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Commentary: Does needle injection cause disc degeneration? News in the continuing debate regarding pathophysiology associated with intradiscal injections

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In the article, "Deleterious effects of discography radio-contrast solution on human annulus cell in vitro: changes in cell viability, proliferation, and apoptosis in exposed cells," Gruber et al. [1] demonstrated in vitro evidence of reduced proliferation and increased cell death of intervertebral disc cells exposed to isovue, the contrast agent commonly used in discography procedures. The study adds to the debate over comorbidities associated with structural disruption from discography procedures with relevant commentary by Kang [2] and provides additional information supporting the concept that discography injection procedures may result in accelerated disc degeneration by reducing disc cellularity. This commentary provides an overview on potential injuries induced by discography and contextualizes the findings of Gruber et al. with the broader discography literature.

Discography is usually performed when other diagnostic modalities have failed to confirm the cause of a patient's low back pain (LBP). Radiographic techniques, especially magnetic resonance imaging, provide evidence of disc degeneration but cannot confirm that the degenerated disc is primarily responsible for a patient's LBP. Discography involves intradiscal injection of 1 to 3 cm^3 of radiopaque contrast materials, evaluation of the patient's clinical response (disc nociception), and postdiscography computed tomography scan to examine disc morphology (ie, annular tears). Even in the most ideal patients (eg, single-level disc degeneration, concordant discography, normal psychometrics, and no pending litigation), surgical success rates are estimated to be only 50% to 60% [3]. Investigators speculate that discography can lead to iatrogenic disc degeneration by injuring the normal control disc from the puncture of the annulus, the injection of contrast agents into the disc, and lack of annular repair. Carragee et al. [4] examined the progression of degenerative pathology between discs that had been subjected to discography with identical disc levels in a matched cohort that did not undergo discography with 7- to 10-year follow-up. Blinded magnetic resonance imaging evaluation revealed qualitative and quantitative changes in Pfirrmann grade, herniation, high intensity zones, end plate changes, disc height, and signal intensity. Discs that underwent discography had greater progression of degenerative findings compared with the noninjected control discs: 54 discs (35%) in the discography group compared with 21 (14%) in controls (p=.03). Furthermore, 55 new herniations in the discography group occurred compared with 22 in controls (p=.0003), and

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these new herniations were more commonly observed on the annular puncture side. Significant loss of disc height (p=.05) and signal intensity (p=.001) were also observed with discography subjects. This important investigation and others have given all practitioners pause about using discography as we may be "robbing Peter to pay Paul."

Discography may predispose to accelerated intervertebral disc degeneration via structural disruption via needle puncture, delamination via injection of pressurized fluid or by cell death, and dysfunction via interactions between native cells and the injected agent. Structural disruption in the annulus from small and large needles is known to occur. Needle puncture creates slowly progressive and repeatable animal model of disc degeneration, with needle size dependence [5,6]. In vitro studies on disc needle injuries show that even small needles produce annular holes of varying size and shape that remain open, create localized strain concentrations, and induce cell death around the injury site [7,8]. Needle puncture holes influence biomechanics of small and large animal discs, and relative size of needle holes to disc height is an important variable influencing biomechanical behaviors [9]. Small needles that penetrate the annulus affect disc height, nucleus pressurization, and neutral zone biomechanics [10]. Large needles and herniation produce injuries that can diminish annular integrity more broadly with increased range of motion and reduced stiffness [10]. A large loss of annular integrity is detectable via increased torsional range of motion in vivo and can be associated with patients' LBP [11]. Injection of pressurized fluid can further injure discs by inducing concentric tears and delamination [12]. Fortunately, the elegant fiber-reinforced and laminated composite structure of the intervertebral disc is highly effective at arresting crack propagation [13], and many small needle injuries in rabbits do not accelerate disc degeneration [5,6]. Human discs are greater in size and have more complex structures than discs in laboratory animals [14] providing even more structural features to arrest crack propagation but also more structural defects that may result in stress concentrations. Consequently, although we can conclude that structural defects have a deleterious effect on disc biomechanics and biology, it is impossible to extrapolate these basic science studies performed largely on animal tissues to suggest that there will be meaningful differences in the human clinical conditions based on structural disruption from discography.

Gruber et al. [1] directly address the question that injectable agents can do unintended harm to disc cells. Cytotoxicity of injectable agents is an essential question for any diagnostic or therapeutic intervention, and the increased awareness created with this study is an important contribution. Results demonstrated significantly increased dead and apoptotic cells and reduced cell proliferation with increasing isovue concentrations. Use of human cells and osmotically equivalent control media adds relevance. An et al. [15] investigated cytotoxicity of anesthetic and contrast agents on bovine disc cells with evidence for increased cell death by anesthetics. Cells in the region of injection are vulnerable, and cytotoxicity of injectable agents is more well known for anesthetics including other recent data showing evidence for bupivacaine cytotoxicity to intervertebral disc cells [16,17]. Bupivacaine and lidocaine also have known cytotoxicity for articular chondrocytes [18,19], and in vivo intra-articular bupivacaine injection reduced cell density [20]. Most studies demonstrating cytotoxicity of agents used during discography and intra-articular injections remain descriptive and do not shed light on intracellular mechanism by which cell death occurs. It remains of interest to know if the compounds are directly cytotoxic or if pH conditions, preservatives, and other chemicals required for production result in the observed loss of cellularity.

Evidence for cytotoxicity when screening potential therapeutics on human annulus fibrosus cells in culture is cause for concern, yet monolayer culture is different from the clinical condition and animal models are different from humans. Gruber et al. [1] found a strong dose response of human disc cells to isovue in ranges from 12.5 to 100 mg/mL and 24-hour exposure time. However, many factors could amplify or dampen the cellular responsiveness

to such agents when applied in vivo. Gruber et al. note that areas of high localized concentration or pressurization may occur in vivo during injection, making their system more conservative. But this monolayer cell culture system did not model the gradual decreases in concentration that would be present during clinical procedures as isovue diffuses out of the disc, suggesting that in vitro culture results presented could also be greater than found in vivo. Furthermore, Gruber et al. [21] describe that disc cells respond differently in monolayer versus three-dimensional culture environments, and both annulus fibrosus and nucleus pulposus cells have a pericellular matrices that could influence the cellular responses to mechanical signals [13,22] and could further diminish responsiveness to injectable agents. Several small and large animal organ culture models offer promise for screening therapeutics [7,14,17,23] and may translate basic science findings to the clinic more directly than simpler cell culture models.

Gruber et al. suggest that their findings provide a plausible cell-based explanation for the accelerated disc degeneration observed in patients receiving discography. Their data support such a hypothesis, but needle injury and structural disruption offer equally plausible explanations for accelerated disc degeneration after discography. With so many differences between experimental systems and the clinic, the damage or cell loss described in these controlled experimental studies intended to induce measurable changes or dose “to effect” do not necessarily translate directly to clinically meaningful acceleration of painful disc degeneration from discography procedures that are intended to induce the smallest possible injury in human discs. Consequently, there is not ample evidence to abandon currently effective treatments until better alternatives are available. We can, however, conclude that there is a need to improve and optimize current injectable agents used in the disc for discography and therapies more broadly. The implications are great and suggest careful usage of discography with consideration of risks as well as benefits. However, the clinician is treating the whole patient, and however disconcerting these data are, there is much less damage to a disc from provocative discography than from a poorly indicated spinal fusion procedure. Consequently, the physician must have the freedom to practice his/her art with available tools informed by current science.

We believe that the most important contributions from this study and similar basic science studies with high translatability to the clinical condition are the directions they point to for improving current treatments. The advent of many novel biologic and tissue engineering treatments increases the relevance of these investigations on pathophysiology from needle injury and injection toward the goal of creating the design envelope for safe and effective treatments to restore disc height and annular integrity, while promoting healthful cell phenotype and proliferation [10]. With knowledge gained from well-controlled cell culture studies, as described by Gruber et al., awareness is heightened at risks associated with current procedures and clarity is gained at the opportunities available for improving current treatments.

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References

1. Gruber HE, Rhyne AL, Hansen KJ, et al. Deleterious effects of discography radiocontrast solution on human annulus cell in vitro: changes in cell viability, proliferation, and apoptosis in exposed cells. Spine J. 2012; 12:329–35. [PubMed: 22424848]
2. Kang JD. Does a needle puncture into the annulus fibrosus cause disc degeneration? Spine J. 2010; 10:1106–7. [PubMed: 21094470]

3. Carragee EJ, Lincoln T, Parmar VS, Alamin T. A gold standard evaluation of the “discogenic pain” diagnosis as determined by provocative discography. Spine. 2006; 31:2115–23. [PubMed: 16915099]
4. Carragee EJ, Don AS, Hurwitz EL, et al. 2009 ISSLS Prize Winner: does discography cause accelerated progression of degeneration changes in the lumbar disc: a ten-year matched cohort study. Spine. 2009; 34:2338–45. [PubMed: 19755936]
5. Masuda K, Aota Y, Muehleman C, et al. A novel rabbit model of mild, reproducible disc degeneration by an anulus needle puncture: correlation between the degree of disc injury and radiological and histological appearances of disc degeneration. Spine. 2005; 30:5–14. [PubMed: 15626974]
6. Sobajima S, Kompel JF, Kim JS, et al. A slowly progressive and reproducible animal model of intervertebral disc degeneration characterized by MRI, X-ray, and histology. Spine. 2005; 30:15–24. [PubMed: 15626975]
7. Korecki CL, Costi JJ, Iatridis JC. Needle puncture injury affects intervertebral disc mechanics and biology in an organ culture model. Spine. 2008; 33:235–41. [PubMed: 18303454]
8. Michalek AJ, Buckley MR, Bonassar LJ, et al. The effects of needle puncture injury on microscale shear strain in the intervertebral disc annulus fibrosus. Spine J. 2010; 10:1098–105. [PubMed: 20971041]
9. Elliott DM, Yerramalli CS, Beckstein JC, et al. The effect of relative needle diameter in puncture and sham injection animal models of degeneration. Spine. 2008; 33:588–96. [PubMed: 18344851]
10. Iatridis JC, Nicoll SB, Michalek AJ, et al. Role of biomechanics on intervertebral disc degeneration and regenerative therapies: what needs repairing in the IVD and what are promising biomaterials for its repair? Spine J. In press.
11. Haughton VM, Rogers B, Meyerand ME, Resnick DK. Measuring the axial rotation of lumbar vertebrae in vivo with MR imaging. AJNR Am J Neuroradiol. 2002; 23:1110–6. [PubMed: 12169466]
12. Fazzalari NL, Costi JJ, Hearn TC, et al. Mechanical and pathologic consequences of induced concentric anular tears in an ovine model. Spine. 2001; 26:2575–81. [PubMed: 11725238]
13. Iatridis JC, ap Gwynn I. Mechanisms for mechanical damage in the intervertebral disc annulus fibrosus. J Biomech. 2004; 37:1165–75. [PubMed: 15212921]
14. Alini M, Eisenstein SM, Ito K, et al. Are animal models useful for studying human disc disorders/degeneration? Eur Spine J. 2008; 17:2–19. [PubMed: 17632738]
15. An HS, Ren J, Zhang Y, Chee A. Effects of local anesthetic and non-ionic contrast agents on bovine intervertebral disc cells cultured in alginate. Proceedings of the Cervical Spine Research Society. 2010:103–4.
16. Quero L, Klawitter M, Nerlich AG, et al. Bupivacaine–the deadly friend of intervertebral disc cells? Spine J. 2011; 11:46–53. [PubMed: 21168098]
17. Wang D, Vo NV, Sowa GA, et al. Bupivacaine decreases cell viability and matrix protein synthesis in an intervertebral disc organ model system. Spine J. 2011; 11:139–46. [PubMed: 21296298]
18. Karpie JC, Chu CR. Lidocaine exhibits dose- and time-dependent cytotoxic effects on bovine articular chondrocytes in vitro. Am J Sports Med. 2007; 35:1621–7. [PubMed: 17664340]
19. Chu CR, Izzo NJ, Papas NE, Fu FH. In vitro exposure to 0. 5% bupivacaine is cytotoxic to bovine articular chondrocytes. Arthroscopy. 2006; 22:693–9. [PubMed: 16843803]
20. Chu CR, Coyle CH, Chu CT, et al. In vivo effects of single intra-articular injection of 0. 5% bupivacaine on articular cartilage. J Bone Joint Surg Am. 2010; 92:599–608. [PubMed: 20194318]
21. Gruber HE, Hanley EN Jr. Human disc cells in monolayer vs 3D culture: cell shape, division and matrix formation. BMC Musculoskelet Disord. 2000; 1:1. [PubMed: 11231882]
22. Cao L, Guilak F, Setton LA. Pericellular matrix mechanics in the anulus fibrosus predicted by a three-dimensional finite element model and in situ morphology. Cell Mol Bioeng. 2009; 2:306–19. [PubMed: 19946619]
23. Gawri R, Mwale F, Ouellet J, et al. Development of an organ culture system for long term survival of the intact human intervertebral disc. Spine. 2011; 36:1835–42. [PubMed: 21270705]