World Journal of Research and Review (WJRR)
ISSN:2455-3956, Volume-2, Issue-2, February 2015 Pages 01-12

Intervertebral Disc Damage & Repair – its Pros And Cons

Mir Mahmoud Mortazavi R ,Annie John

***Abstract*— Incidence of Low Back Pain (LBP) is attributed to the degeneration of the intervertebral disc (IVD) occurring during the second or third decade of life. This has emerged as the most expensive global healthcare problem with costs in billion. The IVD comprises of an inner nucleus pulposus (NP) and an outer Annulus Fibrosis (AF). They act as cushions between the vertebrae of the vertebral column. Current treatment modalities involve conservative management (medication and physical therapy) or surgical intervention (spine fusion, total disc replacement (TDR), or NP replacement. Since the last decade, there has been a surge of interest in applying tissue-engineering principles (scaffold and cells) to treat spinal problems associated with IVD.**

***Index Terms*— Low back pain, Intervertebral disc, Nucleus pulposus, Annulus Fibrosis,**

I. STRUCTURE OF THE VERTEBRAL COLUMN

The vertebral column consists of five regions (cervical vertebrae, thoracic vertebrae, lumbar vertebrae, sacrum region and coccyx region)[1].

Vertebrae in vertebral column are separated by cartilaginous intervertebral discs[2]. "S" shape of back bone gives special features and function to the body to support skull and upper extremities, trunk of muscles, bipedalism, movement and flexibility[3] (Fig1).

Vertebrae consist of special shape on the anterior side "Drum Shape", which is connected to the intervertebral disc above and below. The vertebral arch is connected to the posterior side of the body with two pedicles and two arched laminae. Vertebrae contain special foramen for the passing spinal cord. Spinal cord nerves are passing through intervertebral foramina to the anterior organs[3].

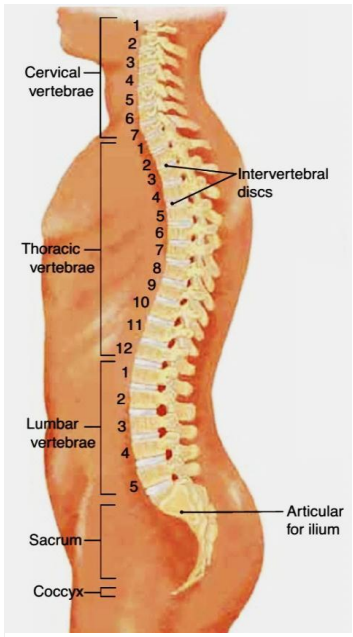


Figure1: Vertebral Column of human body with S-shape. Adapted from clinical anatomy of spine, Gregory D et al)

There are distinctive features for the different vertebrae in cervical vertebrae the transverse foramen is visible. In thoracic vertebrae facets join for connecting to the ribs and the lumbar region vertebrae contain flat spineous process for muscle attachment[3] (Fig2).

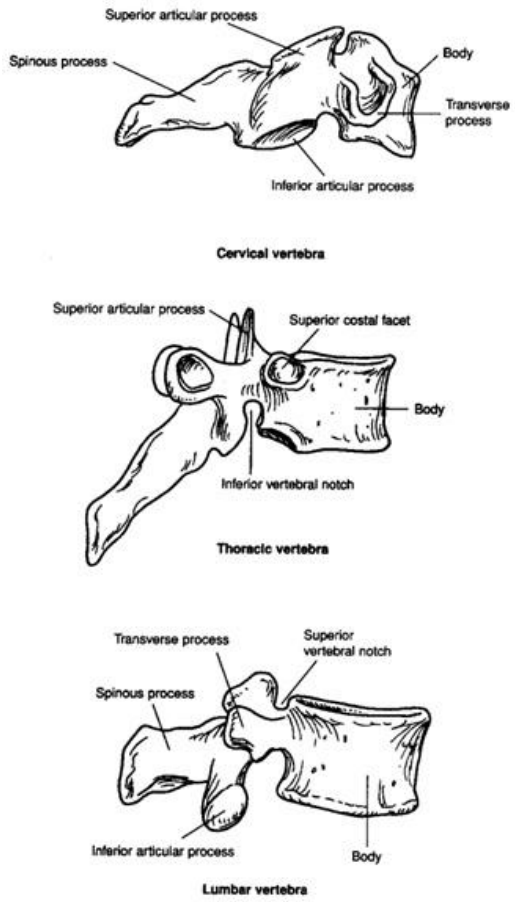


Figure2: Examples of vertebrae from different vertebral regions (adapted from human anatomy and physiology, Kent et al)

II. INTERVERTEBRAL DISC DEVELOPMENT AND COMPOSITION

➢ Intervertebral Disc Development:

Notochord with mesodermal origin makes axial cord at the center of embryo. Mesenchymal cells which are available surrounding the notochord provide a prichordal shape[4]. This structure takes the notochordal cells inside a clear notochordal sheath. By pressure of the sheath some notochordal cells push to the vertebra bodies while the segmentation of

Mir Mahmoud Mortazavi Roudmiane, BMT Wing, SCTIMST, Thiruvananthapuram 695012, India.
Annie John, Biomedical Technology Wing (BMT Wing), Sree Chitra Tirunal Institute for Medical Sciences & Technology (SCTIMST), Thiruvananthapuram 695012, India.

notochord to vertebral body is occurring[5] (Fig3 (A,B,C)).

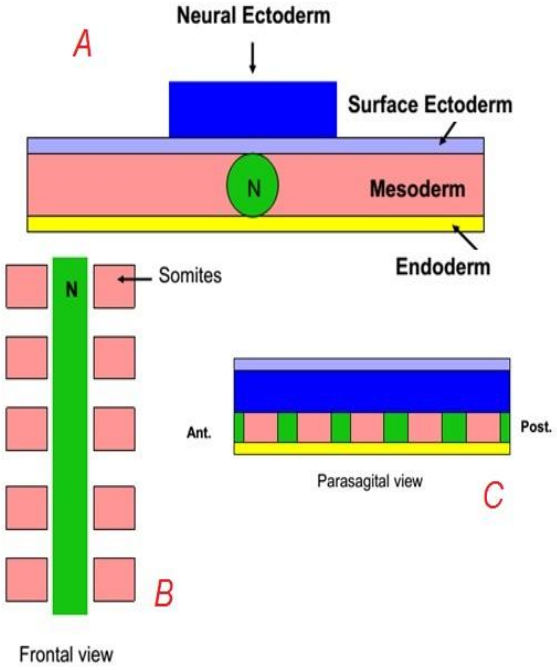


Figure3: Development of intervertebral disc in schematic way. (Adapted from Anatomy and pathophysiology of intervertebral disc disease, Shankar, et al)

Cylindrical sheath of embryonic mesenchymal column segmentation is occurring towards the dorsal region. The cylindrical sheath converts to the segmented dark and light bands. Dark bands are slow growing and will convert to intervertebral disc while the light bands grow rapidly and it develops into cartilage mold of the vertebral bodies[2] (Fig4).

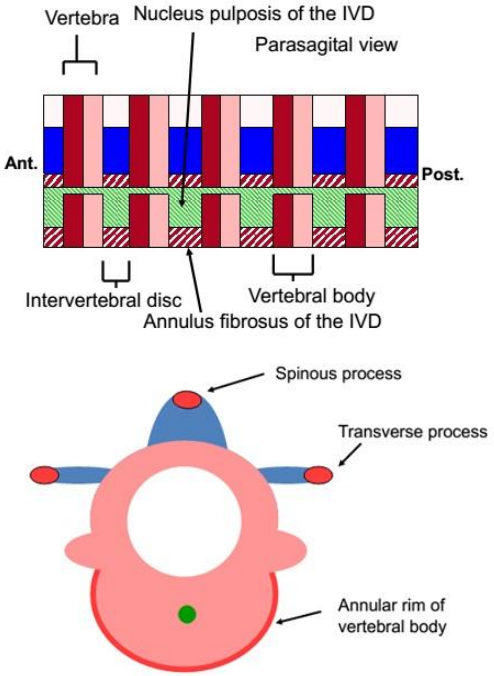


Figure4: schematic sketch shows the construction of the intervertebral disc during embryogenesis (adapted from Anatomy and pathophysiology of intervertebral disc disease, Shankar, et al).

- **Cartilage:**

Cartilage is semisolid tissue with cells trapped in the matrix. Mostly in cartilage there are chondrocyte cells (cartilage cells), Notochordal cells and Matrix. Cartilage is surrounded by dense connective tissue. it is an avascular tissue and therefore any trauma to this tissue will consume a lot of time to cure[3]. Cartilage receives nutrients by diffusion from the prichondrioum and surrounding tissues.

There are three types of cartilage: Hyaline cartilage, fibrocartilage and elastic cartilage based on the different composition and percentage of fiber in the matrix.

Hyaline cartilage: contains very fine structure of collagenous fibers visible by electron microscopy. It shows a glossy and clear appearance under the light microscope[6]. This tissue is visible mostly in the respiratory system, reinforces nose and joints between ribs and sternum. In embryogenesis process most of the bones are in the hyaline state prior to transformation to bone. This process is called endochondral ossification[3] (Fig5).

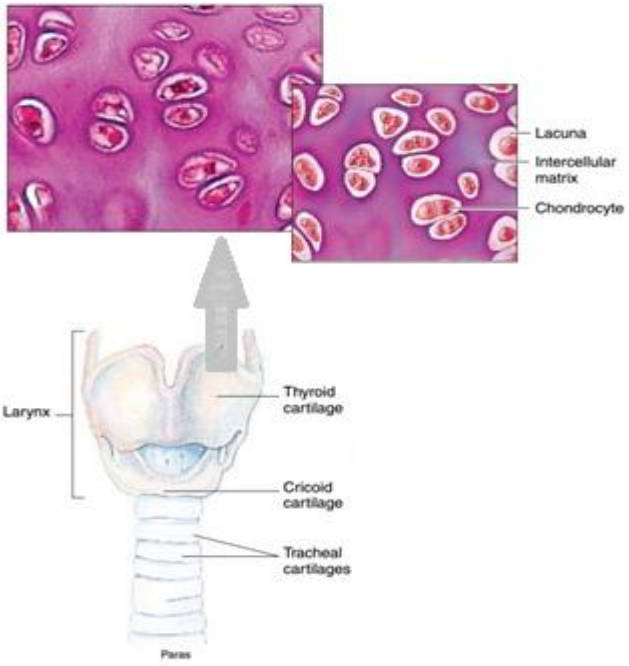


Figure5: Hyaline cartilage. Visible in Trachea (adapted from human anatomy and physiology, Kent et al).

Elastic cartilage: This tissue is very similar to hyaline cartilage but there are abundant of elastic fibers which give flexibility to the cartilage. Elastic fibers give the yellowish appearance. This type of elastic cartilage can be found in the larynx, outer ear and auditory canal[1] (Fig6).

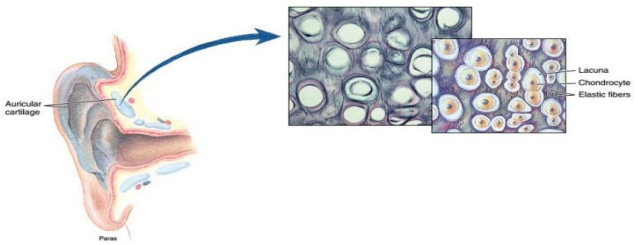


Figure6: Elastic cartilage in the outer ear, auditory canal (adapted from human anatomy, Kent et al).

Fibrocartilage: This type of cartilage has abundant amount of collagenous fiber durable for compression and extension. Mostly this type of tissue is found in the important part of the

skeleton like pelvic bone, knee joint and between vertebrae in the intervertebral discs[7] (Fig 7).

➢ **Intervertebral disc: Structure & composition of IVD**

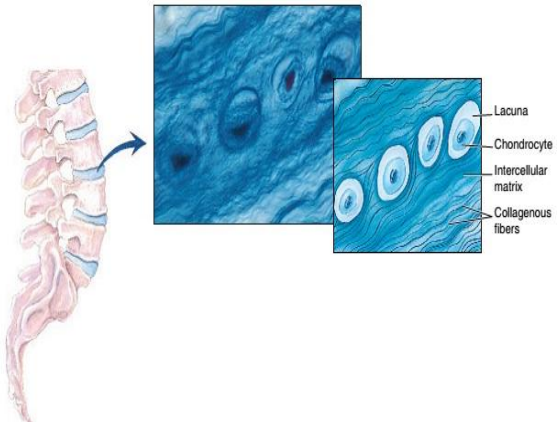


Figure7: Fibrocartilage at the intervertebral disc of vertebral column (adapted from human anatomy, kent et al).

Structure:

In human and rodent there are different numbers of intervertebral discs in the vertebral column. As we know in humans, there are 23 discs in the entire length of the vertebral column. In humans, intervertebral discs are bigger compared to the rodents. (In human each IVD is around 8 to 10 mm in height and 40 mm in diameter. IVDs occupy 25 percent of vertebral column height in human[8].

Intervertebral disc consist of three main structures; a spongy component at the center nucleus pulposus, surrounding lamellar layer annulus fibrosus and two layers of cartilage on the top and bottom of IVD called endplate[2], [8] (Fig 8).

Composition:

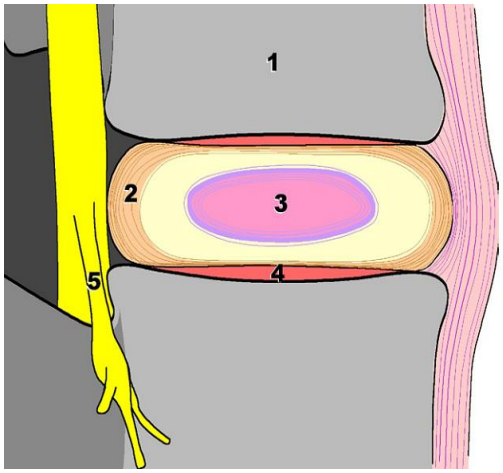


Figure8: Schematic Sketch as sagittal section of vertebrae (1), annulus fibrosis (2), nucleus pulposus (3), endplate (4) and spinal nerve root (5) (adapted from Anatomy and pathology of intervertebral disc, Shankar et al).

A. Nucleus pulposus

A spongy gel-like which consist of type II collagen organized randomly among of proteoglycan molecules (aggrecan), hydrophilic chondroitin, and keratin sulfate. Glycosaminoglycan traps water molecule which gives gel like properties to nucleus pulposus (NP). Extra cellular matrix contains other type of proteoglycan like: Versican, biglycan, decorin, fibromodulin and lumican[8]. Composition of different type of collagen like type I, II and type IV gives more tensile strength to the NP matrix. For more hydration and trapping water molecule aggrecan binds with highly anionic glycosaminoglycan like chondroitin and keratin sulfate which helps to maintain a fluid consistency by osmotic pressure[2]. Water content of nucleus pulposus at the birth time is around 90 percent and during aging are decreases to 70 percent[9] (Fig 9).

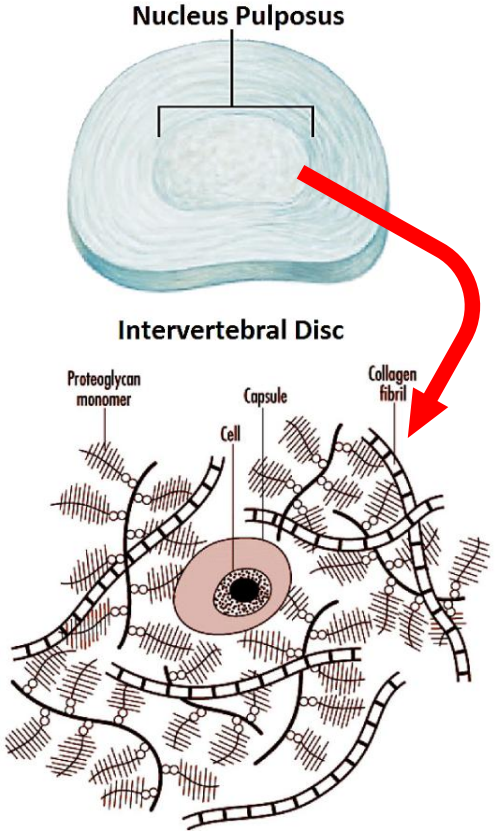


Figure9: the matrix component of NP, (adapted from proteoglycans and sulfated glycosaminoglycans, Jeffry Esko et al).

B. Annulus fibrosus

Several concentrated layers of type I collagen and protein construct a special composition called annulus fibrosus (AF). This structure contains of 10 to 20 sheets of fibers in different orientation and angles called lamellae. The lamellae are thicker in the anterior side compare to the posterior. Orientation of fibers in AF is 60 to 70 in vertical aspect. This feature of AF gives flexibility to vertebral column to turn right and left[2] [10](Fig10).

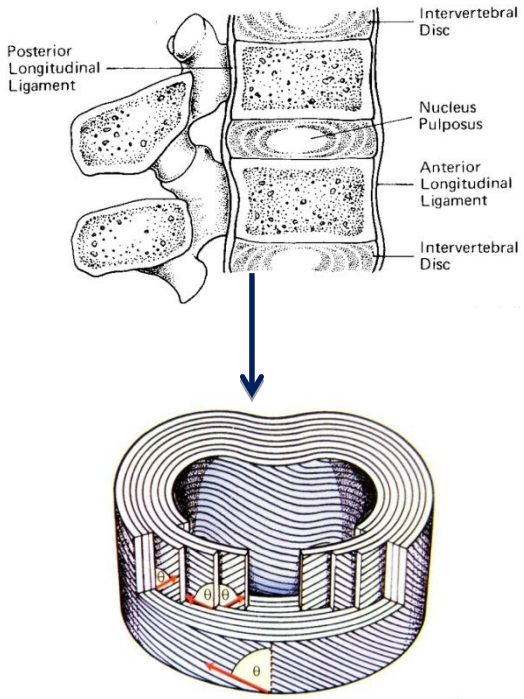


Figure10; schematic sketch of annulus fibrosus, (adapted from spine health and the clinical anatomy, Singer).

C. Endplates:

It is a layer of hyaline cartilage with thickness of (0.6 mm to 1 mm). Endplate covers two side of disc. During first year of life endplate is highly vascularized but the measure of vascularity is decreases during course of time[8] (Fig 11)

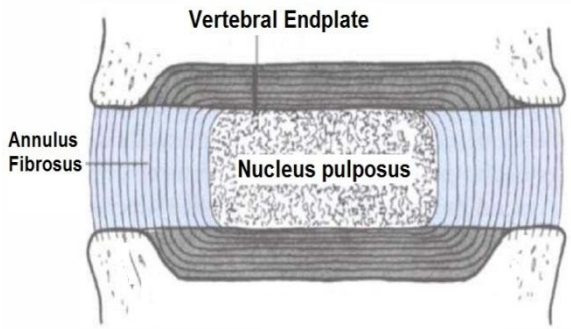


Figure11: Schematic sketch of endplate position, (adapted from anatomy and physiology of intervertebral disc , Shankar et al).

Endplate consist of type II collagen which is favorable for compression/ resistance [2].

Extracellular Matrix (ECM):

Functional properties of intervertebral disc are depending on 3 factors; Composition, orientation and integrity of ECM. As we know NP has heterogeneous structure of water and proteoglycans.

- **Aggrecan**: is the main component of nucleus pulposus which is responsible for hydration and disc height. It absorbs water through osmotic pressure. Aggrecan decreases with age and NP cells fails to keep disc height and increases hydrostatic pressure. By failure of disc height, cracks are appearing in annulus fibrosus and endplates [8].

- **Proteoglycan:** is included of core protein and glycosaminoglycans with Decorin, lumican, Biglycan and fibromodulin as small proteoglycans. Proteoglycans like aggrecan withdraw water from surrounding tissue [9] (Fig12).

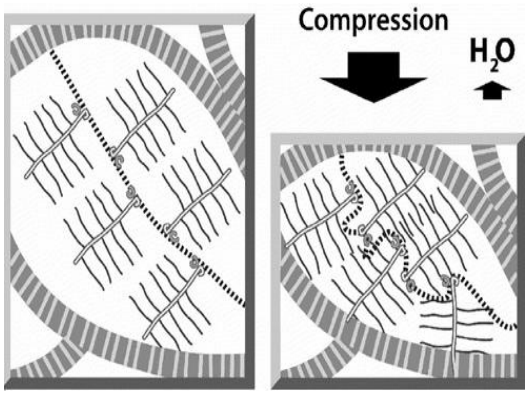
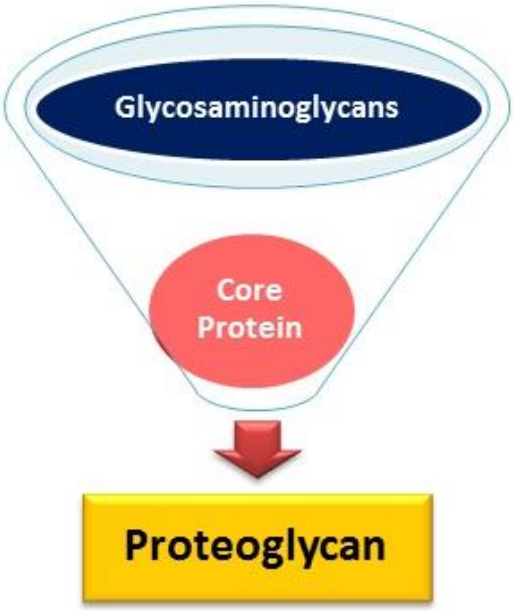


Figure12: Schematic sketch of the compression changes on proteoglycans (adapted from Understanding Human Anatomy and physiology, Singer).



- **Glycosaminoglycans**: they are large molecules with negative charge group like Sulphate and carboxylic. There are different type of glycosaminoglycan like; hyaluronic acid, Keratan sulphate, chondroitin (4-or6-) sulphate, dermatan sulphate [8] (Fig13).

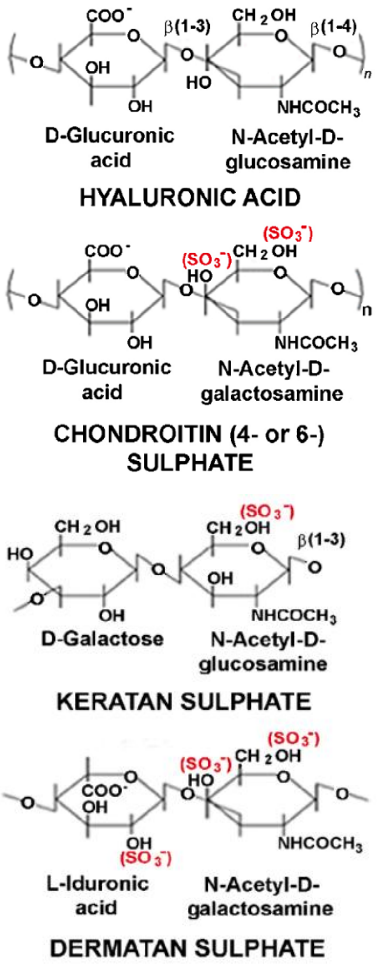


Figure13: Chemical structure of different types of glycosaminoglycans (adapted from Understanding Human Anatomy and physiology, Sylvia et al).

Proteolytic enzymes: called protease or proteinase which can degrade long chain of big protein molecule to small fragment [8] (Fig14).

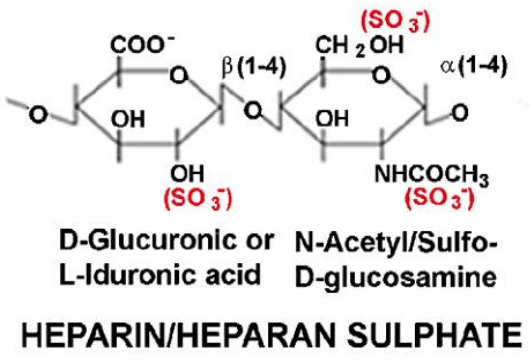


Figure14: Chemical structure of proteolytic enzymes (adapted from Understanding Human Anatomy and physiology, Sylvia et al).

III. Curves of the Spine

Human vertebral column does different duties like protecting spinal cord, nerve root and internal organs. Vertebral column provides flexibility as well as balance for upright posture. While vertebral column loses it balance; different type of deformity occurs. Normally 'S' shape of spinal column contains curves. Curves toward front called lordotic and curves toward outside called kyphotic[3] (Fig 15).

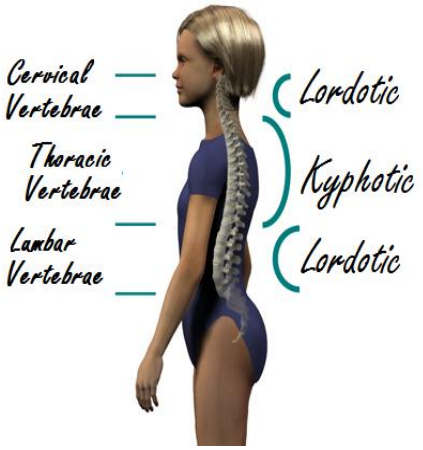


Figure15: Schematic sketch of vertebral column curves,(adapted from The Clinical Anatomy and Management of Low Back Pain, Singer et al).

Deformity of vertebral column:

Curvature disorders includes: Scoliosis, Spondylolisthesis, Kyphosis and Lordosis.

- **Scoliosis**: is a lateral curvature disorder of vertebral column. This disorder can occur in different ways like: thoracic, thoracolumbar, lumbar and double major curve[2] (Fig16).

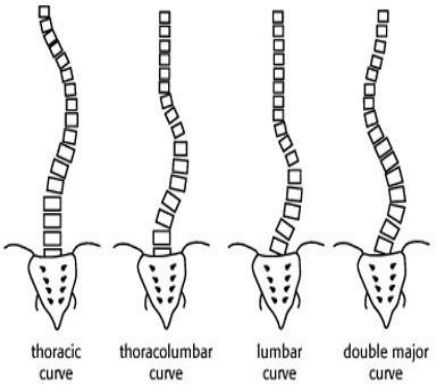


Figure16: schematic sketch shows different type of scoliosis (adapted from The Clinical Anatomy and Management of Low Back Pain).

- **Spondylolisthesis:** another abnormality of vertebral column that one vertebrae slips over another vertebra. This type of abnormality happens in children and adolescents. In most cases it happens on the last vertebral level. Different type of spondylolisthesis includes: Dysplastic (congenital), Iisthemic (stress fracture) and degenerative or traumatic (Fig 17).

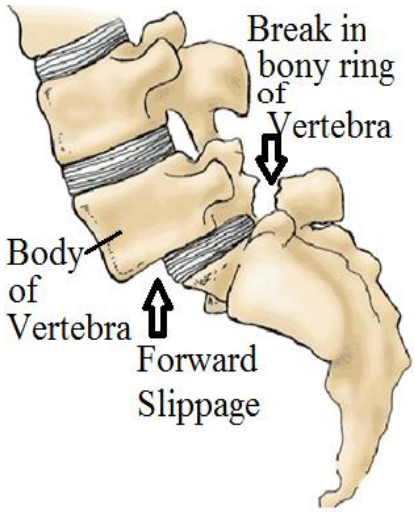
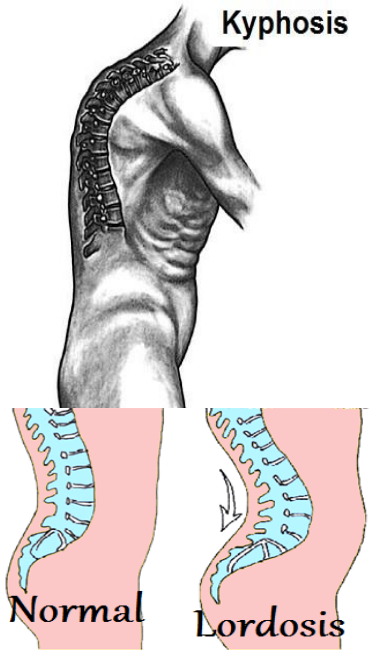


Figure17: Spondylolisthesis at the level of L5/S1 (adapted from The Clinical Anatomy and Management of Low Back Pain).

- **Kyphosis:** is an abnormality that increases posterior thoracic curvature. Also it is called hunchedback[1] with noticeable round back deformity (Fig18).



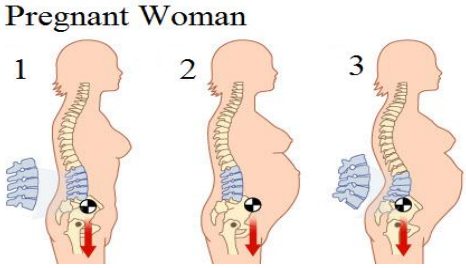


Figure19: schematic sketch shows center of gravity moves forward as the pregnancy progresses (Adapted from low back pain and pregnancy).

- **Lordosis:** abnormal increases of lumbar curvature. It can lead to sway-back appearance[3], [11]. Females are suitable candidate for lumbar lordosis compare to males. This abnormality is visible during pregnancy (Fig 19).

IV. Degenerative Disc Disease (DDD)

Whenever there is an imbalance between synthesis and catabolism in the nucleus pulposus; intervertebral disc leads to degeneration pathway. Increase of catabolism or decrease of anabolism can enhance degradation of proteoglycans. In degradation pathway long chain of proteoglycans become shorter. As a result spongy nucleus pulposus loses negative anionic charges and water content which was already trapped in the NP migrates to surrounding tissue. So disc loses its height and cell senescence occurs because of impaired nutrient supply[12] (Fig 20).

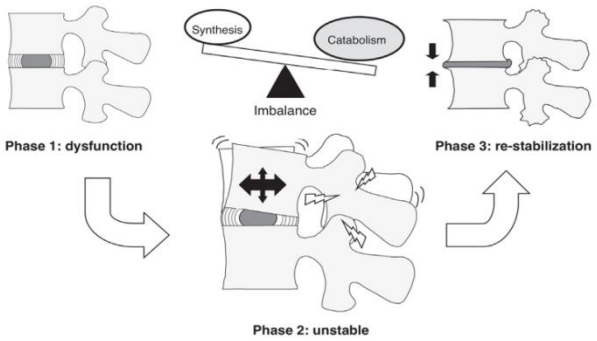


Figure20: Schematic sketch of degeneration of intervertebral disc, loses of water content by increases of catabolism (Phase 1), movement and load on damaged disc (Phase 2), failure or reconstruction of IVD (Phase 3) (Adapted from The potential role of mesenchymal stem cell therapy for intervertebral disc degeneration, Frank Acosta, et al).

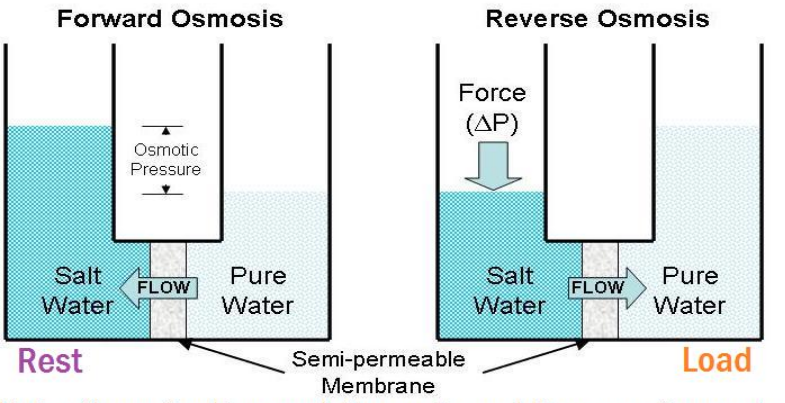


Figure21: Schematic sketch of role of annulus fibrosus during compression ar decompression as Semi-permeable membrane (Adapted from Mechanobiology in intervertebral disc degeneration and regeneration, Lotz. J .C, et al).

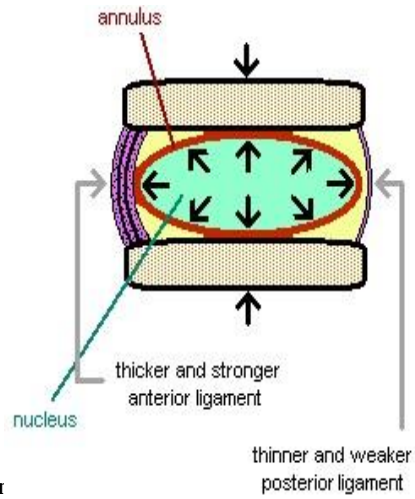


Figure22: Schematic sketch of distribution of applied forces for on the nucleus pulposus.

Nutrient exchange and saving height of intervertebral disc is depending on two major natural phenomenons. One is diffusion of the nutrient material al from capillaries in the outer annulus fibrosus and the other one is osmetic pressure which working in healthy disc during. Nutrient exchange occurs by diffusion which is very essential for avascular tissue like NP[13].

Cell at the center of NP are 8 mm away from closest capillary. Annulus fibrosus is working look like semipermeable membrane. While disc is in the rest condition; it absorbs water from surrounding tissue. While intervertebral disc goes under pressure; water content leak to outside of IVD[14] (Fig 21).

Disc Degeneration Diseases (DDD) cause by different reasons like: Genetic inheritance, impaired metabolite transport, altered levels of enzyme activity, Cell senescence and death, Changes in matrix macromolecules, Changes in water content and Structural failure. Most of Disc Degeneration Diseases (DDD) occurs at the lumbar region which there is huge pressure in these discs (Fig 22).

As the compressive test shows that at the young ages tolerance of weight is high compare to middle age. Degeneration happens during course of time. In the degenerated disc tolerance of compressive stress is very low[14], [15](Fig 23).

Degradation of collagen and proteoglycans is first step of disc degeneration. Collagen fibers are as framework for keep proteoglycan monomers as 3 dimensional networks. Collagen increases from center of nucleus pulposus to ward annulus fibrosus. Swelling pressure depend on ionic concentration in the disc. Space between proteoglycans in a healthy disc is around 0.003 to 0.004 µm. fluid flew through tiny pores are very slow.

While proteolytic enzyme like matrix metalloproteinase (MMPs) activate by different factors; MMPs starts degradation of proteoglycans. By loses of NP framework, space increases between the networks and ions like Na^{+}, Ca^{2+} goes out from NP. At the result by loses of Na^{+} and Ca^{2+} ions water content in NP decreases and NP starting to collapse[14].

Increases of cell death, proliferation and cell senescence occurs by intrinsic and extrinsic factors. Cell proliferation is visualized in the degenerative disc by producing cell cluster. Cell cluster can be seen around nucleus pulposus tear and clefts.

Number of cell clusters increase during course of time. Increases of cell cluster enhanced by osteogenic protein-1, transforming growth factor- β1 (TGF- β1) and bone morphogenic protein -2[16] (Fig 24).

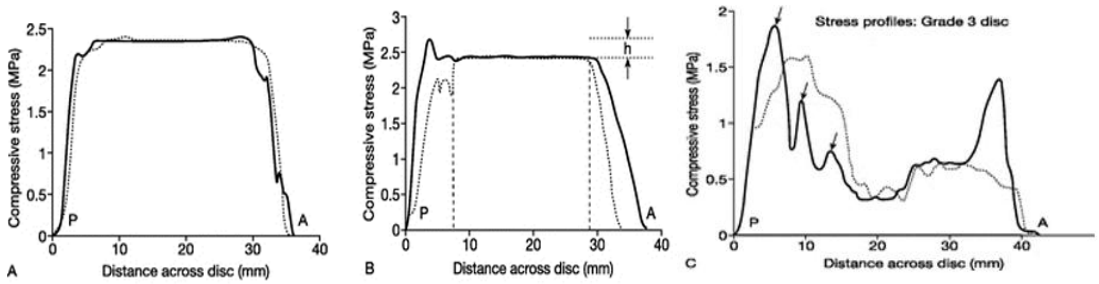


Figure23: Graph shows degeneration of IVD by the course of time. Grade 1: young disc (A), Grade 2: Middle aged and Grade 3: Degenerated (adapted from. potential gene therapy for intervertebral disc degeneration, Masahiro k, et al).

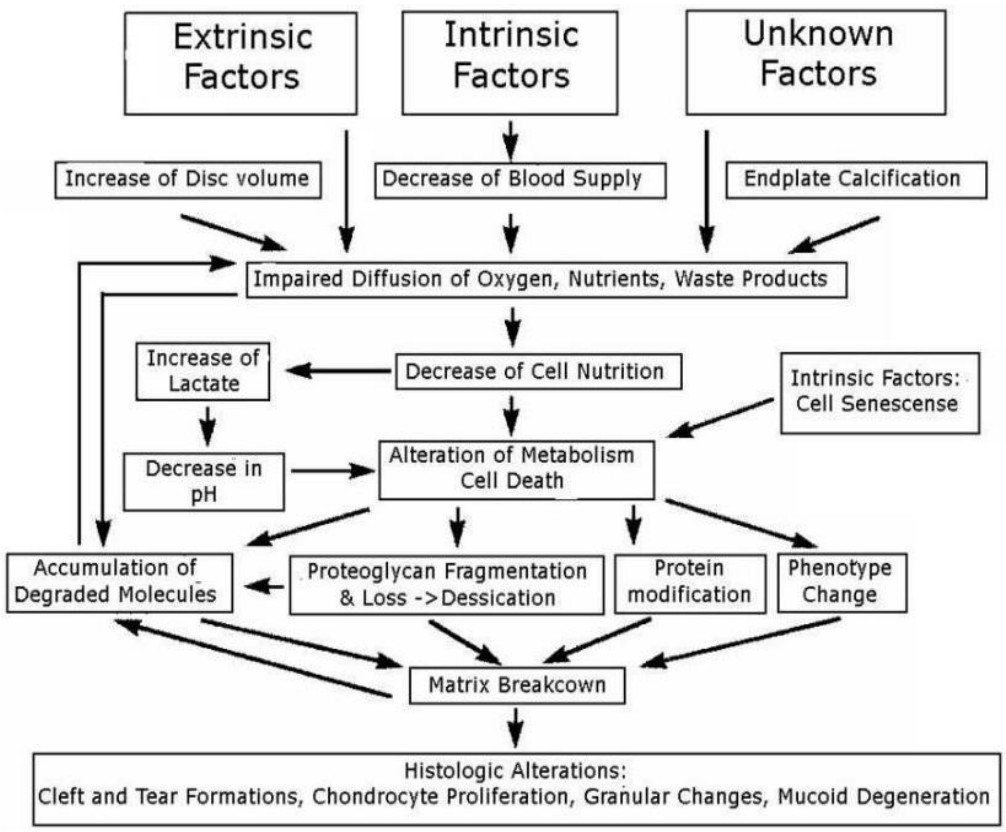


Figure24: a complete chart of Matrix remodeling and disc degeneration (Adapted from implications for physical therapies for discogenic back pain, Michael Adams, et al).

Cell senescence increases while normal cell division stops. It is associated with β-galactosidase in NP clustered cells in herniated disc. Proliferation of degenerated NP is lower than non-degenerated. There are two mechanism of cellular senescence. One is replicative senescence which works by shortening telomerase and cell undergo repeated cell division. The other mechanism is stress-induced premature senescence that is result of various stresses like mechanical load or cytokines such as interleukin-1[17] (Fig 25).

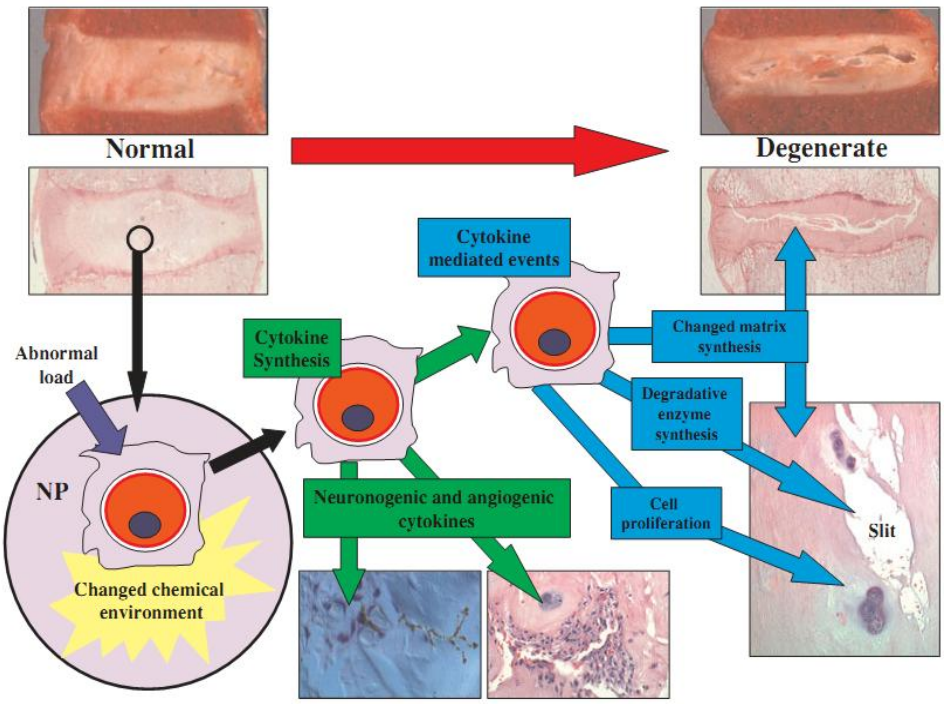


Figure25: A comparison of healthy disc with degenerated disc and schematic sketch of degenerative pathway (Adapted from implications for physical therapies for discogenic back pain Michael Adams, et al).

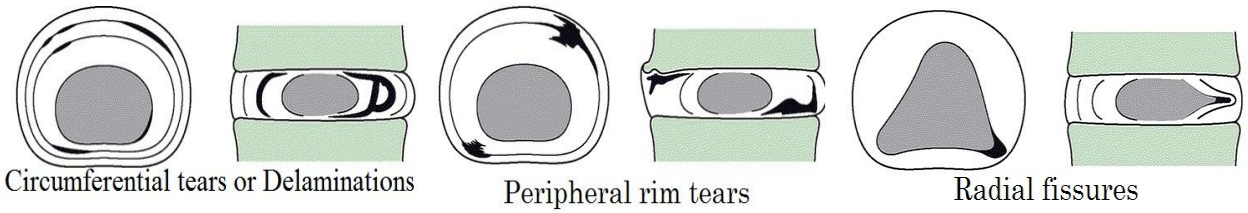


Figure26: Different type of NP bulging (adapted from The Clinical Anatomy and Management of Low Back Pain, Singer . et al).

- **Herniated Disc:**

Any tear of nucleus pulposus due to weakness of surrounding wall toward nerve root provides disc rupture or herniation. There are different types of bulging in the annulus fibrosus area.

In the first condition circumferential tears or Delamination which is present in the anterior and posterior side of IVD. It occurs at interlaminar shear stresses. The second type of disc herniation appear with bony out wards which is called peripheral rim tears and radial fissures appears with bigger bulge of nucleus pulposus toward posterior side. Radial fissures appear with repetitive loading and bending[3] (Fig26).

Progress of radial fissures bulge leads disc to Disc herniation or disc prolapse. Continuation of disc prolapse leads to press sciatic nerve. Disc prolapse may heal naturally by total rest and avoid activities if damage is not grade four[18] (Fig 27).

V. Current therapeutic option for degenerative disc disease

Almost 80 percent of people experience low back pain (LBP) throughout their life. Most people of this group recover without any formal treatment. Those people who could recover spontaneously, they need to undergo non-operative management and in severe cases going through surgical management[19].

a) Non-operative management:

In non-surgical management the most important suggestion is total bed rest for maximum of 2 days. Generally this time should be enough for the patient to recover. This suggestion can be combined with Anti-inflammatory medication, analgesia and physical therapy[2]. A physical therapy benefits patient for more mobility and at the end it is helping to recover faster.

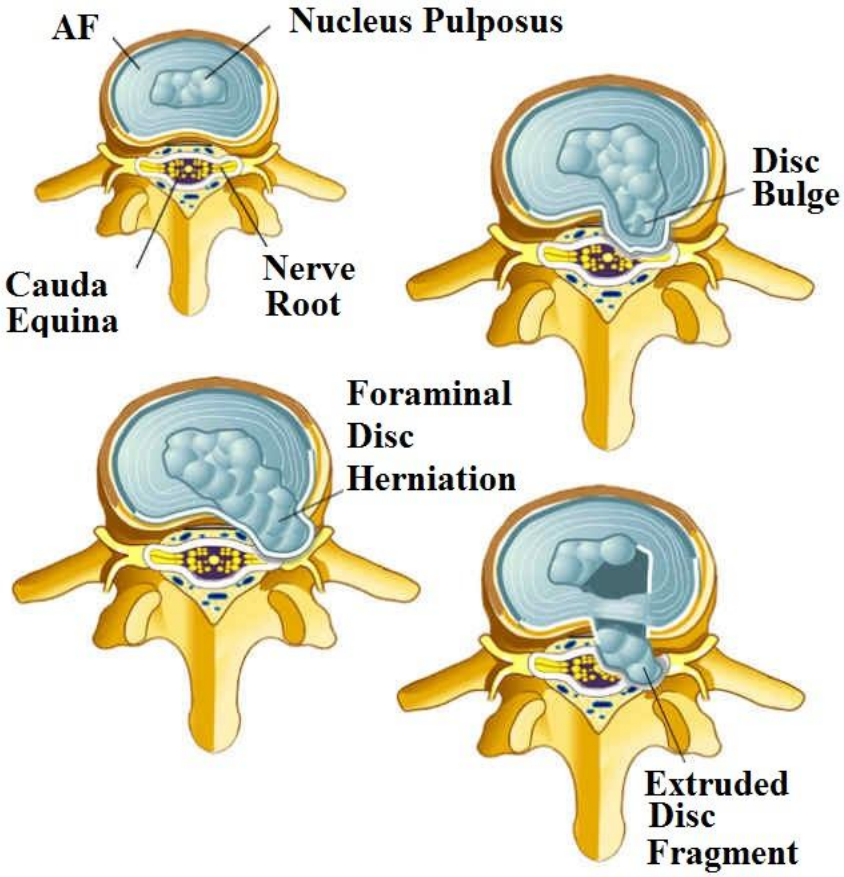


Figure27: Disc prolapses or disc herniation (Adapted from Understanding human Anatomy and physiology, Sylvia).

Figure28: Low Back Pain (LBP) Exercise (Adapted from The Clinical Anatomy and Management of Low Back Pain, Singer).

Ozone Chemonucleolysis is another type of non-operative therapy of interest in Europe. It was developed by C.verga in 1983. This method involves applying of 40 to 60 ml of ozone gas (O_2-O_3 combination) by concentration of 30 mg/ml. This should be applied to the paraventral musculature and herniation area[16] (Fig 28).

b) Surgical management

Surgical interventions are the most successful treatments. But all of these treatments contain their advantages and disadvantages[17].

- **Spinal fusion:**

It occurs when disc is ruptured. It is called (spondylolisthesis). In most cases with curvature of spine which is deformed or fractured; spinal fusion should be performed. Spinal fusion contain so many limitations like adjacent intervertebral disc also damage very fast due to restricted activity of fused vertebrae[17]. So bending on lumbar side provides more pressure to the other IVDs. As a result they undergo fast degeneration (Fig 29).

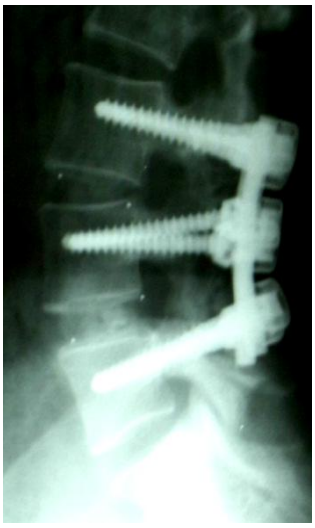


Figure29: Spinal fusion of vertebrae (Adapted from Understanding Human Anatomy and physiology, Sylvia).

- **Total disc Arthroplasty or Total Disc replacement:**

Total disc replacement by artificial disc improves function and reduces pain. Arthroplasty showed significant pain relief compared to other methods. Multi-level arthroplasty is better than multilevel spine fusion. In this method discs are able to shift and move. This method has complete access to L4/L5 and L5/S1(Fig 30).

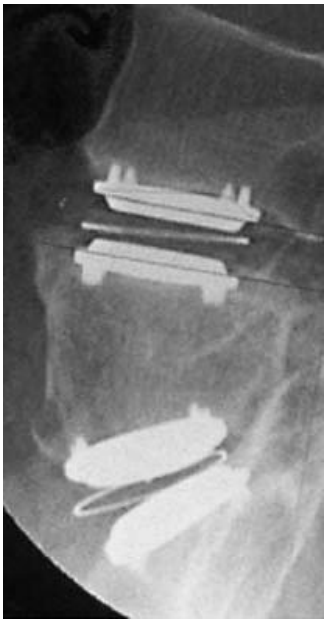


Figure30: Total disc replacement (Adapted from Understanding human Anatomy and physiology, Sylvia).

- **Nucleus pulposus replacement or partial disc replacement (PDR):**

It is a less invasive method compared to other surgical procedures. Mostly PDR intervention can be done in early stage of degeneration of intervertebral disc. Advantage of PDR method is a less invasive method and compared to other surgical procedures and multiple way to approach the target including lateral, posterior and anterior retroperitoneal. The most important problem regarding PDR is their migration and expulsion of device. Because they are not fixed to the end plate[20] (Fig 31).

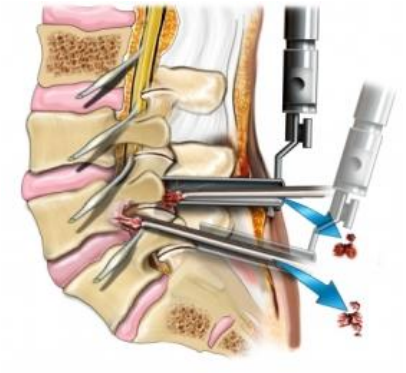


Figure31: Partial disc replacement (PDR) and their approaches. (Adapted from Understanding Human Anatomy and physiology, Sylvia).

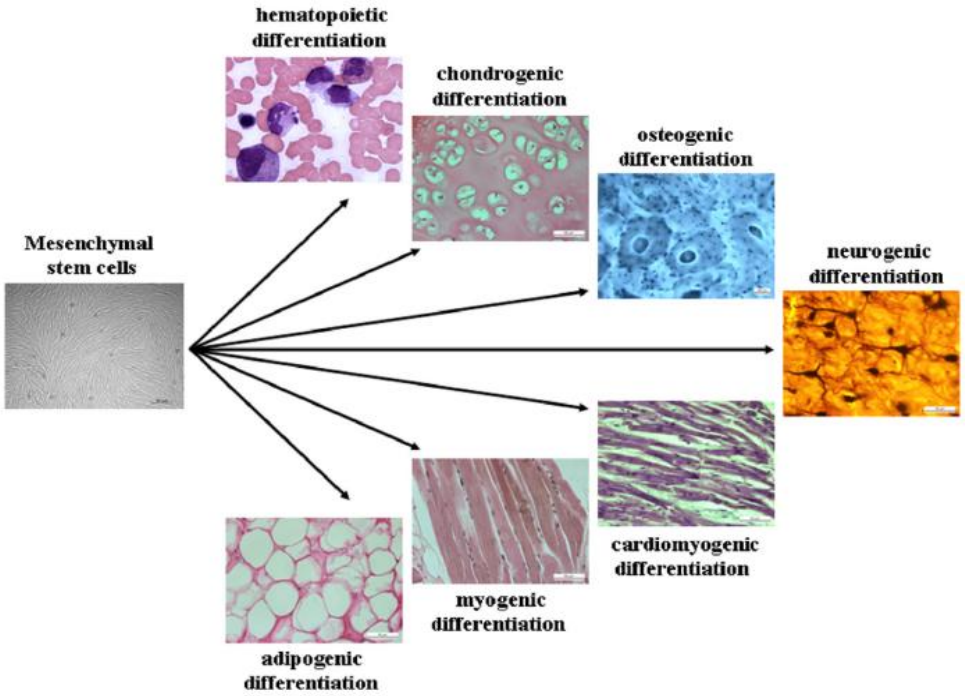


Figure32: Cell based Therapy. Mesenchymal stem cells are able to convert to different cell lineages under appropriate conditions. (Adapted from cell-based therapies used to treat lumbar degenerative disc disease, d. oehme).

CONCLUSION

- **Cellular and molecular Therapy:**

Most of the current treatments are focused on relieving patient pain rather than solving the main problem. Non-operative management like bed rest, analgesia, and usage of relaxant or applying corticosteroids aims to reduce pain. Even surgical methods like discectomy or immobilization of intervertebral discs gave the same result. Eventually, the net result of all these types of treatments are the same [16] The aim of this type of therapy is to repair the degeneration of the disc at the cellular level and increase the extra cellular matrix. Again, direct application of growth factors and cytokines to intervertebral disc is not appreciable due to their short-life[21] (Fig 32).

REFERENCES

[1] Sylvia S.Mader, *Understanding human Anatomy and physiology*. .
[2] L. G. F. G. K. P. Singer, *The Clinical Anatomy and Management of Low Back Pain*. .
[3] M. Kent, V. de Graaff, and R. Ward Rhees, *Human Anatomy and Physiology*. .
[4] N. A. SCOTT, P. F. HARRIS, and K. M. BAGNALL, "A morphological and histological study of the postnatal development of intervertebral discs in the lumbar spine of the rabbit," J. Anat. ( ) 130, , pp. 75-81 1980.
[5] RJW Hoogendoorn, F van Kemenade, PIJM Wuisman, RA Bank, and MN Helder, "Notochordal cells are not present in goat intervertebral discs from foetal age on,".
[6] J. Artner, *Atlas of human Skeletal Anantomy*. .
[7] N. Bergknut, L. A. Smolders, G. C. M. Grinwis, R. Hagman, A.-S. Lagerstedt, H. A. W. Hazewinkel, M. A. Tryfonidou, and B. P. Meij, "Intervertebral disc degeneration in the dog. Part 1: Anatomy and physiology of the intervertebral disc and characteristics of intervertebral disc degeneration," *Vet. J.*, vol. 195, no. 3, pp. 282–291, Mar. 2013.
[8] H. Shankar, J. A. Scarlett, and S. E. Abram, "Anatomy and pathophysiology of intervertebral disc disease," *Tech. Reg. Anesth. Pain Manag.*, vol. 13, no. 2, pp. 67–75, Apr. 2009.
[9] J. D. Esko, K. Kimata, and U. Lindahl, "Proteoglycans and Sulfated Glycosaminoglycans," in *Essentials of Glycobiology*, 2nd ed., A. Varki, R. D. Cummings, J. D. Esko, H. H. Freeze, P. Stanley, C. R. Bertozzi, G. W. Hart, and M. E. Etzler, Eds. Cold Spring Harbor (NY): Cold Spring Harbor Laboratory Press, 2009.
[10] "Annulus Fibrosus," *Spine-health*. [Online]. Available: http://www.spine-health.com/glossary/annulus-fibrosus. [Accessed: 19-Feb-2016].
[11] C. Gregory D and S. Darby, *Clinical Anatomy of the Spine, Spinal Cord, and Ans (Third Edition)*. .
[12] Y.-S. Choi, "Pathophysiology of Degenerative Disc Disease," *Asian Spine J.*, vol. 3, no. 1, pp. 39–44, Jun. 2009.
[13] J. C. Lotz, A. Staples, A. Walsh, and A. H. Hsieh, "Mechanobiology in intervertebral disc degeneration and regeneration," *Conf. Proc. Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. IEEE Eng. Med. Biol. Soc. Annu. Conf.*, vol. 7, p. 5459, 2004.
[14] F. L. Acosta Jr, J. Lotz, and C. P. Ames, "The potential role of mesenchymal stem cell therapy for intervertebral disc degeneration: a critical overview," *Neurosurg. Focus*, vol. 19, no. 3, p. E4, Sep. 2005.
[15] N. Kotaro, M. Koichiro, K. Kakutani, Y. Takashi, and K. Masahiro, "Potential Gene Therapy for Intervertebral Disc Degeneration," Department of Orthopaedic Surgery, Kobe University Graduate School of Medicine, Kobe, Japan.
[16] P. P. Raj, "Intervertebral Disc: Anatomy-Physiology-Pathophysiology-Treatment," *Pain Pract.*, vol. 8, no. 1, pp. 18–44, Jan. 2008.
[17] D. Oehme, T. Goldschlager, P. Ghosh, J. V. Rosenfeld, G. Jenkin, D. Oehme, T. Goldschlager, P. Ghosh, J. V. Rosenfeld, and G. Jenkin, "Cell-Based Therapies Used to Treat Lumbar Degenerative Disc Disease: A Systematic Review of Animal Studies and Human Clinical Trials, Cell-Based Therapies Used to Treat Lumbar Degenerative Disc Disease: A Systematic Review of Animal Studies and Human Clinical Trials," *Stem Cells Int. Stem Cells Int.*, vol. 2015, 2015, p. e946031, May 2015.
[18] M. A. Adams, M. Stefanakis, and P. Dolan, "Healing of a painful intervertebral disc should not be confused with reversing disc degeneration: implications for physical therapies for discogenic back pain," *Clin. Biomech. Bristol Avon*, vol. 25, no. 10, pp. 961–971, Dec. 2010.
[19] A. Abbushi, M. Endres, M. Cabraja, S. N. Kroppenstedt, U. W. Thomale, M. Sittinger, A. A. Hegewald, L. Morawietz, A.-J. Lemke, V.-G. Bansemer, C. Kaps, and C. Woiciechowsky, "Regeneration of intervertebral disc tissue by resorbable cell-free polyglycolic acid-based implants in a rabbit model of disc degeneration," *Spine*, vol. 33, no. 14, pp. 1527–1532, Jun. 2008.

[20] D. Coric and P. V. Mummaneni, "Nucleus replacement technologies," *J. Neurosurg. Spine*, vol. 8, no. 2, pp. 115–120, Feb. 2008.

[21] D. Drazin, J. Rosner, P. Avalos, and F. Acosta, "Stem Cell Therapy for Degenerative Disc Disease," *Adv. Orthop.*, vol. 2012, pp. 1–8, 2012.