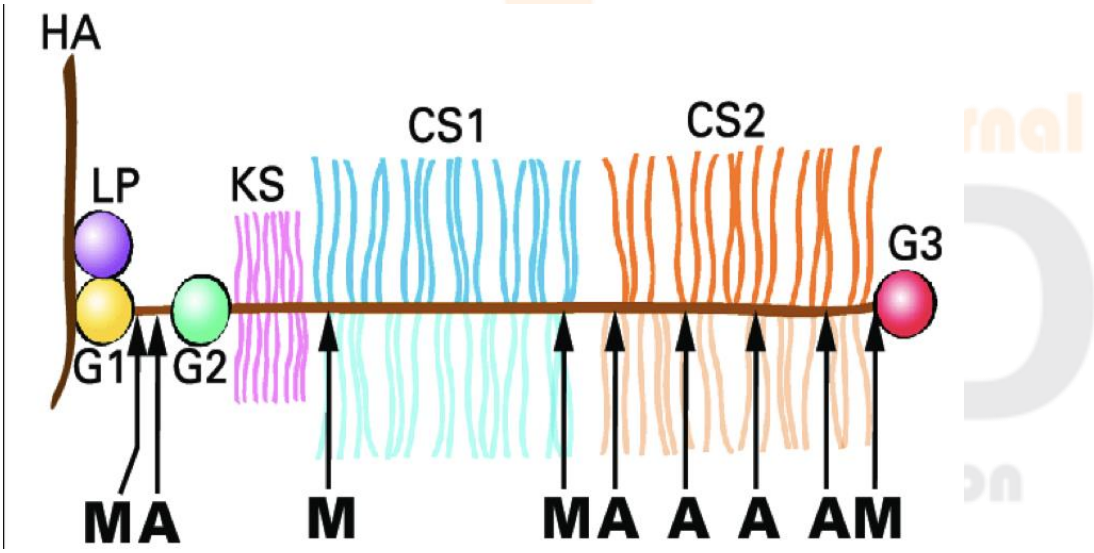


Fig, 6- Basic structure of proteoglycan

Structure of proteoglycans: The GAGs extend perpendicular from the core protein in a bottlebrush- like structure. The linkage of GAGs such as heparan sulfates and chondroitin sulfates of the protein core involves a specific trisaccharide linker. They perform numerous vital functions within the body.

Functions: - The functions can be divided into two classes (**31,32**): the biophysical and the biochemical. The biophysical functions depend on the unique properties of GAGs. The ability to fill the space, bind and organize water molecules and repel negatively charged molecules. Because of high viscosity and low compressibility they are ideal for a lubricating fluid in the joints. On the other hand their rigidity provides structural integrity to the cells and allows the cell migration due to providing the passageways between cells (**32**). The large quantities of chondroitin sulfate and keratan sulfate found on aggrecan play an important role in the hydration of cartilage. They give the cartilage its gel-like properties and resistance to deformation. Aggrecan is one of the most important extracellular proteoglycans. It forms very large aggregates (a single aggregate is one of the largest macromolecules known, it can be more than 4 microns long). Aggrecan molecules are non-covalently bound to the long molecule of hyaluronan (like bristles to the backbone in a bottlebrush) (**33).** It is facilitated by the linking proteins. To each aggrecan core protein multiple chains of chondroitin sulfate and keratan sulfate are covalently attached through the trisaccharide linker. The other, more important biochemical functions of GAGs are mediated by specific binding of GAGs to other macromolecules, mostly proteins. Proteoglycans are also shown to participate in cell and tissue development and it's physiology **(32)**.

Proteoglycans & GAG of Intervertebral disc: Proteoglycans and glycosaminoglycans are the main components of the extracellular matrix of the nucleus pulposus. Major structural proteoglycan found in ECM is aggrecan. The core protein has 100-150 GAG chain attached to it.Majority of the chains are made up of chondrointin and keratan sulphate. The molecule produces a rigid deformable gel that resist compression. It consist of 3 globular domains G1, G2, &G3 that are involved in aggregation, hyaluron binding, cell adhesion and chondrocyte apoptosis **(36)** It provides cartilage and intervertebral disc to resist compressive loads.



Fig, 7- Structure of Aggrecan

Intervertebral disc degeneration due to aging and excessive mechanical loads results in adverse quantitative and structural changes to the macromolecules. Metalloproteinases induced by inflammatory mediators play a key role in degrading proteoglycans. Progressive matrix breakdown decreases water content in the disc (32, 30). Dehydration compromises disc cells function and impairs resistance to compression. Biochemical changes may result in disc prolapse. Modifying the metabolism of proteoglycans and glycosaminoglycans might be an effective therapeutic strategy.

Intervertebral disk degeneration is characterized by increased expression of catabolic enzymes, decreased proteoglycan synthesis, and an overall shift toward synthesis of a fibrotic matrix. When this occurs, the water-binding capacity of the tissue is compromised, resulting in a failure to resist compressive forces and a reduction in disk height (30).

Cytokines are important in the biology and pathology of the IVD because of their potential role in regulating the integrity of connective tissues; they influence the synthesis and degradation of the ECM, in growth of nerves and blood vessels, and accumulation of macrophages that are characteristic of disk degeneration (27). These cytokines include tumour necrosis factor (TNF), TWEAK (TNF-like weak inducer of apoptosis), interleukin (IL)-1, IL- 10, platelet-derived growth factor, vascular endothelial growth factor, insulin-like growth factor, TGF-b, endothelial growth factor (EGF), and fibroblast growth factor (28).

These inflammatory cytokines can increase production of matrix-degradative enzymes, and enhance the breakdown of collagens and proteoglycans. Thus, the expression or activity of a range of matrix metalloproteinases (MMPs) such as MMP-1, -3, -7, -9, -10 and-13, as well as ADAMTS(A Disintegrin and Metalloproteinase with Thrombospondin Motif S)-4 and -5, are increased in disk cells with age and degeneration (29).

Enzymes that breakdown proteoglycans: Matrix Metalloproteinases are calcium dependent zinc containing endopeptidases. They belong from a larger family of proteases known as the metzincin superfamily. There are about 25 types of MMPs, but among them 24 are present in mammals. MMPs are translated as a zymogen (i.e., an inactive enzyme) and contain a signal sequence peptide for targeting to secretory vesicles **(37).** MMPs are secreted or anchored to the cell surface, thereby confining their catalytic activity to membrane proteins or proteins within the secretory pathway or extracellular space.

MMP Family

Subgroup	MMP	Name	Substrate
1. Collagenases	MMP-1	Collagenase-1	Col I, II, III, VII, VIII, X, gelatin
	MMP-8	Collagenase-2	Col I, II, III, VII, VIII, X, aggrecan, gelatin
	MMP-13	Collagenase-3	Col I, II, III, IV, IX, X, XIV, gelatin
2. Gelatinases	MMP-2	Gelatinase A	Gelatin, Col I, II, III, IV, VII, X
	MMP-9	Gelatinase B	Gelatin, Col IV, V
3. Stromelysins	MMP-3	Stromelysin-1	Col II, IV, IX, X, XI, gelatin
	MMP-10	Stromelysin-2	Col IV, laminin, fibronectin, elastin
	MMP-11	Stromelysin-3	Col IV, fibronectin, laminin, aggrecan
4. Matrilysins	MMP-7	Matrilysin-1	Fibronectin, laminin, Col IV, gelatin
	MMP-26	Matrilysin-2	Fibrinogen, fibronectin, gelatin
5. MT-MMP	MMP-14	MT1-MMP	Gelatin, fibronectin, laminin
	MMP-15	MT2-MMP	Gelatin, fibronectin, laminin
	MMP-16	MT3-MMP	Gelatin, fibronectin, laminin
	MMP-17	MT4-MMP	Fibrinogen, fibrin
	MMP-24	MT5-MMP	Gelatin, fibronectin, laminin
	MMP-25	MT6-MMP	Gelatin
6. Others	MMP-12	Macrophage metalloelastase	Elastin, fibronectin, Col IV
	MMP-19		Aggrecan, elastin, fibrillin, Col IV, gelatin
	MMP-20	Enamelysin	Aggrecan
	MMP-21	XMMP	Aggrecan
	MMP-23		Gelatin, casein, fibronectin
	MMP-27	CMMP	Unknown
	MMP-28	Epilysin	Unknown

MMPs are categorized according to the organization of their peptide domains, their substrate specificity, and their sequence similarity (8,12,17,22–24,85–87). MMP, matrix metalloproteinase; MT-MMP, membrane-type matrix metalloproteinase.

Aggrecanases

Aggrecanases are extracellular proteolytic enzymes that are members of the ADAMTS (A Disintegrin & Metalloprotinease with Thrombospodin Motifs) family. It act on large proteoglycans known as aggrecans, which are the major components of connective tissues such as cartilage, IV disc.The metalloproteinase domains of ADAMs are related to snake venom metalloproteinases or reprolysins. ADAMTS proteins are related to ADAMs, but they are not membrane-anchored proteins as they lack a transmembrane domain **(38).**

ADAMTS Family

Enzyme	Other name	Substrate	Activity
ADAMTS 1	**C3-C5**	**Aggrecan, Vesican**	**Cleavage of proteoglycan & core protein.**
ADAMTS 2	**Procollagen N-proteinase**	**Procollagen I Procollagen II**	**Processing N propeptide of procollagen**
ADAMTS 3	**KIAA0336**	**Procollagen II**	**Processing N propeptide of procollagen**
ADAMTS 4	**Aggrecanase -1, ADMP-1**	**Aggrecan, Vesican, Bervican**	**Cleavage of proteoglycan & core protein**

ADAMTS 5	ADAMTS 11, Aggrecanase 2, ADMP 2	Aggrecan	Cleavage of proteoglycan & core protein
ADAMTS 6			
ADAMTS 7			
ADAMTS 8	METH 2		Anti Angiogenic
ADAMTS 9	KIAA1312		
ADAMTS 10			
ADAMTS 12	UNQ1918,A1 605170		
ADAMTS 13	vWFCP, C9 or F8	Von Willebrand factor	Reduced activity result in thrombotic, thrombocytopaenic purpura
ADAMTS 14		Procollagen I	Processing N propeptide of procollagen
ADAMTS 15			
ADAMTS 16			
ADAMTS 17	FLJ32769, LOC123327		
ADAMTS 18	ADAMTS 21		
ADAMTS 19			
ADAMTS 20			

MMP 1, 2, 8, 13, & 9 mainly cleave aggrecan and collagen fibres of intervertebral disc which leads to disc degeneration. Aggrecanases are extracellular proteolytic enzymes that are the member of ADAMTS family. It mainly act on large proteoglycans known as aggrecans which is the main extracellular proteoglycan of the disc (35). It cleaves the interglobular domain (IGD) of aggrecan, thereby releasing the bulk of the aggrecan molecule from the tissue.

ADAMTS-4 and ADAMTS-5 are also designated as aggrecanase-1 and aggrecanase-2, respectively, because they can specifically cleave proteoglycans.

Unlike cartilage, in the nucleus pulposus (NP), both ADAMTS-4 and ADAMTS-5 expressions are elevated in human degenerative disc disease

Conclusion

Low back pain is a common symptom that can lead to disability and major socio professional repercussions. Despite of advances in imaging, the main cause of the pain often remains unknown. Morphological changes related to normal ageing of the disc appear on MR imaging without any symptoms. The molecular changes which taking place includes various proteolytic enzymes cleaving the aggrecans of the disc and the inflammatory cytokines which enhances the breakdown of collagens and proteoglycans plays a major rule in disc degeneration. These changes of the disc structure alters the MR signal which is required for diagnosing the degeneration. This study will help in understanding the molecular changes of disc degeneration and will help the surgeons, physicians to give exact treatment of the low back pain.

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