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Degenerative disc disease: analysis of treatments, tissue, and market

Abstract

The prevalence of intervertebral thinning discs and the degradation of spinal discs as a whole has created a new market and area of research to find a solution to this age-related problem. The loss of the cartilage cushioning two vertebrae is called degenerative disc disease, or DDD. DDD can impact a patient's quality of life greatly – putting them in severe pain, limiting mobility, and decreasing their ability to perform daily activities. The market for DDD treatment shows promising growth, both globally and in the US. Most of the drugs and devices that are currently on the market aim to alleviate pain or reduce inflammation, addressing the symptoms of DDD rather than regenerating the lost disc tissue. However, there are many new treatments that are in development or are being tested in clinical trials that could satisfy this need. In the context of tissue engineering, regeneration of the intervertebral disc is a prime target. A scaffold could fulfill the need for mechanical support in between the vertebrae and growth factors and cells could stimulate the regrowth of the injured tissue.

Keywords: Degenerative disc disease, Market analysis, Intervertebral disc, Tissue engineering, Pain management, Regeneration

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Abbreviations: DDD, degenerative disc disease; CAGR, compound annual growth rate; Nonsteroidal anti-inflammatory drugs (NSAID); Cyclooxygenase (COX); Intradiscal electrothermal therapy (IDET); Bone marrow concentrate (BMC); Adipose-derived stem cells (ADSCs); Nucleus pulposus cells (NPCs); nucleus pulposus mesenchymal stem cells (NPMSCs); Platelet-rich plasma (PRP); Mesenchymal stem cells (MSCs)

Introduction

To be able to discuss degenerative disc disease, it is essential to have an understanding of the disc anatomy. Figure 1 is a diagram labeled with the main components of this cartilage. In the context of thinned discs, the classification is defined based on what part of the disc anatomy is affected. In one condition, thinning is caused by the necrosis and loss of moisture in the nucleus pulposus. Here, the cartilaginous plate and annulus fibrosus remain healthy. In contrast, the other type is characterized by rupture of the annulus fibrosus or numerous defects in the cartilaginous end-plate. As both types are caused by desiccation as aging occurs, this review will refer to them as the collective condition called intervertebral thinning disc.[1]

The symptoms caused by this thinning arise mostly from the compression of nerve roots around the disc.[2] One condition that can develop as a result of thinning is lumbar foraminal stenosis.[3] In this disease, patients experience a variety of symptoms, including back pain, paresthesias, weakness, limited lumbar extension, among others. In many cases, patients will need to get spinal decompression surgery, which brings about limited results.[4] Another degenerative disease that can occur as a result of thinned discs is spondylosis. The cartilage cushioning two vertebrates can wear away, promoting the formation of bone spurs and subsequent friction between them. Patients afflicted with spondylosis may experience pain, numbness, headaches, trouble keeping balance, and much more.[1] These diseases, among others, can be broadly referred to as degenerative disc disease (DDD). Because many people will experience thinning discs with age, there is a large impetus to find solutions to alleviate the pain associated with this condition and improve quality of life. In this review article, we will be discussing the nature of the market for degenerative disc disease treatments, as well as existing and developing products.

Healthy tissue

The main purposes of the intervertebral discs are to absorb the shock applied on the spine throughout the day, facilitate movement between vertebral bodies, and propagate the loads throughout the spinal column.[5] As with all tissues, the structure of the intervertebral disc provides its function. Figure 1 depicts a labeled structure of the anatomy of the cartilage. The nucleus pulposus is found at the center of the disc and has type II collagen, water, and proteoglycans as the main components. The cells (although sparse) within the disc deposit ECM molecules and provide the strength and flexibility of the nucleus pulposus.[6] Based on histology, nucleus pulposus cells have a similar spherical morphology to chondrocytes.[7] Surrounding the nucleus pulposus is the annulus fibrosus.[6] It is made out of highly organized fibrous connective tissue. The specific configuration of collagen within this part of the disc provides additional strength. Outer annulus fibrosus cells are densely packed and have a similar elongated morphology to fibroblasts.[7] In contrast, the inner annulus fibrosus cells are more chondrocyte-like. Another major part of the intervertebral disc is the cartilaginous endplate. Found between the vertebral endplate and nucleus pulposus, this structure is a mechanical barrier and a path for nutrients to diffuse into the disc.[2]

Within the entirety of the spine, the cross section of the disc will vary depending on what region it is located in. Figure 2 breaks down the three regions of the spine. For a thoracic disc, the force of torsion will be evenly distributed due to its circular geometry, allowing the vertebrae to withstand larger loads. For a lumbar disc, the cross section is shaped like an ellipse. This allows for the discs to withstand any bending movements. The cervical discs have the smallest area, as they have the smallest load to support.[5] The vasculature (or lack thereof) is another characteristic distinguishing the different parts of the cartilage. There are blood vessels on the periphery of the disc that supply blood to the outermost parts. In contrast, the supply of blood to the majority of the disc is achieved via diffusion through nearby vertebral surfaces.[8]

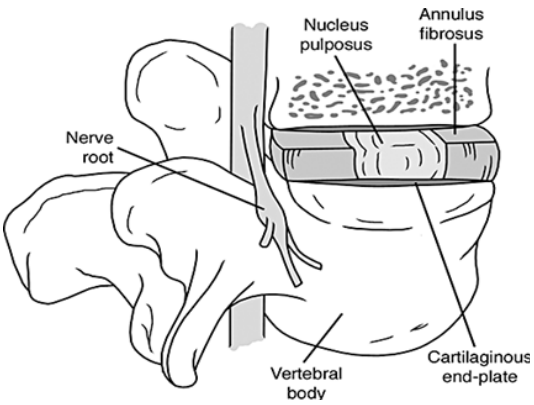

Figure 1 Diagram of the anatomy of the intervertebral disc.[42] The components of the cartilage are the nucleus pulposus, annulus fibrosus, and cartilaginous end-plate.

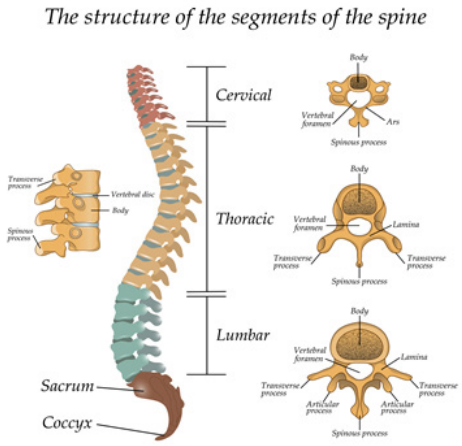

Figure 2 Overview of the spinal structure.[43] The spine can be broken down into 3 major regions: the cervical, the thoracic, and the lumbar.

Healthy discs are innervated, and these nerves are responsible for the pain associated with injuries to the spine. The sinuvertebral nerve is connected to the spinal nerve and the sympathetic nervous system. In addition, there are complex nerve endings in the posterior longitudinal ligament, the anterior longitudinal ligament, and the annulus fibrosus. Figure 3 shows the locations of all of these ligaments. An interesting property of these nerve roots is the difference in the anatomical position within the lumbar and thoracic regions. Nerve roots in the thorax are lateral to the disc and run along the top surface. This difference in anatomy may explain why pain in the lumbar spine is more common than pain in the thorax.[8]

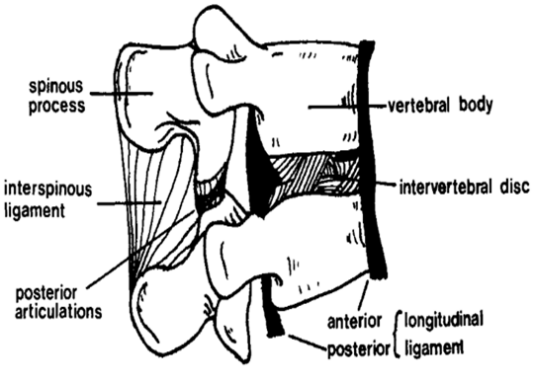

Figure 3 Labeled diagram of the vertebral unit.[8] The anterior and posterior longitudinal ligaments contain a network of nerve endings.

Healthy discs will contain water and maintain a constant level of osmotic pressure. Other main constituents include collagen, elastin, and aggrecan.[9] Collagen fibers are found in the ECM of connective tissues and are insoluble[7]. They provide strength to tissues.[7] Similarly, elastin fibers are found in the ECM of connective tissue. Their main function is to bring elasticity and resilience.[10] Aggrecan is a type of proteoglycan that is responsible for the cartilage's ability to resist changes under compression.[11] Within the ECM, the aggrecan molecules are found in aggregates, interacting with hyaluronan and a stabilizing link protein.[12] In disc degeneration, these components are cleaved.[11]

Diseases

This review focuses primarily on degenerative disc disease (DDD), an ailment in which the cartilage in the vertebral unit wears down and loses hydration over time. This is a normal part of aging – as such, a wide portion of the geriatric population suffers from the symptoms. The loss of cartilaginous tissue causes pain and other symptoms that greatly decrease quality of life.[13] Most commonly, this pain is continuous and low in intensity with occasional flare-ups into high intensity pain.[14] Another symptom is numbness and/or tingling in the extremities. If there is damage to the nerve root, the patient may experience weakness in the legs or feet.[3] With the spinal instability caused by DDD, the patient may notice an inability for the neck and/or back to provide basic support to the rest of the body. This spinal instability can also result in muscle tension or muscle spasms.[14] The risk factors for DDD are alcohol use and smoking, as both activities impair the body's ability to absorb calcium. Obesity and a family history of diseases of the spine also increase the likelihood of DDD. If the patient performs heavy physical labor, excessive loads are applied onto the spine and puts them at risk for developing the disease.[12]

There are some other spinal diseases that are associated with DDD and may even be caused by it. Bulging discs occur when the nucleus pulpous protrudes into the annulus fibrous space. The patient will be asymptomatic until the disc begins to press on a nerve. When the nerve is compressed, the symptoms are dependent on the location of the bulged disc and the magnitude of compression. If the disc is in the cervical spine, the patient will experience pain, tingling, numbness, and weakness. If the disk is in the thoracic spine, the pain will mostly be felt in the back. In some cases, the pain migrates to the stomach and the chest. A bulging lumbar disc leads to pain in the hips, legs, buttocks, and feet. There are various causes for a bulging disc. Relating back to DDD, aging and the general degeneration of discs can be the precursor to this injury. If the annulus fibrosus is weak, it will be easier for the nucleus pulposus to permeate through. Spinal trauma associated with automobile accidents and sports injuries are also a cause. A person with poor posture and improper or heavy lifting can also bring about bulging discs. Obesity, physically demanding jobs, and genetics are also risk factors.[15]

A herniated disc is a similar pathology to a bulging disc and can also result from DDD. It is a more extreme case, as the nucleus pulposus tears the annulus fibrosus and sticks out from the outer boundary of the cartilage. Most patients are asymptomatic, and those that do experience symptoms find that they improve over time. The affected disc is most often in the lumbar spine. In most cases, the injury can cause arm or leg pain, numbness or tingling, and weakness. In a more serious form of a herniated disc, the symptoms mentioned previously worsen so much that daily activities are impacted. Patients may also experience bladder or bowel dysfunction, struggling with incontinence or difficulty urinating. Another severe symptom is saddle anesthesia. In this affliction, people progressively lose sensation in the inner thighs, back of the legs, and the area around the rectum.[16]

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Market analysis

Disc degeneration is considered a normal part of aging – studies have shown that approximately 30% of people will have some level of disc degeneration by the age of 35. By 60, more than 90% of people will show evidence of degeneration. Although these numbers represent both painless degeneration and degenerative disc disease (DDD), any defect in the cartilage between two vertebrates has the potential to cause pain and other symptoms.[17] Globally, the market for DDD treatment (which includes treatment for intervertebral thinning discs) was valued at $27.87 billion in 2022. The market is projected to grow steadily, increasing to $45.92 billion by 2029.[18] The Compound Annual Growth Rate (CAGR), which is a metric of an investment's annual growth rate, has been calculated as 9% for 2020-2025.[19] Market demand is driven by the increasing rate of growth of the elderly population. This growth creates a greater need for solutions, as there is a higher prevalence of bone degenerative diseases in geriatric patients. In terms of market size by geography, North America has the largest share of the DDD treatment market. Figure 4 shows the DDD market broken down further into geographical regions. The North American market can be broken down further into the United States and Canada. Figure 5 shows the DDD market size for the United States only.[20]

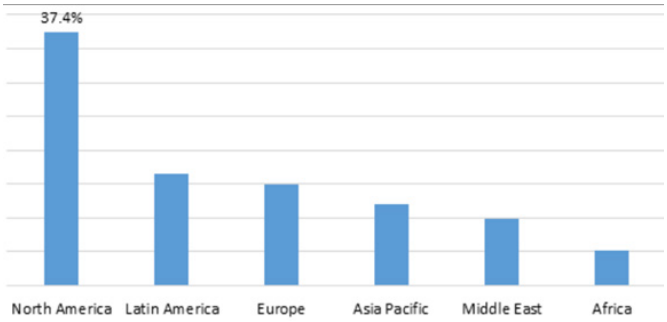

Figure 4 Share of DDD market.[44] This graph shows what percentage each region holds of the market. North America accounts for the largest segment.

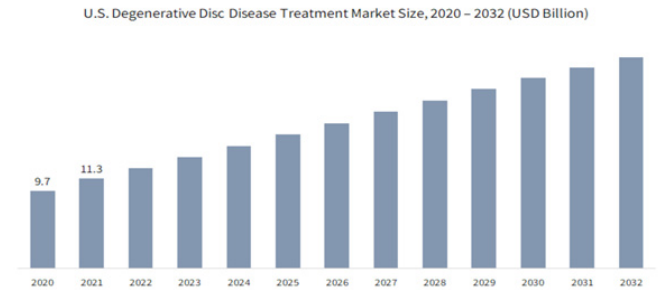

Figure 5 DDD market size in the United States.[20]

The market has been divided into two different types of products: drugs and devices.[21] Figure 6 depicts this segmentation and the share taken up by each. In 2022, drug treatment accounted for more than 51% of the market and is forecasted to have steady growth. The market can also be segmented into end-users; specifically, hospitals, clinics, and others. Figure 7 provides a visual of this market segmentation.[20] The key leaders in the DDD treatment market globally include Novartis AG, Pfizer Inc., and Eli Lilly and Company.[11]

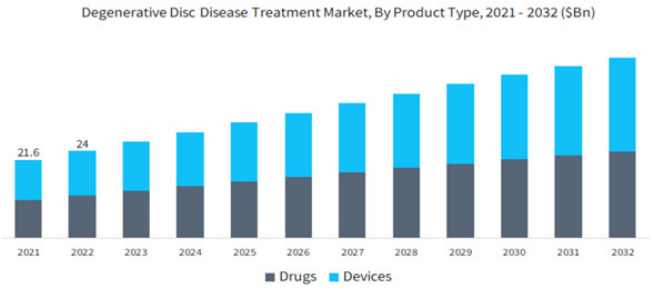

Figure 6 Segmentation of the DDD market by treatment.[20] Drugs alleviating symptoms associated with DDD account for the majority of the market.

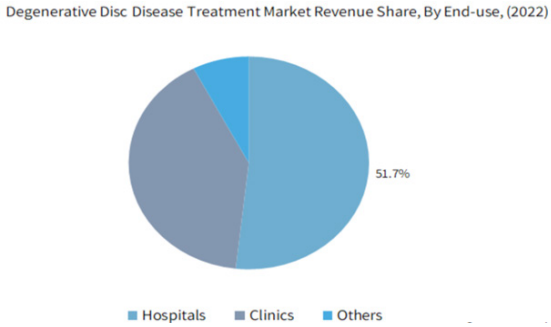

Figure 7 Segmentation of the DDD market by end-user.[20]

Existing products

Many of the products on the market to treat DDD are focused on pain management. To alleviate some of the back pain caused by a thinned disc, there are multiple over-the-counter medications patients can take.[22] These treatments fall into two main categories: nonsteroidal anti-inflammatory drugs (NSAID) and pain relievers.[23] Acetaminophen is a common example of a pain reliever. It works by blocking the brain's perception of nerve pain signals. It does not reduce inflammation.[4] Aspirin, ibuprofen, and naproxen are common types of NSAIDs. NSAIDs block an enzyme called cyclooxygenase (COX). COX mediates the production of prostaglandins, which contribute to inflammation and pain.[24]

Medications for DDD can also be prescribed if symptoms are more severe. These include antidepressants, muscle relaxants, neuropathic agents, narcotics, and prescription NSAIDs.[4] Antidepressants target and lower the perceived pain associated with DDD, alongside psychological effects. In low doses, these medications may not have an effect on the patient's mood. In higher doses, antidepressants may serve two functions: pain relief and treatment of depression.[25] Muscle relaxants relieve the pain caused by muscle spasms, a common result of chronic back pain.[4] These medications are usually prescribed for a short period (5-7 days).[23] Neuropathic agents are used to treat neuropathic pain, which is caused by damage to nerve fibers and results in overactivity.[26] Narcotics attach to pain receptors in the brain and block signals from nerves. They have more serious side effects, such as making the patient sleepy and confused.[27] The prescription NSAIDs are stronger than their over-the-counter counterparts. A doctor may recommend them if the over-the-counter medications are not providing sufficient relief.[4]

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Treatments may also come in the form of injections to the spine. In an epidural injection, corticosteroids are injected into the fluid-filled area surrounding the spinal cord called the epidural space. Corticosteroids reduce inflammation around the nerves and the spinal cord.[28] These steroids are very strong and require a professional to execute the injection under fluoroscopy. This treatment can have severe side effects, and patients may need two or three injections.[4] Another type of injection is the facet joint injection. Similarly to the epidural, it administers corticosteroids and relieves inflammation. The injection targets the facet joints (joints of the spine).[28]

Intradiscal Electrothermal Therapy (IDET) involves the gradual heating of an electrode placed into the damaged disc in order to reduce the bulge of inner disc components. Small tears in the disc wall are sealed and the heat destroys painful nerve endings. IDET is an outpatient procedure.[29]

For more extreme cases, patients with DDD can undergo surgical procedures for treatment. In spinal fusion, surgeons will first perform a discectomy, which removes the defective part of the disc. The vertebrae above and below the disc space are permanently joined. This eliminates movement and can alleviate pain.[30] It is common for autografts to be used in spine fusions since they can promote bone growth.[48] Most patients will be able to walk the next day after the procedure. For those younger than 65, artificial disc replacement may be the better alternative to spinal fusion. In this surgical procedure, a disc made out of synthetic material is inserted between two vertebrae. This preserves spinal flexibility and stability without any screws or plates required to keep it in place. This disc replacement procedure may be able to provide better long-term results and fewer complications compared to spinal fusion.[30] Table 1 provides a summary of all of these existing products and procedures.

Table 1 Summary of existing products and procedures to treat DDD [4,23–30]

Treatment	Method	Advantages
Pain relievers[4]	Taken orally. Over-the-counter.	Helps treat pain flare ups from DDD. Easily accessible.
NSAIDs – over-the-counter[24] and prescribed[4]	Anti-inflammatory and relieves pain. Taken orally.	Helps treat pain and addresses inflammation from DDD.
Antidepressants[25]	Pain reliever. May also reduce feelings of depression depending on the dosage.	Helps treat pain and can help patients sleep better (a major concern for those in chronic pain). Can bring a beneficial psychological effect.
Muscle relaxants[23]	Relieves the pain associated with muscle spasms.	Need to be taken for a short period of time. May help patients sleep better.
Neuropathic agents[26]	Targets the nerves.	Generally tolerated well – makes this medication suitable for chronic back pain.
Narcotics[27]	Prevents pain signals from reaching the brain.	Strong relievers of pain.
Spinal Injections[4,28]	Administered via injection. Injects corticosteroids into the spine.	Done in one or a few sessions. Reduces inflammation and pain
Intradiscal Electrothermal Therapy[29]	Outpatient procedure. Uses the heat from electrodes to provide pain management.	Reduces pain and prevents small tears in the damaged disc from propagating. Minimally invasive. Meant for patients that have not seen results from other treatments.
Spinal Fusion[30]	Surgical procedure that brings vertebrae back to their original positions and fuses them together.	Alleviates pain. Addresses the root cause: loss of cartilage.
Artificial Disc Replacement[30]	Surgical procedure that inserts a synthetic disc into the area where the degenerated disc once was.	Addresses the root cause: loss of cartilage. Long-term solution. Relatively short recovery time. Less complications than spinal fusion.

Products in clinical trials

Within the US, many researchers are coming up with solutions for DDD and putting them through clinical trials to be able to market them. There are a large majority that have been withdrawn or terminated, but others are being tested in one of the phases or have already completed clinical trials. Many of these potential products employ tissue engineering principles and revolve around creating a device that can be implanted into the body during spinal fusion. ViviGen Cellular Bone Matrix is in Phase IV of clinical trials and is being tested as a bone graft for spinal fusion.[31] ViviGen is a cellular allograft that is already on the market for foot/ankle injury, but has not yet been verified for use in the spine. It contains osteoblasts, osteocytes, and bone lining cells. The corticocancellous bone matrix provides a scaffold that promotes cell attachment, migration, and proliferation. The demineralized bone exposes natural growth factors in the scaffold that can stimulate bone formation.[32] BioSurface Engineering Technologies, Inc has a product currently in Phase II called Prefix (AMPLEX) B2A Peptide Enhanced Ceramic Granules. This is a ceramic bone scaffold that carries a growth factor called B2A. The product is meant for use in spinal fusion.[4] Kuros Biosurgery AG has a product in Phase II called the KUR-113 Bone Graft. This device is TGplPTH1-34 (a synthetic hormone that assists in the formation of new bone) in fibrin and is designed to improve upon the use of autografts in spinal fusion procedures.[33] Intradiscal delivery of bone marrow concentrate (BMC) is currently in Phase III of clinical trials. BMC injection is meant to use bone marrow in order to heal the degenerated disc tissue, reducing pain and reviving function.[34] The Wallis system (an interspinous process implant) is in Phase III of clinical trials. The studies aim to show that the Wallis system is equivalent to total disc replacement in the treatment of DDD and to evaluate its ability to relieve the back pain associated with DDD.[35] Table 2 summarizes these devices currently in clinical trials.

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Table 2 Summary of products designed to treat DDD in clinical trials[4,31,33–35]

Product	Company/group running the study	Potential advantages	Potential disadvantages	Clinical trial phase
ViviGen Cellular Bone Matrix[31]	DePuy Synthes and Ohio State University	Cheaper than an autograph for spinal fusion procedures. Various components that make the device osteogenic, osteoconductive, and osteoinductive.	Could become immunogenic. May not be suitable long term.	4
Prefix (AMPLEX) B2A Peptide Enhanced Ceramic Granules[4]	BioSurface Engineering Technologies, Inc.	Cheaper than an autograph for spinal fusion procedures. Contains a growth factor that can mediate bone growth.	Does not contain any cells – therapeutic benefits may not last long. Ceramic material may be incompatible with surrounding native tissues.	2
KUR-113 Bone Graft[33]	Kuros Biosurgery AG	Cheaper than an autograph for spinal fusion procedures. Contains a synthetic hormone that can promote bone growth. Fibrin material is biocompatible with the surrounding tissues.	Does not contain any cells – therapeutic benefits may not last long.	2
Intradiscal delivery of bone marrow concentrate[34]	Stem Cures	Uses bone marrow in order to heal the degenerated disc tissue, reducing pain and reviving function.	Variability in therapeutic outcome due to the nature of stem cells and how they will interact with the patient's body.	3
Wallis system[35]	Zimmer Spine	Equivalent to total disc replacement in the treatment of DDD and to evaluate its ability to relieve the back pain associated with DDD. Cheaper than total disc Replacement.	The device is made out of polyetheretherketone (PEEK). This material may be insufficiently compatible with surrounding tissues.	3

Products in development

Current DDD research focuses more on the innovation in the device side of the market. Many of them aim to regenerate the lost intervertebral tissue. One research group was able to achieve partial regeneration of the nucleus pulposus *in vivo*. They created a scaffold called a nucleus pulposus cell-derived efficient microcarrier (NPCM) and seeded it with adipose-derived stem cells (ADSCs). The nucleus pulposus cells (NPCs) synthesize and deposit chondroitin sulfate and type II collagen. These ECM components regulate the NP-specific differentiation of stem cells; as such, the microcarrier promotes the differentiation of ADSCs into NPCs. However, NPCMs are microspherical bioscaffolds that do not possess the proper mechanical properties to support the vertebrates. More work needs to be done to improve these properties such that the scaffold can be used as a regenerative treatment for the intervertebral discs.[36] Another proposed strategy for tissue restoration is *in situ* 3D printing using silk fibroin (a natural fibrous protein commonly used to form 3D porous structures). The silk hydrogels, once enzymatically cross-linked, were determined to have good mechanical properties and stability. The process is also tunable and the gels induce cell adhesion, migration, and differentiation. Again, this study is recent and significant clinical evidence must be procured before this treatment can come to market.[37] A product in development termed BIOGEL (bioorthogonal hydrogel) is an injectable gel that can be encapsulated with growth factors to regenerate discs. The aim of BIOGEL is to satisfy requirements for complete regeneration that are not being satisfied by current scaffold technology. These include biodegradability, noninvasive injection, recapitulated healthy intervertebral disc biomechanics, predictable crosslinking, and matrix repair induction. In this BIOGEL study, the researchers were looking at the behavior of the device in an *in vivo* rat intervertebral disc degeneration/nucleotomy model; therefore, more studies and clinical trials must be conducted for BIOGEL to be a product on the market.[38]

Some of these scaffolds are designed to release drugs in a controlled manner over a period of time in order to regenerate the disc. One such gel encapsulates antagomir-21 in an injectable self-strengthening hydrogel delivery system. Antagomir-21 is an inhibitor of miRNA-21 and has the ability to regenerate the ECM; however, antagomir-21 on its own has limited applicability for treatment of degenerated intervertebral discs. With the hydrogel delivery system, the release of the drug into the nucleus pulposus is controlled and sustained via a three-stage mechanism. The device was able to alleviate local inflammation, regulate the metabolic balance in the ECM, and restore the tissue functions lost to the degradation. The results of this study were determined from testing in an *in vivo* rat mode. Although the hydrogel showed a lot of promise in the animal model, it also needs to undergo rigorous clinical testing in order to prove safety and efficacy.[39] Another gel is used specifically for interbody spinal fusion. It is a biodegradable polymer that releases bone morphogenetic protein 2 (BMP-2) over a period of one month. BMP-2 is a protein that activates osteogenic genes. This gel is an example of a regenerative matrix, a controlled biomaterial that creates optimal conditions promoting high quality tissue formation. To achieve this environment, researchers employ principles in surface chemistry, materials architecture, and drug delivery kinetics. To validate this system, the researchers performed both *in vitro* tests and *in vivo* tests in rabbit models. Similarly to the other scaffolds in development, this matrix would need to undergo much more rigorous testing.[40]

In addition to the research being conducted on how to make implantable scaffolds, some of the research on DDD focuses on identifying the compounds responsible for the promotion of degradation. One of the main driving forces leading to the degeneration of intervertebral discs is excessive oxidative stress. In a study conducted by Zhou et al., the antioxidant Fisetin was found to reduce levels of apoptosis and inflammation of nucleus pulposus mesenchymal stem cells (NPMSCs) caused by oxidative stress *in vitro*. They also found that inhibition of an enzyme called SIRT1 may decrease the effect Fisetin has on NPMSCs, making SIRT1 a potential therapeutic target. Although more studies need to be conducted to further understand this pathway, Fisetin and SIRT1 expose a potential new method of treatment for DDD.[41]

Other research has analyzed platelet-rich plasma (PRP) treatment as a way to combat the degeneration of a disc. PRP is an autologous source of growth factors and cytokines and has been used before in the

treatment of musculoskeletal diseases. This treatment has the potential to promote tissue regeneration and has even been used in clinics for spinal diseases. More basic studies need to be conducted, but current scientific evidence suggests that intradiscal injection therapy of PRP is safe and effective.[9]

Conclusion

In this review, we took a comprehensive look at the market size/trends, existing products, and products currently being tested for the treatment of DDD. With the need to improve the quality of life for people with thinning discs (and with any other condition that would lead to the degradation of the intervertebral disc), the market shows healthy growth and will continue to increase in size. The existing products available for DDD treatment are mostly drug related and are pain management measures. Some are over-the-counter and are milder in nature. Others are prescription and must be taken in low dosages to prevent serious side effects. Beyond drug treatments, there are surgical procedures (spinal fusion, artificial disc replacement, etc.) available that will attempt to solve the problem at the root cause. These have high costs and higher risks, but may provide long term relief.

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Conflicts of interest

The author declares that there are no conflicts of interest.

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