Pilot Study

Nucleus Pulposus Allograft Supplementation in Patients with Lumbar Discogenic Pain: Initial 6-month Outcomes from a Prospective Clinical Pilot Study

Douglas P. Beall, MD[1], Timothy T. Davis, MD[2], Kasra Amirdelfan, MD[3], Ramana K. Naidu, MD[4], Michael J. DePalma, MD[5], Shrif Costandi, MD[6], Jacob W. Fleming, MD[1], Edward S. Yoon, MD[7], Timothy Ganey, PhD[8], Jon E. Block, PhD[9], and Nagy Mekhail, MD, PhD[6]

From: [1]Comprehensive Specialty Care, Edmond, OK; [2]Source Healthcare, Santa Monica, CA; [3]Boomerang Healthcare, Inc., Walnut Creek, CA; [4]MarinHealth Spine Institute, Larkspur, CA; [5]Virginia iSpine Physicians, Richmond, VA; [6]Cleveland Clinic, Cleveland, OH; [7]Hospital for Special Surgery, New York, NY; [8]VIVEX Biologics, Miami, FL; [9]Jon Block, PhD Consulting, San Francisco, CA

Address Correspondence:
Jon E. Block, PhD
2210 Jackson Street, Ste. 401
San Francisco, CA 94115
E-mail: jb@drjonblock.com

Disclaimer: VIVEX Biologics, Inc. (Miami, FL) sponsored this study and contributed to study design, data monitoring, statistical analysis, and reporting of results and paid for independent data collection, core laboratory, and EDC services.

Conflict of interest: See pg ### for this information.

Article received: 05-19-2024
Revised article received: 06-01-2024
Accepted for publication: 07-09-2024

Free full article: www.painphysicianjournal.com

Background: Preventing disc degeneration remains a clinical challenge; patients experiencing chronic lumbar discogenic pain have limited treatment options. Minimally invasive intradiscal procedures such as allogeneic nucleus pulposus (NP) injection have the potential to fill the treatment gap between failed conservative care and spine surgery.

Objectives: Our study sought to evaluate the magnitude and durability of improvement in back function in patients with chronic lumbar discogenic pain followed for 6 months after a single intradiscal injection of minimally manipulated, off-the-shelf processed NP allograft (VIA Disc NP®, VIVEX Biologics, Inc.) at up to 2 vertebral levels.

Study Design: Single-arm, prospective, multicenter, pilot study.

Setting: Academic and private practice outpatient clinics.

Methods: A total of 29 patients with symptomatic lumbar discogenic pain refractory to conservative care who had a back function score of 40-80 points on the Oswestry Disability Index (ODI), ≥ 6 on an 11-point back pain Numeric Rating Scale (NRS-11) and corresponding imaging evidence of disc degeneration were enrolled. A single dose, intradiscal injection of approximately 100 mg of NP allograft mixed with sterile saline was administered to the affected level or levels.

Results: The average ODI and NRS-11 improvements between baseline and 6-months postprocedure were 54.8% (95% CI, 41.3-68.3) and 52.9% (95% CI, 34.7-71.1) respectively ($P < 0.001$). A minimal clinically important difference of ≥ 30% improvement over baseline was achieved in 79% (22 of 28) and 68% (19 of 28) of patients for ODI and NRS-11, respectively. At 6-months postprocedure, 64% (18 of 28) of patients had an NRS-11 score ≤ 3.

Limitations: This pilot study did not employ a concurrent control group and the clinical follow-up was limited to 6 months.

Conclusions: These pilot findings demonstrate the feasibility of treating patients with symptomatic lumbar disc degeneration with a single intradiscal injection of allogeneic NP to provide significant and durable improvements in back function and pain.

Key words: Disc degeneration, nucleus pulposus allograft, low back pain, tissue supplementation, Oswestry Disability Index, discogenic

Pain Physician 2024: 27:E865-E871

An enormous amount of theoretical and experimental research has definitively identified the intervertebral disc as a distinct, potent, and relatively common pain generator (1-4). Lumbar discogenic pain results from spinal degeneration originating initially in the lumbar intervertebral disc as early as the second decade of life (5-8). The nucleus pulposus (NP) is normally highly hydrated, but degeneration substantially reduces its ability to cushion physiological loads due to the loss of its capacity to bind water under compression (9).

The result of diminishing pressure within the nucleus is reduced disc height (10,11). Consequently, degenerative disc disease is often identified as the catalyst of more widespread arthritic deterioration of the adjacent vertebral structures including end plate changes, osteophyte formation, and trabecular microfractures (6). Additionally, aberrant loading patterns resulting from disc degeneration are also borne by the facet joints, leading to arthrosis, hypertrophy, and possible compression of neural elements (7,12,13). Recent evidence suggests a strong pathophysiological interdependence across the entire 3-joint complex of the lumbar spine, with the cascade of arthritic degeneration originating in the disc and eventually propagating to involve the facet joints (14,15).

Preventing disc degeneration remains a clinical challenge (16). When lumbar discogenic pain becomes chronic and conservative management fails to provide symptom relief, therapeutic options are limited to surgical discectomy often coupled with total disc arthroplasty or instrumented interbody spine fusion. Thus, there exists a dire need to fill the extensive treatment gap between conservative management and traditional spine surgery. NP allograft supplementation involves the direct implantation of native disc material by intradiscal injection to restore the structure of the degenerated intervertebral disc. NP treatment is a nonsurgical, minimally invasive, outpatient procedure that does not alter the normal spinal anatomy.

Herein, we report the 6-month clinical outcomes from a pilot investigation of intradiscal injection of a proprietary formulation of NP allograft in patients with chronic lumbar discogenic pain.

Methods

This was a prospective, single-arm, multicenter pilot study carried out at 6 clinical sites in the United States. The aim was to enroll approximately 30 eligible patients in accordance with sample size requirements for feasibility trials (17,18).

The primary objective was to evaluate the magnitude and durability of improvement in back function in patients with chronic lumbar discogenic pain followed for 6 months after a single intradiscal injection of NP allograft at up to 2 vertebral levels. Improvement in back pain severity served as a confirmatory secondary outcome. All patients provided informed consent. The study was reviewed and approved by Sterling Institutional Review Board. The trial was conducted in accordance with the Declaration of Helsinki and prospectively registered at ClinicalTrials.gov (NCT05201287).

Patients were eligible for inclusion if they were ≥ 18 years old with a body mass index of < 35 kg/m^2 and exhibited chronic lumbar discogenic pain of ≥ 6 months duration refractory to conservative care. Discogenic pain was defined as axial midline low back pain with or without nonradicular/nonsciatic referred leg pain in a sclerotomal distribution. All patients demonstrated sitting intolerance, pain with flexion, positive provocation with sustained hip flexion, and an absence of motor/sensory/reflex changes. Study eligibility required a baseline back function score of 40-80 points on the Oswestry Disability Index (ODI) and ≥ 6 on a 11-point (0 to 10) back pain numeric rating scale (NRS). A magnetic resonance imaging scan was needed to verify moderate degeneration of up to 2 intervertebral discs from L1 to S1, a modified Pfirrmann grade of 3-7, and no Modic changes or if changes, ≤ 2. Discography was not required. Patient eligibility for enrollment was made by an independent core lab (Medical Metrics) after reviewing imaging studies and patient baseline characteristics.

Patients were excluded from the study if they had any of the following: known allergies to components of the NP allograft, gentamicin, or vancomycin; contraindications to the proposed sedation/anesthetic protocol; experiencing radicular pain greater than back pain by history or evidence of radicular pain or neurological deficit within the past 6 months. Additional exclusions at the index level included: contained disc protrusion > 5 mm, disc extrusion, or spondylolisthesis > 5 mm; seronegative spondyloarthropathy; moderate to severe symptomatic spinal stenosis; chronic facet syndrome; spondylodiscitis; bilateral spondylolysis; current or history of osteoporotic or tumor-related vertebral compression fracture; and a previous lumbar spine fusion surgery or disc arthroplasty. Other exclusion criteria included a history of sacroiliac (SI) joint pain or injections during the past 3 months or SI joint fusion within the past 2 years; previous chemonucle-

olysis or percutaneous treatment of the affected disc; epidural steroid injections within 4 weeks prior to study treatment; any lumbar intradiscal treatment injection or procedure (e.g., methylene blue, dextrose, glucosamine, and chondroitin sulfate, or biacuplasty), or any nerve ablation procedures at the same or adjacent level (e.g., basivertebral nerve ablation, medial branch of the dorsal ramus or sinuvertebral nerve ablations) within the past 12 months.

All patients were treated with VIA Disc NP® (VIVEX Biologics, Inc.). This product is a minimally manipulated, off-the-shelf processed human NP tissue allograft intended to supplement degenerated intervertebral discs. It is processed from donated cadaveric disc tissue, lyophilized, and morselized to particles that are ≤ 250 µm in size. The morselized tissue is then aliquoted into a volume size of 100 mg (+/- 10%) and aseptically sealed in a double-tray configuration. The particulate is terminally sterilized via electron-beam irradiation. The tissue is reconstituted with 2 mL of sterile saline for delivery into the target intervertebral level or levels. The micronized VIA Disc NP, when reconstituted, has a high viscosity but remains flowable through a 20G cannula.

Under moderate conscious sedation, local anesthetic, and fluoroscopic guidance, a spinal needle was advanced through Kambin's triangle into the intervertebral disc's NP in order to facilitate intradiscal injection. A single dose, intradiscal injection of approximately 100 mg of VIA Disc NP mixed with sterile saline (0.9% sodium chloride) was administered to the affected level or levels according to the product's Instructions for Use. A postprocedure follow-up appointment was required for all patients at 4 weeks in order to evaluate symptom amelioration and any postprocedure complications. Further clinical follow-up was at 3 and 6 months. All procedures were performed by a qualified interventional pain-trained physician.

Using SAS 9.4 TS1M8 (Catalyst CR, Wilmington, NC) to calculate our statistics, our findings are presented as means (95% CI); average improvement in clinical outcomes from baseline through all follow-up intervals was assessed using repeated measures analysis of variance (ANOVA). The difference between baseline values and the 6-month endpoint was confirmed using a 2-tailed paired t test. The primary endpoint of this pilot study was the proportion of patients who achieved a minimal clinically important difference (MCID) of ≥ 30% over baseline in the ODI (19). Additionally, baseline and 6-month ODI values were categorized by functional impairment severity as minimum (0-20), medium (21-

Table 1. *Study patients' demographic data.*

	Patients (n = 29)
Women, n (%)	12 (41)
Age, mean (SD) yrs	44 (13)
BMI, mean (SD) kg/m2	27 (4.7)
Number of treated levels, n (%)	
One	13 (45)
Two	16 (55)
Levels treated, n (%)	
L4-L5/L5-S1	10 (34.5)
L4-L5	6 (20.7)
L5-S1	6 (20.7)
L2-L3/L5-S1	2 (6.9)
L3-L4/L4-L5	2 (6.9)
L2-L3/L3-L4	1 (3.4)
L3-L4	1 (3.4)
L3-L4/L5-S1	1 (3.4)
Pfirrmann grade, n (%)	
3	9 (31.0)
4	10 (34.5)
5	2 (6.9)
6	4 (13.8)
7	4 (13.8)
Modic changes, n (%)	
0	17 (58.6)
1	1 (3.4)
2	11 (37.9)
Oswestry Disability Index, mean (SD)	53.3 (14.5)
Back pain Numeric Rating Scale score, mean (SD)	7.0 (1.6)

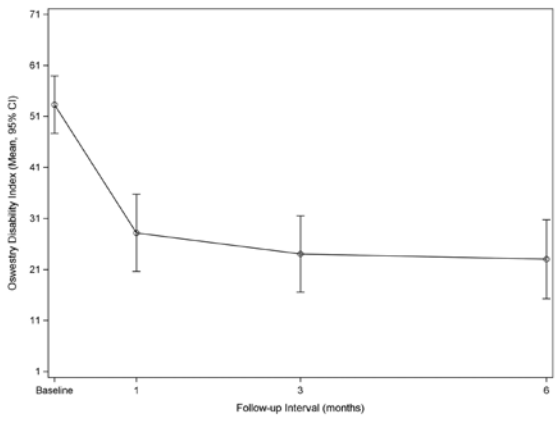

Fig. 1. *Line graph showing average Oswestry Disability Index values (mean, 95% CI) at baseline and all postprocedure follow-up intervals. Mean values were 53.3 (baseline), 28.2 (one month postprocedure), 24.1 (3 months postprocedure), and 23.0 (6 months postprocedure). The overall improvement was significant ($P < 0.001$).*

40), severe (41-60), and crippled (61-80) and compared using the Wilcoxon signed-rank test.

Secondary outcomes included responder rates for the NRS-11 for the MCID (≥ 30% improvement) and substantial clinical benefit (≥ 50% improvement) (19,20). Responder rates for NRS-11 patient acceptable symptomatic state (PASS) score were also computed with success thresholds set at ≤ 4 and ≤ 3 (21). Adverse events were captured at each postprocedure follow-up interval.

Results

A total of 53 patients were prescreened for potential study eligibility based on case history; 29 patients met all inclusion criteria and were enrolled in the study. Table 1 shows study patients' demographic data. Clinical follow-up was excellent: follow-up data were obtained from 28 patients at one month, from 27 patients at 3 months, and from 28 patients at 6 months.

There was a significant decrease in ODI values from baseline across all follow-up intervals ($P < 0.001$). The average improvement from baseline to 6-months postprocedure was 54.8% (95% CI, 41.3-68.3; $P < 0.001$). Figure 1 shows the ODI mean values (95% CI) at baseline and at each follow-up interval. At 6-months postprocedure, approximately 79% (22 of 28) of the patients achieved the MCID for ODI. Figure 2 illustrates the distribution of ODI functional impairment categories at baseline and at 6-months postprocedure, showing a significant ($P < 0.0001$) shift in the physical status of the overall study population. For example, at baseline 82% of the patients reported either a severe or crippled level of back function. By 6-months postprocedure, that percentage was reduced to less than 20%.

For back pain NRS-11 scores, there was also a significant decrease in values across all follow-up intervals ($P < 0.001$); the paired analysis between baseline and at 6-months postprocedure confirmed the significant decline ($P < 0.001$). The corresponding percentage improvement was 52.9% (95% CI, 34.7-71.1) (Fig. 3). At 6-months postprocedure, approximately 69% (19 of 28) of the patients achieved the MCID as well as the substantial clinical benefit for NRS-11, meaning all responders demonstrated at least a 50% improvement in back pain severity at 6-months postprocedure relative to baseline. Correspondingly, 69% (19 of 28) and 64% (18 of 28) had a PASS score ≤ 4 and ≤ 3 at 6 months postprocedure, respectively.

Treatment effect was not associated with the baseline Pfirrmann grade or the presence of Modic changes, although there was a trend toward improved clinical outcomes in patients with less severe disc degeneration. There were no reports of procedure-related adverse events in this pilot study.

Discussion

The results of this pilot study show significant and durable improvement in back function and pain fol-

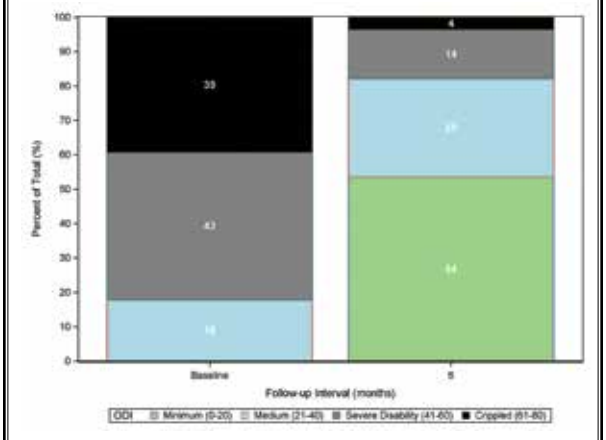

Fig. 2. *Comparative distributions of Oswestry Disability Index functional impairment categories at baseline and 6 months postprocedure. The distributions were significantly different ($P < 0.0001$).*

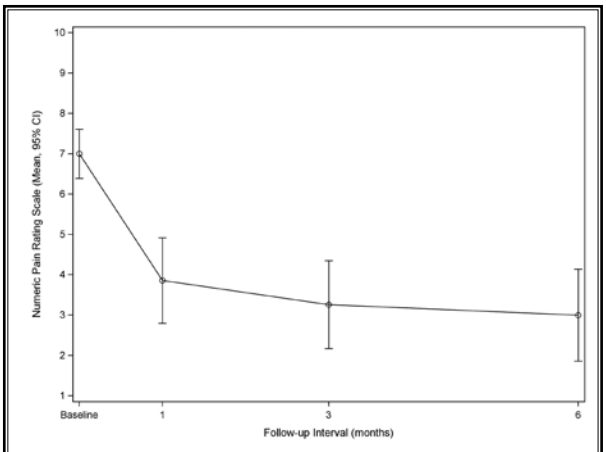

Fig. 3. *Line graph showing average Numeric Rating Scale score (mean, 95% CI) at baseline and all postprocedure follow-up intervals. Mean values were 7.0 (baseline), 3.9 (one month postprocedure), 3.3 (3 months postprocedure), and 3.0 (6 months postprocedure). The overall improvement was significant ($P < 0.001$).*

lowing a single intradiscal injection of allogeneic NP. Clinical improvement was realized as early as the first month of follow-up, with maintenance of symptom amelioration through 6 months.

The degrees of ODI and NRS-11 improvement (approximately 55% and 53%, respectively) in our study are strikingly similar to the findings from a previous randomized controlled trial of a similar cellular NP product (53% and 54% at 12 months, respectively) (22). However, while the product they used (VIA Disc Allograft; VIVEX Biologics, Inc.) was also allograft processed from a human cadaver nucleus pulposus, lyophilized and ground, it included a minimum of 6 x 10^6 cells suspended in 1 mL of non dimethyl sulfoxide (DMSO) cryoprotectant. This cellular component was provided in a separate cell vial, and the cell and tissue allograft components were mixed with approximately 1 mL of saline for delivery into the treated level or levels. The product used in our pilot study (VIA Disc NP), in contrast, does not contain live cells and is regulated as a tissue under section 361 of the Public Health Service Act and is commercially available in the United States. Thus, a primary aim of our study was to assess the feasibility of treating patients with a single intradiscal injection of off-the-shelf allogeneic NP without the addition of live cells and to ascertain the magnitude of symptom relief.

It is noteworthy that treatment responders in our study realized substantial clinical benefit, with 64% reporting a final back pain NRS-11 score $\leq$ 3. We also observed a significant redistribution of functional impairment categories within the overall study group with 52% of patients achieving the minimum ODI grade (0-20) at 6 months. Indeed, it has become increasingly important, particularly for subjective symptoms such as pain, activity limitations, and participation restrictions, that feeling well rather than feeling better is what matters most to a patient (23).

We included patients with Modic 1 and Modic 2 changes, but as with the baseline Pfirrmann grade, we did not identify an association between this radiographic feature and patient-reported outcomes. While Modic changes have been acknowleged as pathognomonic for vertebrogenic pain emanating from the endplate, there is likely substantial overlap with the patient population who have chronic low back pain of discogenic origin due to the intimacy of these vertebral structures with degeneration occurring pari passu or hand-in-hand (24,25). Additional research is warranted to assess whether treatments for these pain syndromes are complementary.

The novel technology used in our study was developed to supplement a degenerated NP with an allogeneic product that is similar to native, healthy tissue by allowing for water-binding, improved hydration, and mechanical cushioning.

The limitations of our study include no comparison group, a small sample size, a relatively short postprocedure follow-up, and no follow-up magnetic resonance imaging to evaluate disc morphology. While the improvements in patient-reported outcomes were robust and encouraging, the findings should be considered cautiously until corroborated with additional evidence involving controlled trials with larger study groups. Disc height preservation and mechanics are necessary factors for preventing spinal degeneration and potentially postponing or averting spinal surgery (11). Thus, it will also be important to address the fundamental question of whether intradiscal NP treatment slows spinal degeneration progression, particularly subsequent facet involvement.

Conclusions

The results of our pilot study provide additional evidence that nucleus supplementation with intradiscal NP injection is associated with clinically significant functional improvement and pain palliation (26). This minimally manipulated, off-the-shelf product is reconstituted with saline providing a nonsurgical option that can be delivered through a standard spinal needle without altering the normal anatomy of the spine. Ease of use and delivery underscore the potential for clinical adoption of this procedure to bridge the current treatment gap for patients experiencing chronic, severe lumbar discogenic pain.

Acknowledgments

Statistical analyses were conducted by Liwei Chen (Catalyst Clinical Research, Wilmington, NC USA).

Conflicts of Interest

DB is a scientific advisor to Vivex Biologics; received grants or contracts from Medtronic, Medical Metrics, Avanos, Relievant, Boston Scientific, Stryker, Sollis Pharmaceuticals, Simplify Medical, Lenoss Medical, Spine BioPharma, Eliem Therapeutics, Smart Soft, Tissue Tech, Vivex, Stratus Medical, Restorative Therapies, Kolon, TissueGene, Companion Spine, DiscGenics; royalties from VIVEX and IZI; consulting fees from Medtronic, Spineology, Merit Medical, Johnson & Johnson, IZI, Techlamed, Peterson Enterprises, Medical Metrics, Ava-

nos, Boston Scientific, Sollis Pharmaceuticals, Simplify Medical, Stryker, Lenoss Medical, Spine BioPharma, Piramal, ReGelTec, Nanofuse, Spinal Simplicity, Pain Theory, Spark Biomedical, Micron Medical Corp, Bronx Medical, Smart Soft, Tissue Tech, RayShield, Stayble, Thermaquil, Vivex, Stratus Medical, Genesys, Abbott, Eliquence, SetBone Medical, Amber Implants, Cerapedics, Neurovasis, Varian Medical Systems, Companion Spine, DiscGenics, Discure, SpinaFX, PainTEQ; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Artio, Sophiris, Eleven Biotherapeutics, Flow Forward, Lenoss Medical, ReGelTech, Spark Biomedical; and support for attending meetings and/or travel from Medtronic, ReGelTec, Nanofuse, Talosix, Spinal Simplicity, Pain Theory, Spark Biomedical, Smart Soft, Tissue Tech, Bronx Medical, Thermaquil, Vivex, Genesys, SetBone Medical, Amber Implants, Cerapedics, SpinaFX.

TD received consulting fees from Abbott, Boston Scientific, Biotronik; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Abbott, Boston Scientific, Biotronik.

RN received consulting fees from Vivex, Boston Scientific, Ferring Pharmaceuticals.

MD is a scientific advisor to Vivex Biologics; received grants or contracts from Spine BioPharma, Restorative, Novartis, SPR, Saol, Paradigm; royalties from Springer; patents from iSpine Ingenuity.

SC received grants or contracts from the Cleveland Clinic.

JF received support for attending meetings and/or travel from Medtronic, Stryker, Nevro, Seattle Science Foundation, HMP Global, American Society of Neuroradiology, American Society of Spine Radiology; received stock or stock options from BackTable LLC.

EY received consulting fees from Neurovasis.

TG is a Vivex Biologics employee; received royalties or licenses from Vivex; patents from Vivex; stock or stock options from Vivex.

JB received support for medical writing from Vivex Biologics; consulting fees from Vivex.

NM received consulting fees from Vivex Biologics.

The other author reports no additional conflicts of interest.

References

1. Bogduk N, Aprill C, Derby R. Lumbar discogenic pain: State-of-the-art review. *Pain Med* 2013; 14:813-836.
2. Fujii K, Yamazaki M, Kang JD, et al. Discogenic back pain: Literature review of definition, diagnosis, and treatment. *JBMR Plus* 2019; 3:e10180.
3. Lorio MP, Beall DP, Calodney AK, Lewandrowski KU, Block JE, Mekhail N. Defining the patient with lumbar discogenic pain: Real-world implications for diagnosis and effective clinical management. *J Pers Med* 2023; 13:821.
4. Jha R, Bernstock JD, Chalif JI, et al. Updates on pathophysiology of discogenic back pain. *J Clin Med* 2023; 12:6907.
5. Boos N, Weissbach S, Rohrbach H, Weiler C, Spratt KF, Nerlich AG. Classification of age-related changes in lumbar intervertebral discs: 2002 Volvo Award in basic science. *Spine (Phila Pa 1976)* 2002; 27:2631-2644.
6. Buckwalter JA. Aging and degeneration of the human intervertebral disc. *Spine (Phila Pa 1976)* 1995; 20:1307-1314.
7. Kushchayev SV, Glushko T, Jarraya M, et al. ABCs of the degenerative spine. *Insights Imaging* 2018; 9:253-274.
8. Miller JA, Schmatz C, Schultz AB. Lumbar disc degeneration: Correlation with age, sex, and spine level in 600 autopsy specimens. *Spine (Phila Pa 1976)* 1988; 13:173-178.
9. Vergroesen PP, Kingma I, Emanuel KS, et al. Mechanics and biology in intervertebral disc degeneration: A vicious circle. *Osteoarthritis Cartilage* 2015; 23:1057-1070.
10. Mohd Isa IL, Teoh SL, Mohd Nor NH, Mokhtar SA. Discogenic low back pain: Anatomy, pathophysiology and treatments of intervertebral disc degeneration. *Int J Mol Sci* 2022; 24:208.
11. Teichtahl AJ, Urquhart DM, Wang Y, Wluka AE, Heritier S, Cicuttini FM. A Dose-response relationship between severity of disc degeneration and intervertebral disc height in the lumbosacral spine. *Arthritis Res Ther* 2015; 17:297.
12. Roberts S, Evans H, Trivedi J, Menage J. Histology and pathology of the human intervertebral disc. *J Bone Joint Surg Am* 2006; 88 Suppl 2:10-14.
13. Mulholland RC. The myth of lumbar instability: The importance of abnormal loading as a cause of low back pain. *Eur Spine J* 2008; 17:619-625.
14. Fine N, Lively S, Seguin CA, Perruccio AV, Kapoor M, Rampersaud R. Intervertebral disc degeneration and osteoarthritis: A common molecular disease spectrum. *Nat Rev Rheumatol* 2023; 19:136-152.
15. Rustenburg CME, Emanuel KS, Peeters M, Lems WF, Vergroesen PA, Smit TH. Osteoarthritis and intervertebral disc degeneration: Quite different, quite similar. *JOR Spine* 2018; 1:e1033.
16. Buckley CT, Hoyland JA, Fujii K, Pandit A, Iatridis JC, Grad S. Critical aspects and challenges for intervertebral disc repair and regeneration-Harnessing advances in tissue engineering. *JOR Spine* 2018; 1:e1029.
17. Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: Recommendations for good practice. *J Eval Clin Pract* 2004; 10:307-312.
18. Lewis M, Bromley K, Sutton CJ, McCray G, Myers HL, Lancaster GA. Determining sample size for progression criteria for pragmatic pilot RCTs: The hypothesis test strikes back! *Pilot Feasibility Stud* 2021; 7:40.

19. Ostelo RW, Deyo RA, Stratford P, et al. Interpreting change scores for pain and functional status in low back pain. Towards international consensus regarding minimal important change. *Spine (Phila Pa 1976)* 2008; 33:90-94.
20. Glassman SD, Copay AG, Berven SH, Polly DW, Subach BR, Carreon LY. Defining substantial clinical benefit following lumbar spine arthrodesis. *J Bone Joint Surg Am* 2008; 90:1839-1847.
21. Pham T, Tubach F. Patient acceptable symptomatic state (PASS). *Joint Bone Spine* 2009; 76:321-323.
22. Beall DP, Davis T, DePalma MJ, et al. Viable disc tissue allograft supplementation; One- and two-level treatment of degenerated intervertebral discs in patients with chronic discogenic low back pain: One year results of the VAST randomized controlled trial. *Pain Physician* 2021; 24:465-477.
23. Tubach F, Dougados M, Falissard B, Baron G, Logeart I, Ravaud P. Feeling good rather than feeling better matters more to patients. *Arthritis Rheum* 2006; 55:526-530.
24. Lotz JC, Fields AJ, Liebenberg EC. The role of the vertebral end plate in low back pain. *Global Spine J* 2013; 3:153-164.
25. Maatta JH, MacGregor A, Karppinen J, Williams FM. The relationship between Modic changes and intervertebral disc degeneration. *BMC Musculoskelet* Disord 2016; 17:371.
26. Beall DP, Wilson GL, Bishop R, Tally W. VAST clinical trial: Safely supplementing tissue lost to degenerative disc disease. *Int J Spine Surg* 2020; 14:239-253.