DOI: https:/doi.org/10.56981/M0000242

Intl. J. Med. Sci. 2022; 2(4) 05-13

International Journal of Medical Sciences
E. ISSN: 2961-3019
journal homepage: www.mespj.com/ijms

Document heading

A REVIEW ON CARTILAGINOUS ENDPLATES AND THE DEGENERATION OF INTERVERTEBRAL DISC

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Article Info.
Article history:
Received 05 September 2022
Revised 12 November 2022
Accepted 11 December 2022
Keywords:
Cartilaginous Endplates, Intervertebral Disc Degeneration, Low back pain, proteoglycans, Magnetic Resonance Imaging, Artificial Intelligence.
How to cite:
Zakiyah Mohammed Abid Sulayman Ataya Allah. A review on cartilaginous endplates and the degeneration of intervertebral disc. Int J Med Sci. 2022;2(4):05-13. https:/doi.org/10.56981/M0000242

ABSTRACT

Cartilaginous Endplates (CEP) acts as a mechanical barrier and forms the anatomical structure of intervertebral disc. It allows the nutrients to get transported into the disc from the nearby blood vessels. Low back pain is a primary complication raised by Intervertebral Disc Degeneration (IVDD). The objective of the current review article is to provide an overview about the composition and the functions of Cartilaginous Endplates, development and the progression of the IVDD, application of modern techniques for its treatment. CEP primarily contains water, type II collagen, glycosaminoglycans (GAGs) while it also has type X collagen. The study provided an overview about the IVDD, causal factors, diagnostic methods, and the application of different types of treatment methods. The authors recommend validating the stem cell-based therapies at clinical levels since such therapies have been proposed and validated so far, only in in vitro and animal models. Further, the study recommends to develop novel diagnostic tools that are not only cost-effective, but also non-invasive by leveraging the Artificial Intelligence and Machine Learning techniques in the diagnostics methods.

INTRODUCTION

Cartilaginous Endplates (CEP), along with the central Nucleus Pulposus (NP) and fibrocartilaginous Annulus Fibrosus, form the anatomical structure of intervertebral disc, the largest avascular tissue of the human beings and is a thin layer of hyaline cartilage [1]. Figure 1 shows the structure of a healthy intervertebral disc [2] in which the placement of CEP is clearly shown. CEP includes the inferior and superior boundaries of the intervertebral disc [3] and its prominent function is to act as a mechanical barrier between the vertebral bone and the pressurized NP. Further, it also allows

the nutrients to get transported into the disc from the nearby blood vessels [2,4–7]. Though there is a substantial difference exhibited by the cartilaginous endplate cells and articular chondrocytes, based on their cell markers, both exhibit a similar rounded morphology [3]. According to [8], both NP cells as well as CEP cells do not possess any marker proteins.

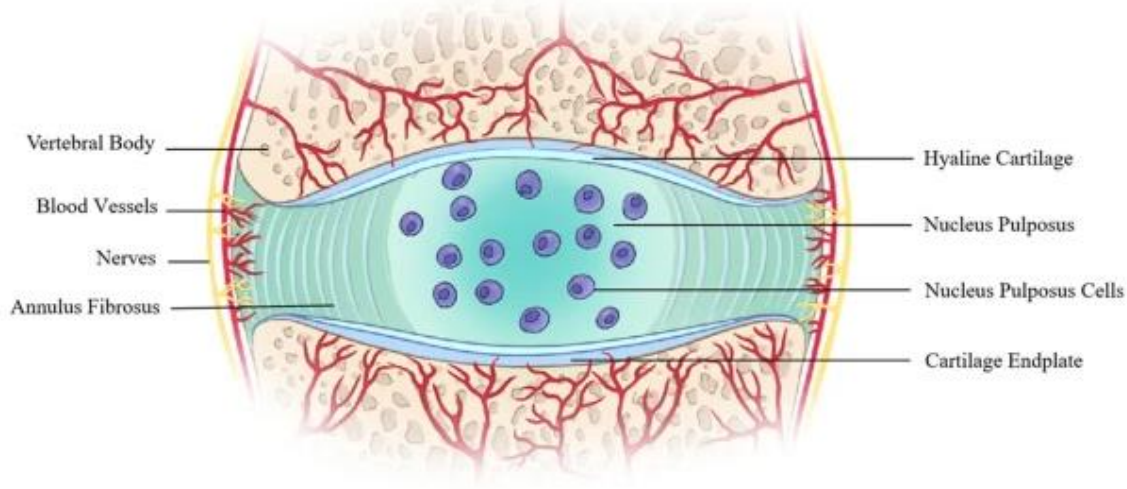

Figure 1. A healthy intervertebral disc Source: (2)

Low back pain is a primary complication raised by Intervertebral Disc Degeneration (IVDD). Across the globe, the degenerative disease of the intervertebral disc remains an alarming health issue among the adults while various causal factors have been identified such as the lifestyle, genetic and occupational factors [9]. According to the World Health Organization report [10], musculoskeletal conditions are reported among 1.71 billion people across the globe, in which Low back pain is the main contributor with 570 million cases globally. As per the literature [11], the annual and lifetime prevalence of LBP in India stands at 51% (95% CI 45-58%) and 66% (95% CI 56-75%) respectively.

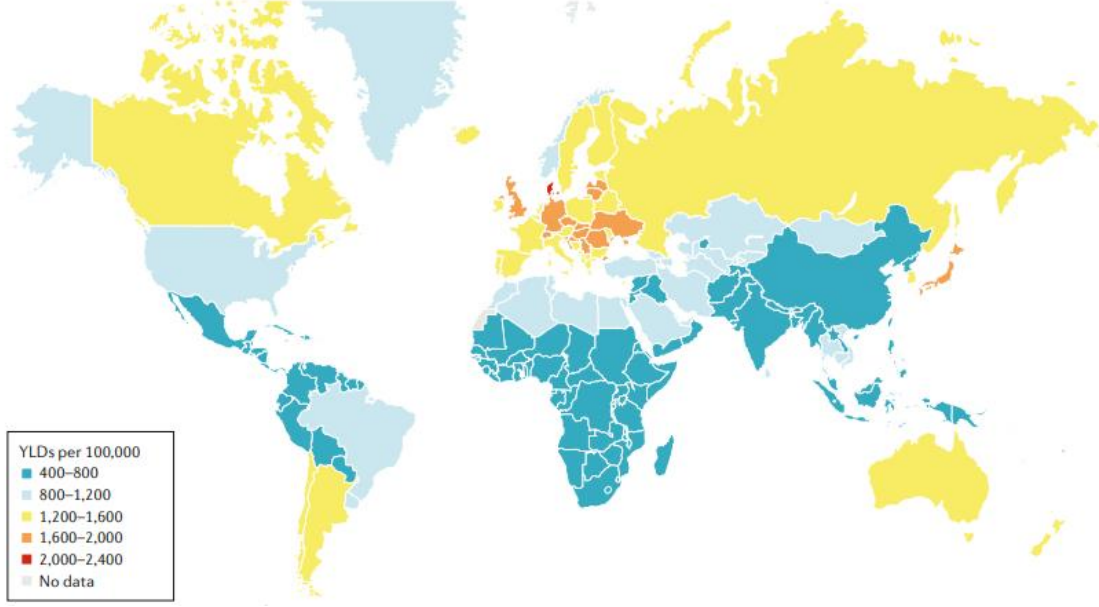

Figure 2. Years lived with disability for low back painSource: Vlaeyen et al., 2018 [12]

Intervertebral disc is largely avascular, hypoxia, low pH, high osmotic pressure and executes high mechanical load [13–15] and such an unique environment makes it challenging for the exogenous cell therapy to accomplish the objective i.e., treatment of IVDD. Though Minimally Invasive Spine (MIS) surgery is conducted for degenerative disc disease, it incurs heavy cost and the patient also suffers from physical and mental complications during the post-surgery period. At times, the surgical

complications also worsens the immune-mediated tissue damage [16]. In this background, a few researchers have proposed the development of non-invasive surgical methods to treat the IVDD [17]. Patients with IVDD can be treated via autologous reinfusion using the exosomes developed from the stem cells of the patients themselves, thus reducing the chances of immune rejection [17]. In literature [18], the exosomes developed from the CESCs (Cartilage Endplate Stem Cells) were involved in the treatment of IVDD.

In this background, the objective of the current review article is to provide an overview about the composition and the functions of Cartilaginous Endplates, development and the progression of the IVDD, application of modern techniques for its treatment etc. Due to the lack of a comprehensive review that provides holistic information about these topics, the current review has been conducted.

Biochemical composition of CEP

Various researchers mentioned that it is challenging to determine the biochemical composition of CEP in individuals, since it plays a vital role in degeneration and regeneration of the intervertebral disc [19]. Further, there is a lack of clear information exists about the relationship between the biochemical composition of CEP and the adjacent disc health or vertebral vascularity. However, the modern medical imaging techniques such as magnetic resonance imaging (MRI), especially the ultra-short echo-time (UTE) MRI, helps in determining the CEP T2* relaxation times that can decode the glycosaminoglycan (GAG) content, water content, and collagen-to-GAG ratio in the Cartilaginous Endplates [20]. The authors, in literature [21], recommended that MRI scanning is an appropriate tool to accurately identify the degeneration of CEP, its lesion locations and the type of its degenerative characteristics.

The endplates are made up of hyaline cartilage and are generally less than 1 mm thick [22]. According to [22,23], CEP primarily contains water (50-60%) [24], type II collagen and glycosaminoglycans (GAGs). The CEP has cartilaginous hyaline which encompass the top of the bony endplate that is combined with the central part loosely [21]. In addition to the type II collagen, CEPs contain type X collagen too [25] as it acts as a marker for hypertrophic chondrocytes and involves in the calcification process. The composition of the CEP tends to change based on age (reduction of proteoglycans) [2], while it's degeneration mitigates the transportation of nutrients and permeability [26]. The degenerated CEP contributes to the progression of low back pain as well as the degeneration of the disc [26]. In literature [27], it has been found that the CEPs with low T2* values have an association with high disc degeneration since the less CEPs correlate to high ratio of collagen-to-GAG, less hydration, low GAG content.

The substitution pattern of the chondroitin also changes with location and ageing of the individuals, in addition to the amount of GAG in CEP [28]. The study also found that the adult intervertebral disc had high quantity of Di-4S whereas in children, Di-6S was abundantly found.

In literature [29], the authors opined that the CEP's biochemical composition exerts a significant impact on the equilibrium tensile properties. The collagen to GAG ratio influences about 58% of the overall variations in equilibrium tensile modulus. This study also confirmed that the reduced tensile modulus has a relationship with low collagen content and collagen/GAG ratio. In literature [27], the authors made use of two advanced neural networks to conduct the automated tissue segmentation and non-invasively assessed the composition of CEP using a novel MRI biomarker (mean CEP T2*). The study found that in case of any deficits in the composition of CEP, in terms of low T2* values, it infers a severe degeneration of the disc.

IVDD – Overview and diagnosis and treatment methods

Low back pain is caused by increased synthesis of pain-causal factors like calcitonin gene-related peptide, aseptic inflammation and the vertebral endplate trauma. The degeneration of the intervertebral disc is commonly found within 10 years of life, according to [30]. Disc degeneration can be diagnosed at the early stages through the loss of proteoglycan. An imbalance between the matrix anabolism and catabolism results in the degeneration of the disc. When catabolic processes are excessively executed,

it activates the proinflammatory cell signalling processes which weaken and replace the matrix and the collagenous components [31]. Most disc degeneration issues are a result of matrix components getting destructed due to overexpression of the proteases such as matrix metalloproteinases (MMP) and ADAMTS. As mentioned earlier, cytokines are accountable for activation as well as regulation of these MMPs and ADAMTS and also its subsequent effects [32]. With increasing age [21], the vertebral endplate blood vessels get reduced whereas the CEP gets ossified and undergoes local calcification, as a result of injury, inflammation. However, changes in the mechanical environment does not induce calcification in the CEP [33]. These issues confine the permeability of the CEP which eventually results in insufficient nutrient supply and accordingly the dehydration of the intervertebral disc.

As per the study conducted earlier [21], the CEP undergoes natural, stress and damage-induced degeneration which has a heavy negative influence on weight bearing and its biochemical metabolism. The authors [34] opined that the Ca2+ content was found to be significantly higher in the CEP tissues that recorded disc degeneration. When the Ca2+ levels got increased, it reduced the secretion as well as the accumulation of type I, II collagens as well as the proteoglycan which are the important biochemical components of the CEP.

Those patients with Degenerative Disc Disease generally complain about mechanical lower back pain that gets worse on forward flexion and whenever they lift heavy load. In case of advanced IVDD, the spine shows morphological changes like the intervertebral disc bulge, disc herniation, facet hypertrophy and thickening of the ligamentum flavum which results in spinal stenosis and neural compression [35]. Some of the techniques that are useful in the diagnosis of IVDD include Plain roentgenogram, Magnetic Resonance Imaging (MRI), Computer Tomography, Diffusion-weighted imaging, biomarker-based assessment using type II collagen, Chemokine (C-C motif) ligand CCL5 and Cartilage Oligomeric Matrix Protein COMP and so on.

Medical professionals can gain knowledgeable insights from the evidence-based predictive analytics can improve preoperative patient selection, surgical indications and individualized postoperative care [36]. Though the application of ML/AI is still in a nascent stage, the domain's true potentials are yet to be tapped which can positively reduce the surgeon fatigue and improve technical precision. In literature [37], the authors successfully determined the degeneration of intervertebral disc endplate (DIDCE) using the Magnetic Resonance-Ultrashort Time of Echo (MR-UTE) imaging technology in line with Convolution Residual Network (CRN) algorithm.

Various treatment options are available for IVDD [38] such as the physical therapy, anti-inflammatories and analgesics i.e., non-surgical (based on non-intrusive pain) for early stage [39], surgical procedures (Decompression, Fusion, Motion preservation and Deformity), scaffolds and support matrices, injectable biomaterials (growth factors such as Bone Morphogenic Proteins (BMPs) and Transforming Growth Factor-beta (TGF-β) members [40,41], recombinant protein copolymer [42], platelet-rich plasma [43], exosomes etc., Figure 2 shows different treatment methods available. In addition to these, the literature has a number of studies with a prominent strategy to treat the IVDD include the prevention of cell loss due to excessive PRCD by targeting the mRNAs [44], ncRNAs [45], hormones [46], proteins related to PRCD [47], autophagy [48] and cellular homeostasis [49] or utilizing vitamins [50], natural compounds [51] and traditional Chinese medicine [52].

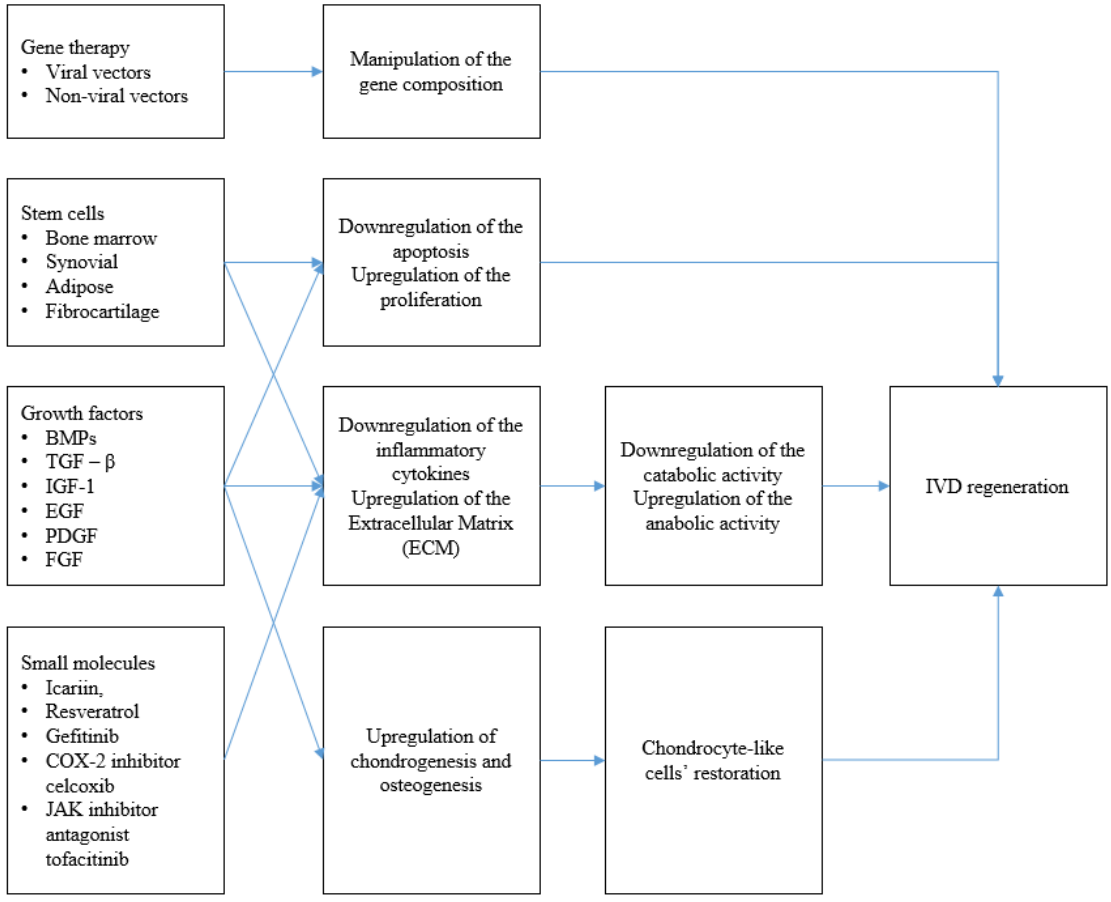

Figure 2. IVDD treatment mechanisms Source: Romaniyanto, 2022 [39]

In a study conducted recently [8], the researchers found that the degenerative NP cells-derived exosomes aggravate the apoptosis of CEP cells, downgrade the synthesis of ECM (Extracellular Matrix) and boost the degeneration of IVD as well as ECM. Though the mechanisms are still unclear, various studies [53–56] confirm the active role played by CESCs in the inhibition of IVDD by promoting the regeneration of NPCs and the regulation of the homeostasis of the intervertebral disc. In literature [57], it has been observed that the *in vitro* human disc cells develop cytokines and inflammatory responses, when exposed to high tension as a result of intervertebral disc degeneration. From bio-mechanical point of view, it is possible to regenerate the disc under appropriate pressure and load distribution within the disc [2]. In the study conducted earlier [58,59], the researchers evaluated the potentials of regulating the IVD cell apoptosis pathways such as the death receptor pathway, mitochondrial pathway and the Endoplasmic Reticulum Stress (ERS) pathway to treat the IVDD, while the preliminary animal and cell experiments proved to be effective. However, there is a need to establish the effectiveness of the proposed models in clinical applications. In literature, it has been found that, in addition to apoptosis, other types of cell deaths such as necroptosis, pyroptosis, and ferroptosis play an important role in IVDD.

CONCLUSION

The current study provides an overview on the biochemical composition of CEP and its role upon the vertebral health. IVDD has become a public health phenomenon incurring heavy cost on the governments and the individuals across the globe. Various methods, of both invasive and non-invasive types, are available to diagnose the disease at its early stages. While the genomic-cellular therapies are still in a nascent stage, with studies already proved to be successful in *in vitro* and animal modes, novel research has to be conducted to improve the results for human beings as well. The discs under stress

must be diagnosed at early stages and the degenerated ones must be treated with hybrid approaches based on the stage of the disease to ensure that the patient is provided an appropriate, non-invasive, cost-effective treatment. Advanced cell therapy, non-invasive diagnostic and treatment methods, targeted drug delivery and Artificial Intelligence (AI) and Machine Learning-based surgical treatments must be leveraged in the course of action. Further, research is needed to develop new tools for diagnosing painful discs that require cell therapy, to develop alternative pathways to eliminate the nociceptors growing in painful discs, to further understand the fate and action mechanism of the transplanted cells and to restore the mechanical environment of degenerate discs without affecting the adjacent cells.

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