Discogenic Pain Relief by Re-Establishing Fluid Exchange between Disc and Circulation

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Abstract

Background: Discs are avascular oxygen and nutrients are diffused from capillaries in endplates into thick discs. Calcified layers begin to fortify the cartilaginous endplates around age 16, (1) Blocking many capillaries, (2) Reducing diffusion depths, (3) Causing starvation and hypoxia in the mid-disc layer. Starvation triggers enzymatic degradation of proteoglycans in mid-disc layer, leading to desiccation and voids in nucleus, and fissure in annulus. Hypoxia triggers production inflammatory cytokines and lactic acid, leading to pH 5.5-6.5 in mid-disc layer, 5-50X acidity of blood plasma. Lactic acid leaks through the annulus fissure to cause discogenic pain from lactic acid burn, as shown in figure. Conversely, discs matrices near superior and inferior endplates are in the diffusion zones of bicarbonate (pH buffer), oxygen and nutrients from body circulation, and have neutral pH 7.2.

Proposed intervention: Percutaneous Disc Scaffold (PDS) is a multi-spiral fluid absorbing filament, a braided nylon #3 suture, for bridging diffusion zones near superior and inferior endplates to re-establish interstitial fluid exchange between the mid-disc and body circulation. Bicarbonate in blood plasma neutralizes the lactic acid. Oxygen inhibits hypoxic inflammation and is essential to biosynthesize the most water-retaining chondroitin sulfate in proteoglycans. Constant supply of nutrients relieves starvation.

Methods: In-vitro and in-vivo studies are used to verify the intended use, safety and efficacy of the PDS. (1) Fluid transport through the #3 braided nylon sutures is verified by capillary action of drawing pork blood. (2) Lactic acid neutralization is verified by titration with fresh pork blood. (3) Safety is verified in sheep discs by histology on tissue response at euthanized time point 1, 3, 12 and 30 months. (4) Efficacy is verified in a pilot clinical study after confirming discogenic pain. PDS is implanted through the discography needle. Visual Analog Pain Score (VAS) and Oswestry Disability Index (ODI) are used to evaluate therapeutic efficacy of PDS at 1-week, 3-12 and 24-months.

Results: (1) Fluid transport through the #3 braided nylon sutures as PDS is demonstrated by capillary action of drawing pork blood 10.3 ± 1.2 cm against gravity. (2) Approximately 0.51-1.51 cc of pork blood is required to neutralize 1 cc of 2-6 mM lactic-acid, common concentration in painful disc. (3) PDS is inert, elicited no immune response in sheep discs euthanized at 1, 3, 12 and 30-months. (4) Baseline or pre-PDS VAS was 6.1 ± 1.6, and 2-Year VAS after PDS is 1.2 ± 0.7. Baseline ODI was 37.9 ± 15.1%, and 2-Year ODI is 9.8 ± 5.1%.

Conclusion: Acid-base neutralization is instantaneous, which may be the reason for rapid reduction of discogenic pain from lactic acid burn.

Keywords: Discogenic pain; Lactic acid; Endplate; Bicarbonate; Oxygen; Nutrient; Percutaneous Disc Scaffold (PDS); Re-establish fluid exchange

Key points

- Percutaneous Disc Scaffold (braided nylon suture) transports blood through capillary action.
- Daily fluid circulation is sufficient to neutralize lactic acid in painful disc.
- No immune response to the PDS within intervertebral discs of sheep.
- Significant discogenic pain relief by 1-week, and beyond 2 years after implanting PDS.

Introduction

Approximately 85% back pain patients show no impingement [1-3] but nearly all have one or more desiccated disc under MRI. It is generally recognized that shallow diffusion of oxygen and nutrients from cartilaginous endplates into avascular discs causes mid-layer hypoxia and starvation, leading to progressive disc degeneration [4-16]. Degenerated discs show an average 48% decrease in proteoglycans, 8% decrease in water content, 2-26X increase in acidity, compared to none painful discs [17-19]. In addition, proteoglycans in healthy nuclei are gelatinous, but degenerated nuclei become fibrotic, porous or nearly hollow. Painful discs contain high concentration of lactic acid [17,18,20-23] (Figures 1-3).

Discography is used to diagnose discogenic pain by injecting X-ray contrast into a desiccated disc. Intradiscal injection usually is painless when X-ray contrast remains in the nucleus; but when the contrast...
chondroitin sulfate, keratan sulfate and hyaluronate in proteoglycans to feed starving disc cells. Lactic acid is produced through anaerobic metabolism and accumulated in the mid-layer of degenerated discs. Discogenic pain gradually subsides with age, probably due to depletion of sugars in proteoglycans, leading to diminished production of lactic acid [24-27].

However, sugars in disaccharides are responsible for retaining water to sustain compressive load on the disc. Depletion of sugars in proteoglycans desiccates and flattens the disc; average disc space narrowing is 3% annually [28-30]. Load is transferred from thinning disc to facet joints, causing erosion and pain [31-33]. Facet pain is common after age 55, inflicting pain in 15-40% back pain patients [26,27,29,30]. Origins of pain seem to be sequential with progressive disc degeneration; from discogenic to facet pain [28-33]. Continual disc flattening and facet erosion lead to spinal instability and/or stenosis.

Methodology

In-vitro methods

According to animal and human studies, nylon sutures are most biocompatible [34-42].

- Capillary action is used to evaluate fluid transport capability. One end of the braided #3 nylon suture is submerged in pork blood. Height of capillary action is measured in 0.5, 1.0, 1.5 and 2.0 hour.

- Lactic acid titration with fresh pork blood is used to evaluate amount of blood needed for lactic acid neutralization. Common concentration of lactic acid in painful discs is 2-6 mM [43]. Fresh pork blood is loaded in a 20cc syringe with an 18G needle, slowly dispensed into 10 cc of magnetic stirring 2, 4 or 6 mM lactic acid solutions. The blood syringe is weighed and pH of the stirring lactic acid solution is recorded after each dispensing, until pH 7.14, which is the average acidity found in none painful discs. 17 Titration curve is plotted, cc of fresh blood vs. pH of lactic acid solutions.

In-vivo methods

Thirty-six skeletally matured sheep approximately 3 years old, weighing between 165-210 pounds (75-96 kg), are used to evaluate biocompatibility of braided nylon suture as PDS inside and outside the intervertebral discs. Pre-anesthetics, anesthetics and sedatives are valium 7.5 mg IV, midazolam 0.1 mg/kg IV, ketamine 4 mg/kg IV, isofluorane 1.5-3% inhalation and oxygen 2 L/minute. Post-surgical analgesia is 10 mg and 5 mg fentanyl patches for 3 days, phenylbutazone 1 g oral pre- and 3 days post-op, and morphine 2-4 mcg/kg/hour IV. Antibiotics are cefazolin sodium 1 gram IV at induction of anesthesia, midway through the surgery and during closure, procaine penicillin 3 million units intramuscularly, once daily for 3 days postoperatively.

Lateral lumbar area is shaved and prepared for open surgery. Lateral incision and dissection are made toward the transverse processes of the lumbar spine. The psoas major muscle is dissected from the transverse processes to expose L1-2, L2-3, L3-4, L4-5 discs. Braided #2 nylon suture is used as Percutaneous Disc Scaffold (PDS). Half of the PDS is in lumen and another half draped outside the 19G needle [44]. As the needle punctured into the intervertebral disc, the outside strand is press-fitted into the disc. During withdrawal of the needle, friction between the outside strand and the disc grips and deploys the PDS from the needle. The tail of PDS is extended outside the disc with the repositioned psoas muscles on the spine. Routine closure of external muscular fascia is performed with size 0 Polysorb, subcutaneous tissue
with 2/0 Polysorb, and skin with 2/0 monofilament nonabsorbable suture.

Sheep were randomly divided into 4 euthanize time points at 1-month, 3-month, 12-month and 30-month for histology to evaluate cellular response to the braided nylon suture inside and outside lumbar discs.

**Patient selection method**

The PDS procedure is conducted with approval of Ethics Committee of the First Affiliated Hospital of Soochow University. Pain location was marked on dermatome, and black discs were shown in T2 MRI to identify likely painful discs. Fourteen patients (6 males, 8 females) showed positive discograms; average age was [44] 6 ± 8.3 years old (range 27–63). All patients had long history of low back pain, without radiculitis or numbness. Average duration of pain was 7.0 ± 3.9 years (range 4-20 years), but no history of spinal procedure. Average VAS score was 6.1 ± 1.6 (range 4-9); Average ODI score was 37.9% ± 15.1% (range 22-76%). All patients had at least one black disc under T2 MRI. Nine discs showed high-intensity zones in the posterior portion of annulus. MRI showed no obvious disc herniation.

Patients have PDS in the following levels: one L3-4 patient, six L4-5 patients, six L5-S1 patients, and one L3-4 and L4-5 patient. Spirals of PDS are implanted to reach the diffusion zones of endplates to draw blood plasma containing bicarbonate, oxygen and nutrients into the mid and acidic layer of the painful discs.

**Surgical procedures**

Antibiotics and local anesthesia are used before procedure. Patients are in prone positions under C-arm fluoroscope for guiding discographic needles into black discs. The treatment kit includes discography needles and PDS delivery devices to combine diagnostic with therapeutic procedures in approximately 20-65 minutes per disc, including training time.

Patient is prone and fully alert with local anesthetic, 1% lidocaine. Discography needle (18G) is guided by C-arm fluoroscope under AP and lateral views toward the Kambin’s triangle of a black disc. A small discography needle (22G) is inserted into the 18G needle to puncture and conduct diagnostic discography to avoid sizable disc puncture which can accelerate disc degeneration of none painful disc. After confirming discogenic pain by intradiscal injection of IsovueTM, the 18G needle slides over the 22G into the disc. The 22G discography needle is replaced with a guide wire into the lumen of the 18G needle. The 18G needle is replaced with a cone-head dilator, sliding over the guide wire into the painful disc. A cannula with snagging points slides over the dilator into the disc. The dilator and guide wire are replaced by a PDS needle into the disc. The extended PDS from the distal end of the PDS needle is hooked and retained by snagging points of the cannula. Slight withdrawal (2 cm) of the needle deposits 2 cm of PDS in the lumen of the cannula. Re-advancement of the PDS needle pushes the 2 cm of PDS into the porous or near hollow nucleus. The distal end of the PDS needle contains teeth to grip and rotate the deployed 2 cm of PDS to form a soft spiral in porous disc matrix by twisting the PDS needle. The PDS needle is also gently pushed forward to pack the soft spiral to fill voids in the porous nucleus. Slight withdrawal, re-advancement, twisting and pushing of the PDS needle are repeated to pack individual soft spirals, reaching and bridging the superior and inferior diffusion zones with 16-33 cm braided nylon suture. When the disc is full, re-advancement became difficult, and the PDS is cut at the proximal end of the PDS needle. The cannula and PDS needle are withdrawn. The extended PDS is cut approximately 1 cm above skin, then tucks 3-4 cm beneath the skin with a thin and blunt forceps along the cannula track. The puncture wound is covered with a Steri-Strip and the patient is observed for 1-2 hours before being discharged from the minimally-invasive procedure. No antibiotic is used after operation. No analgesic is used beyond one day after PDS procedure (Table 1).

**Method of clinical evaluation**

Clinical outcome is compared between follow up and baseline VAS and ODI. Follow-up time points are one-week, three-months, one-year and two-years after the procedure. Two independent orthopedic surgeons evaluate VAS and ODI score in Graph 1.

**Statistical analysis of clinical evaluation**

All analysis is calculated by Excel of Microsoft. P-value (2 tails) <0.05, and t stat > t critical (2 tails) are considered statistically significant; and P-value (2 tails) <0.001 is considered highly significant.

**Results**

**Blood transport through capillary action**

Most of the capillary height drawing pork blood is within half hour. Average capillary height after 2 hours is 10.3 ± 1.2 cm, as shown in Figure 4.

**Lactic acid titration**

Figure 5 shows rapid pH increase from 3.11 to 6.0 with small amount of fresh blood. However, significantly more blood is required to raise pH from 6.0 to 7.1. This indicates significant amount of interstitial fluid exchange between painful disc and body circulation is required to neutralize the lactic acid for discogenic pain relief (Table 2).

Assuming 1 cc lactic acid is in the porous nucleus of painful disc, approximately 0.51-1.51 cc of blood is required to raise pH to 7.14. Average water content in human lumbar disc is approximately 8.5 cc.

<table>
<thead>
<tr>
<th>Dimension of PDS delivery device [45].</th>
<th>18G spinal needle</th>
<th>22G spinal needle</th>
<th>Guide wire</th>
<th>Dilator (cone head)</th>
<th>Cannula</th>
<th>PDS needle</th>
<th>Braided nylon suture as PDS in disc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length (cm)</td>
<td>15.3</td>
<td>20.3</td>
<td>49.2</td>
<td>33.8</td>
<td>18.4</td>
<td>22.9</td>
<td>10.8-50.7</td>
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<td>OD (mm)</td>
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<td>0.81</td>
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<td>2.41</td>
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<td>0.66</td>
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<tr>
<td>ID (mm)</td>
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<td>0.25</td>
<td>--</td>
<td>0.89</td>
<td>1.96</td>
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</tr>
</tbody>
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Table 1: Dimension of PDS delivery device [45].

**Week Follow-Up [1-Week to 2-Year]**

**% Improvement from Pre-PDS of 14 Disc Pain Patients**

**Graph 1:** % Improvement from pre-PDS of 14 disc pain patients.
lactic acid, as the worst-case scenario. Therefore, interstitial fluid exchange by bridging endplate diffusion zones with PDS is sufficient to neutralize the lactic acid within one day.

Sheep study

Degenerated, desiccated or black discs in human often contain fissures. Disc puncture for diagnostic discography probably is inconsequential, especially using a 22G needle. For sheep study, a 19G needle is used to press-fit the PDS, sealing the annulus puncture to minimize loss of swelling pressure. Sheep discs remain healthy after 2.5 years with the press-fitted PDS, as shown in Figure 6. An untouched adjacent disc in Figure 7 is in similar condition as the PDS disc in Figure 6.

The PDS disc looked similar as the adjacent and untouched T12-L1 disc in Figure 7. Probably due to the avascular nature of intervertebral discs, no immune response to the PDS is observed during euthanized time points of 1-, 3-, 12- and 30-months. Furthermore, proteoglycans begin to grow within nylon filaments at 3-month. Progressive growth of proteoglycans in sheep discs can be seen from 1-month in Figures 8 and 9, 3-month in Figure 10, 12-month in Figures 11-13 and 30-month in Figures 14 and 15.

Pilot clinical study

Fourteen patients are diagnosed with discogenic low back pain by discography. PDS are implanted under local anesthesia through discography needles. Average operation time is 43 minutes (20-65 minutes) including training; blood loss is less than 3 cc. Total of 15 discs undergoes PDS implantation, two L3-4, seven L4-5, and six L5-S1. The average length of nylon sutures implanted into disc is 26.41 ± 5.03 cm (16.0 cm~32.5 cm). The VAS and ODI score in pre- and post-procedure are listed in Table 3.

Average fluid loss and gain of the disc from compression and relaxation during vertical and supine positions is 18%. Average fluid exchange between lumbar disc and body circulation is 1.53 cc per day, which is greater than 1.51 cc blood plasma needed to neutralize 1 cc of 6 mM lactic acid.
Degrees of straight leg raises during follow-up are similar to pre-PDS conditions. No vascular, neurologic injuries or infection is reported.

Discussion and Conclusion

Etiology of disc degeneration followed by back pain is a blood plasma transport problem, resulting in hypoxic, acidic and starvation conditions in the avascular disc. Disc cells extracted from highly degenerated Thompson Grade 5 discs resumed production of proteoglycans and collagen in vitro with nutrients and pH neutral buffer [45,46]. In addition, skeletal progenitor (stem) cells were found inactive within degenerated human intervertebral discs [47] (Figure 16).

These studies support starvation creates and sustain disc degeneration by hindering cellular maintenance and repair of disc matrix [4-16]. Re-establishing blood plasma transport may neutralize lactic acid from irritating chronic inflammatory tissue to relieve discogenic pain and nourish starving disc cells to slow or halt disc degeneration (Figure 17).

Blood transport study and selection of nylon suture

Braided nylon suture is selected as PDS for biocompatibility, wicking capability, and reduced regulatory burden for approval. The amide bonds in braided nylon provide hydrophilicity, capillary action, and fluid absorbing capacity as a conduit. The purpose of PDS is to re-establish interstitial fluid exchange between avascular disc and body circulation by bridging between diffusion zones of endplates, delivering bicarbonate, oxygen and nutrients into the acidic and starvation zone in mid-disc layer as shown in Figures 1 and 2.

Nylon sutures are the most biocompatible suture [38,40-42]. Histiocytes occasionally occurred with mild giant cells around nylon sutures in animal tissues [35,39]. In rat muscle, thin fibrotic encapsulations formed over nylon sutures after 3 months.39 However, no immune response to the braided nylon suture was found in sheep discs (Figure 18).

Residual tensile strength is commonly used to estimate rate of suture degradation in-vivo. Residual tensile strength of nylon sutures

![Figure 7: Sagittal cuts of the untouched T12-L1 disc, adjacent to the PDS L1-2 disc in Figure 6, after 2.5 years.](image-url)
Figure 8: H&E histology stain shows no immune response to the nylon filaments (round circles) of PDS (No 2 braided nylon suture) in nucleus pulposus (NP) after 1 month.

Figure 9: Saf-O stains proteoglycans red and shows no immune response to the nylon filaments of PDS in nucleus pulposus (NP) after 1 month.

Figure 10: Saf-O shows no immune response to the nylon filaments of PDS in nucleus pulposus (NP) between vertebral bodies (VB) after 3-month. Proteoglycans (arrows) appear to grow between strands of nylon sutures.

Figure 11: Saf-O shows no immune response to the nylon filaments of PDS in nucleus pulposus (NP) after 12 month. Proteoglycans (red) grow around nylon filaments.

Figure 12: H&E shows no immune reaction or fibrotic encapsulation over PDS after 2.5 years in sheep nucleus pulposus (NP).

Lactic acid neutralization study

Lactic acid has a pKa 3.9; bicarbonate is the primary pH buffer in blood with pKa 6.4 and 10.3. Bicarbonate is much more alkaline than varies, depending on suture size, animal model and tissue in human, but has retained up to 80% strength after 10 years. 35-37 Durability of PDS as a blood plasma absorbing and dispersing sponge within intervertebral disc is unknown; discogenic pain relief in pilot study is on-going, beyond 2 years (Figure 19).

Before utilizing the braided nylon suture, selecting a device for drawing blood plasma from endplate diffusion zones was challenging. Annular fissures are commonly found in painful discs. Intradiscal gel injection flattens and extrudes through fissure during hydraulic simulation. Similarly semi-solid cross-linked hydrogel fractures, then extrudes through fissure. In addition, gel or hydrogel has no penetrating capability into healthy and firm disc matrix in diffusion zone, incapable of drawing sufficient bicarbonate, oxygen and nutrients from circulation into mid-disc layer.
lactic acid with both pKa well above the pKa of lactic acid. Therefore, titration curve of lactic acid solution showed rapid pH increase by adding just a small amount of blood. After reaching pH 6.4 (the first pKa 6.4 of bicarbonate) in the mixture of lactic acid and blood, the acid neutralizing equivalent of bicarbonate in blood is reduced by half; only the second pKa 10.3 is remaining to further neutralize the acid. Therefore, much more blood is required to neutralize the lactic acid solution from pH 6.4 to pH 7.14, the average acidity of none painful discs [17].

Sheep study

Histology of sheep study shows no immune response, granuloma or fibrotic tissue over the nylon filaments of PDS in sheep discs after 1-, 3-, 12- and 30-months. However, the extended PDS outside the annulus is covered with thin granuloma and mild giant cells, as anticipated.

Saf-O stain shows gradual accumulation of proteoglycans between nylon filaments of PDS, beginning at 3-months. Concentration of proteoglycans in human degenerated disc is low, leading to desiccation. Producing new proteoglycans around the PDS may increase hydration and swelling pressure of the degenerated disc.

Figure 15: Saf-O in 10x magnification shows no immune response or fibrotic encapsulation over nylon filaments of PDS in sheep nucleus (NP) after 2.5 years. Proteoglycans grow between nylon filaments.

Figure 16: Trichrome stain shows no immune response and no fibrotic encapsulation over PDS in nucleus pulposus (NP) near endplate (EP) and vertebral body (VB) after 2.5 years.

Figure 17: Trichrome shows the junction between annulus (AF), PDS and psoas major muscle (PM). A thin layer of fibrotic cap (FC) covers the entry of PDS into L3-4 of Sheep after 2.5 years.

Figure 18: H&E (10x) shows granuloma (G) with mild giant cells (arrows) over the extended #2 braided nylon suture outside the disc but no lymphocytes or plasma cell are present after 2.5 years adjacent to psoas major muscle (PM).
Water within the disc. However, biosynthesis of chondroitin sulfate contains one negative charge. Hence, chondroitin sulfate retains most of the negative charges, while disaccharides of keratan sulfate contain only 18% negative charges. Disaccharides of chondroitin sulfate contain two negative charges. Hence, chondroitin sulfate contains two negative charges, while disaccharides of keratan sulfate contain only one negative charge. Hence, chondroitin sulfate retains most of the water within the disc. However, biosynthesis of chondroitin sulfate consumes oxygen from circulation for converting UDP-glucose (uridine-diphosphate glucose) to UDP-glucuronic acid before incorporating into disaccharide of chondroitin sulfate. Calcified endplates create anaerobic condition in mid-disc layer, hindering biosynthesis of the most water-retaining chondroitin sulfate. In healthy disc, chondroitin and keratan ratio is 1:1; but in degenerated disc, the ratio is 1:3, leading to desiccation [48,49].

In acidic extracellular fluid, uptake of sulfate into disc cells for making chondroitin sulfate and keratan sulfate is greatly reduced, by 68%. The negative charges of sulfate (SO4-2) bind with the positive charge of acid (H+). As the result, the charge–charge binding retains the sulfate in the acidic extracellular fluid, hindering uptake of sulfate into disc cells. Hence, acid neutralization and re-establishing transport of oxygen and nutrients are crucial for rebuilding chondroitin sulfate and keratan sulfate in degenerated discs.

Anaerobic metabolism of each glucose molecule produces only 2 ATP and two lactic acids. On the other hand, aerobic metabolism of each glucose produces 36 ATP and 6 carbon dioxide through glycolysis, citric acid cycle and electron transport chain. Re-establishing transport of oxygen within avascular disc may provide energy needed to biosynthesize new disc matrix.

PDS spirals are too large to pass through the fissures. Furthermore, the spirals are interconnected and surrounded or enclosed by the annulus rings, as a donut. Spiral is formed and deposited one at a time to fill vacancy in the porous nucleus. Physicians can feel fullness of the nucleus by advancement of the PDS needle. When the disc is full, advancement of the PDS needle becomes difficult. PDS can be cut at the proximal end of the PDS needle. The cannula is then slightly withdrawn to create head space in the nucleus to allow implanting the remaining PDS in the lumen of the needle, without extending the PDS outside the disc.

Nucleus in mid-layer of degenerated disc is porous, desiccated and lacking viscoelasticity to support compression. In contrast, nucleus near endplates of the degenerated disc is firm and resilient, capable of cushioning the soft suture spirals to prevent rupture of capillary buds in the cartilaginous endplates. PDS patients showed no modic change in endplates or adverse effect in 3-, 6-, 12- and 24-month MRI.

PDS spirals can also glide over another in the porous nucleus surrounded by annulus to accommodate dynamic spinal motion. Sheep study indicates accumulation of proteoglycans between nylon filaments, which may provide lubrication, hydration and cushioning to further facilitate dynamic motion of the PDS disc.

Acid-base neutralization is instantaneous. The most significant pain reduction occurs in 1-week, which supports the cause of discogenic pain from lactic acid burn.

Discogenic pain occurs during early disc degeneration. Progressive disc degeneration is inevitable, leading to decrease of disc height 3% per year. Load gradually transfers from the thinning disc to facet joints causing facet pain, erosion and spinal stenosis. Re-establishing blood plasma transport through PDS within the intervertebral disc may slow, halt or even reverse the progressive disc degeneration.

Most of the water in the disc is retained by the negative charges on the disaccharides of chondroitin sulfate and keratan sulfate of proteoglycans. Disaccharides of chondroitin sulfate contain two negative charges, while disaccharides of keratan sulfate contain only one negative charge. Hence, chondroitin sulfate retains most of the water within the disc. However, biosynthesis of chondroitin sulfate

References