Bionate Lumbar Disc Nucleus Prosthesis: Biomechanical Studies in Cadaveric Human Spines

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ABSTRACT: Design: cadaveric spine nucleus replacement study. Objective: determining Bionate 80A nucleus replacement biomechanics in cadaveric spines. Methods: in cold preserved spines, with ligaments and discs intact, and no muscles, L_3-L_4, L_4-L_5, and L_5-S_1 nucleus implantation was done. Differences between customized and overdimensioned implants were compared. Flexion, extension, lateral bending, and torsion were measured in the intact spine, nucleotomy, and nucleus implantation specimens. Increasing load or bending moment was applied four times at 2, 4, 6, and 8 Nm, twice in increasing mode and twice in decreasing mode. Spine motion was recorded using stereophotogrammetry. Expulsion tests: cyclic compression of 50−550 N for 50,000 cycles, increasing the load until there was extreme flexion, implant extrusion, or anatomical structure collapse. Subsidence tests were done by increasing the compression to 6000 N load. Results: nucleotomy increased the disc mobility, which remained unchanged for the adjacent upper level but increased for the lower adjacent one, particularly in lateral bending and torsion. Nucleus implantation, compared to nucleotomy, reduced disc mobility except in flexion-extension and torsion, but intact mobility was no longer recovered, with no effect on upper or lower adjacent segments. The overdimensioned implant, compared to the customized implant, provided equal or sometimes higher mobility. Lamina, facet joint, and annulus removal during nucleotomy caused more damaged than that restored by nucleus implantation. No implant extrusion was observed under compression loads of 925−1068 N as anatomical structures collapsed before. No subsidence or vertebral body fractures were observed under compression loads of 6697.8−6812.3 N. Conclusions: nucleotomized disc and L_1-S_1 mobility increased moderately after cadaveric spine nucleus implantation compared to the intact status, partly due to operative anatomical damage. Our implant had shallow expulsion and subsidence risks.
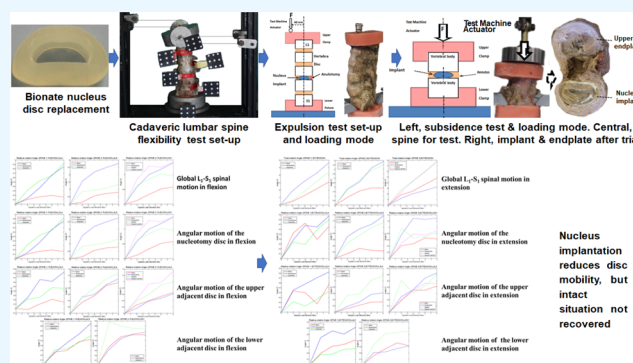
1. INTRODUCTION

Worldwide, low back pain is one of the most common ailments.[1] Although its etiology is quite broad, degenerative disc disease and disc herniation are some of its causes.[2] Often, we can treat patients conservatively, but some may eventually require surgical treatment.[3] Surgical procedures addressing these pathologies are spinal fusion[4,5] or motion preservation techniques, like total disc[6] and nucleus replacement.[7] However, the spinal fusion changes the spine biomechanics irreversibly, inducing adjacent long-term arthritic changes that cause chronic pain. Thus, all techniques designed to preserve motion are to be preferred. The nucleus replacement is a minimally invasive alternative to more aggressive approaches like total disc replacement or spinal fusion. It aims to improve pain and lumbar spine biomechanics with minimal disruption to nearby anatomical structures. It is indicated mainly for disc herniation and perhaps early disc degeneration if the annulus fibrosus is still competent.[8]

Many attempts in this arena have ended in implant removal from the market.[9,10] There have been many problems, but extrusion[11] and subsidence[12] are the leading drawbacks. The search to find the ideal material has proven the polycarbonate urethane group to be one of the most valuable compounds for nucleus disc replacement.[11] As a result, engineers have progressively improved designs to ease its insertion through a minimal annulotomy. After all, the annulus defect to which the surgeon removes the extruded nucleus pulposus is also how the nucleus implant may extrude in the future. This way, a substantial effort has been made to find techniques to close the

annulotomy and prevent the dreaded nucleus implant extrusion.[12] Endplate subsidence is the next challenge, particularly in rigid implants transmitting the load in a reduced endplate area.[13]

We have developed a new nucleus replacement implant made of polycarbonate urethane (Bionate, The Polymer Technology Group DSM-PTG, Berkeley, California, USA),[11,14] manufactured by injection molding.

We performed the biomechanical evaluation with cadaveric human spines to assess the suitability of our nucleus replacement, including implant mechanical behavior, mobility analysis, and extrusion and subsidence risk assessment. In addition, we evaluated the implant interactions with the treated spinal segment and its surrounding structures and tissues, such as annulus fibrosus, vertebral endplates, and facet joints.

2. MATERIALS AND METHODS

Previous studies selected a Bionate 80A ring-like design for nucleus replacement (Figure 1). This polycarbonate urethane has properties that resemble the intact intervertebral disc.[15] Therefore, the present study evaluated it in cadaveric lumbar spine specimens.

Figure 1. Bionate 80A nucleus replacement.

We did the tests according to ASTM WK4863 (Guide for Mechanical and Functional Characterization of Nucleus Devices) international standards.

We performed tests on three male cadaveric lumbar spines, 42, 48, and 50 year old, provided by the Facultat de Medicina i Odontologia, University of Valencia, Spain, and cold preserved since the death. Exclusion criteria: lumbosacral spine previous surgical procedures, trauma, tumors, infection, or inflammatory diseases. We ruled out osteoporosis with plain X-ray studies and dual-energy X-ray absorptiometry scans. We removed soft tissues, keeping ligaments and intervertebral discs, and sectioned the spine on the T_{12}-L_1 intervertebral disc and

sacroiliac joints. We examined each specimen with magnetic resonance imaging to customize nucleus implants.

The L_1 vertebra and sacrum were potted with acrylic bone cement (**SR Triplex Cold**, Ivoclar Vivadent AG, FL-9494 Schaan; Liechtenstein), keeping the L_3-L_4 disc horizontal.

We thawed the specimens for 4−5 h at room temperature and performed the tests at 22−23 °C, 40% humidity, spraying every 5 min with 0.9% sodium chloride solution to prevent tissue desiccation.[16]

Each specimen had nucleus implantation performed in a different intervertebral disc, L_3-L_4 for spine 1, L_4-L_5 for spine 2, and L_5-S_1 for spine 3. On spine 3, the L_5-S_1 disc was tested with the customized and overdimensioned nucleus implants, checking for differences in spine biomechanics. We compared different situations for the same specimen and not between them.

To implant the nucleus disc replacement, we did a unilateral partial laminectomy with a partial medial side facetectomy, just like we do it surgically to remove a prolapsed lumbar disc in an alive patient. Then, we did a 12 mm annulotomy and removed the nucleus pulposus completely. With an ad hoc designed instrument, we inserted the Bionate nucleus disc replacement through the annulotomy, making sure that the implant is entirely inside the disc and not protruding through the annulus (Figure 2).

2.1. Flexibility Tests. We measured the L_1-S_1 specimen motion in six main degrees of freedom (flexion, extension, right and left lateral bending, and right and left torsion) in the intact spine, nucleotomy, and nucleus implant.

We applied motion to the spine using pulleys and cables that converted force into a pure bending moment (Figure 3). We reproduced the six degrees of freedom by modifying the spine position in the machine and the pulleys' connection to the spine.

We applied an increasing load or bending moment for every movement in several steps at 2, 4, 6, and 8 Nm and used it four times per test, twice in increasing mode and twice in decreasing mode, considering the average curve for result analysis and comparison.

We recorded the spine motion using stereophotogrammetry with nine reflective markers rigidly attached to the spine (Figure 3), and two video cameras used for motion recording
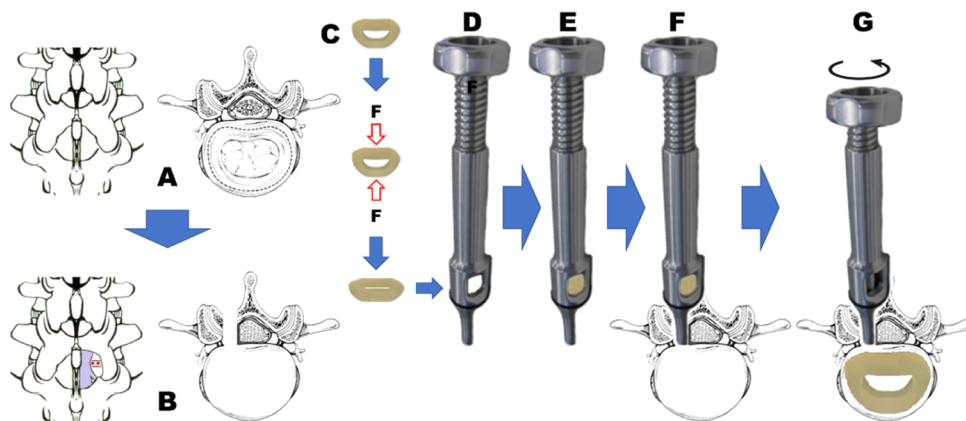

Figure 2. Surgical procedure to implant the Bionate nucleus replacement. (A) Normal lumbar spine specimen. (B) Partial hemilaminectomy plus medial facetectomy. (C) Implant compressed sideways to insert it inside the *ad hoc* created surgical instrument. (D) Surgical instrument without the Bionate implant. (E) Surgical instrument with the nucleus replacement inside it. (F) Surgical instrument placed inside the spinal canal with its mouth in the annulotomy. (G) Bionate nucleus replacement once inserted inside the disc space.
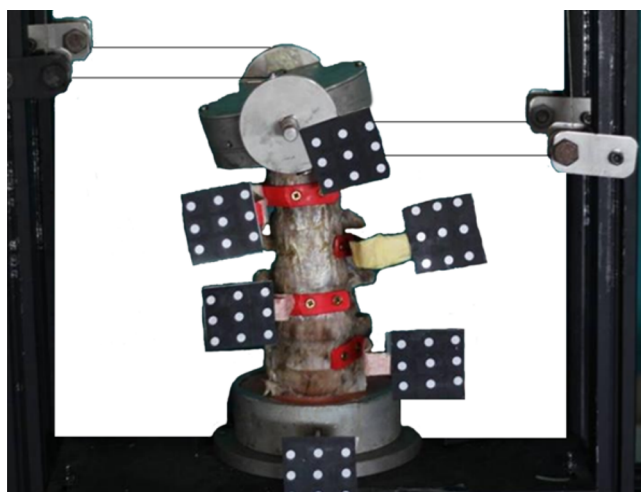
Figure 3. Cadaveric lumbar spine flexibility test setup.

and video-data processing. Then, with a Kinescan-IBV,[17] we calculated the markers' spatial coordinates.

2.2. Expulsion Tests. These tests aimed to evaluate the implant expulsion probability from disc space through annulotomy under compression load combined with a flexion moment opposite the annulotomy (Figure 4).
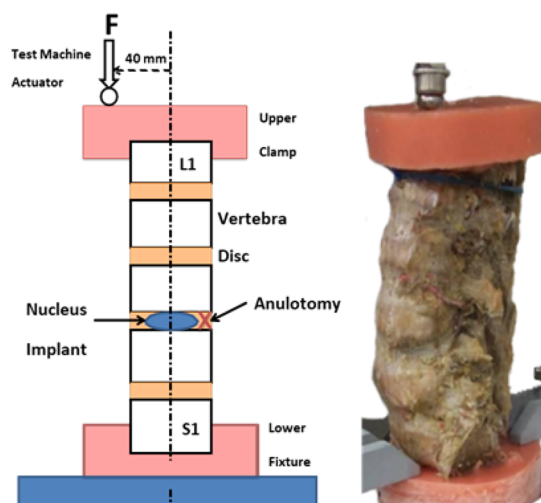

Figure 4. Expulsion test setup and loading mode.

Two different expulsion tests, dynamic and static, were performed on every specimen.

We applied a cyclic compression of 50−550 N for 50,000 cycles in the dynamic test. Spine loaded 40 mm eccentrically, equivalent to 2−22 Nm flexion moment (higher than the maximum during daily lumbar spine activities). We controlled the implant position and orientation inside the disc at the beginning, during, and after the test.

The static expulsion test was destructive, so we carried it out after the dynamic one. We applied an increasing compression load in the same manner as in the previous test, continuing until an extreme flexion was reached, implant's extrusion or any anatomical structure collapsed.

2.3. Subsidence Test. This test aimed to determine the nucleus implant subsidence risk inside the endplates under high compression loads. We sectioned the three cadaveric lumbar spines used in the flexibility and expulsion tests, leaving only the implanted disc spinal segment and fixing the upper and lower vertebrae with acrylic bone cement (Figure 5).

We applied a pure increasing compression 6000 N load (published lumbar vertebra maximum compression resistance[18]) on the upper vertebral center. Once the test was over, we sectioned the disc annulus, checking for subsidence (Figure 5).

3. STATISTICAL ANALYSIS

We did descriptive statistics using Excel (Microsoft Corporation, Redmond, WA, USA) and SPSS 26 (IBM Corporation, Armonk, New York, US), and the GNU Octave software was employed to calculate the movement's angles and parameters (GNU General Public License, https://www.gnu.org/software/octave/index). In addition, we used the statistical analysis R (R Development Core Team) (Kirby and Gerlanc, 2013; "R: The R Project for Statistical Computing," n.d.) in combination with the Deducer user interface (I. Fellows, "Deducer: A Data Analysis GUI for R", Journal of Statistical Software, vol. 49, no. 8, 2012).[19,20]

4. RESULTS

None of the specimens harbored any spinal pathology or osteoporosis.

4.1. Flexibility Tests. We will depict flexibility, equivalent to intervertebral motion, concerning the applied bending moment. We recorded intervertebral disc movements for every specimen in the intact L_1-S_1 spine, nucleotomy disc, and upper and lower adjacent discs.
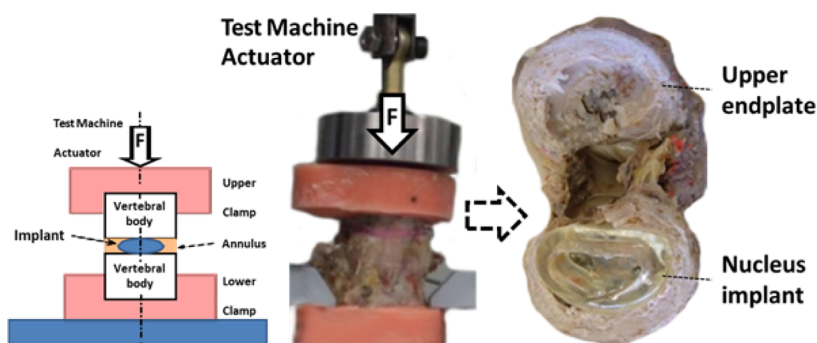
Figure 5. Left image shows the subsidence test setup and loading mode. Central image shows the lumbar spine segment ready for the test. Right side shows the implant and endplate after the trial, with the disc cut to look for subsidence.
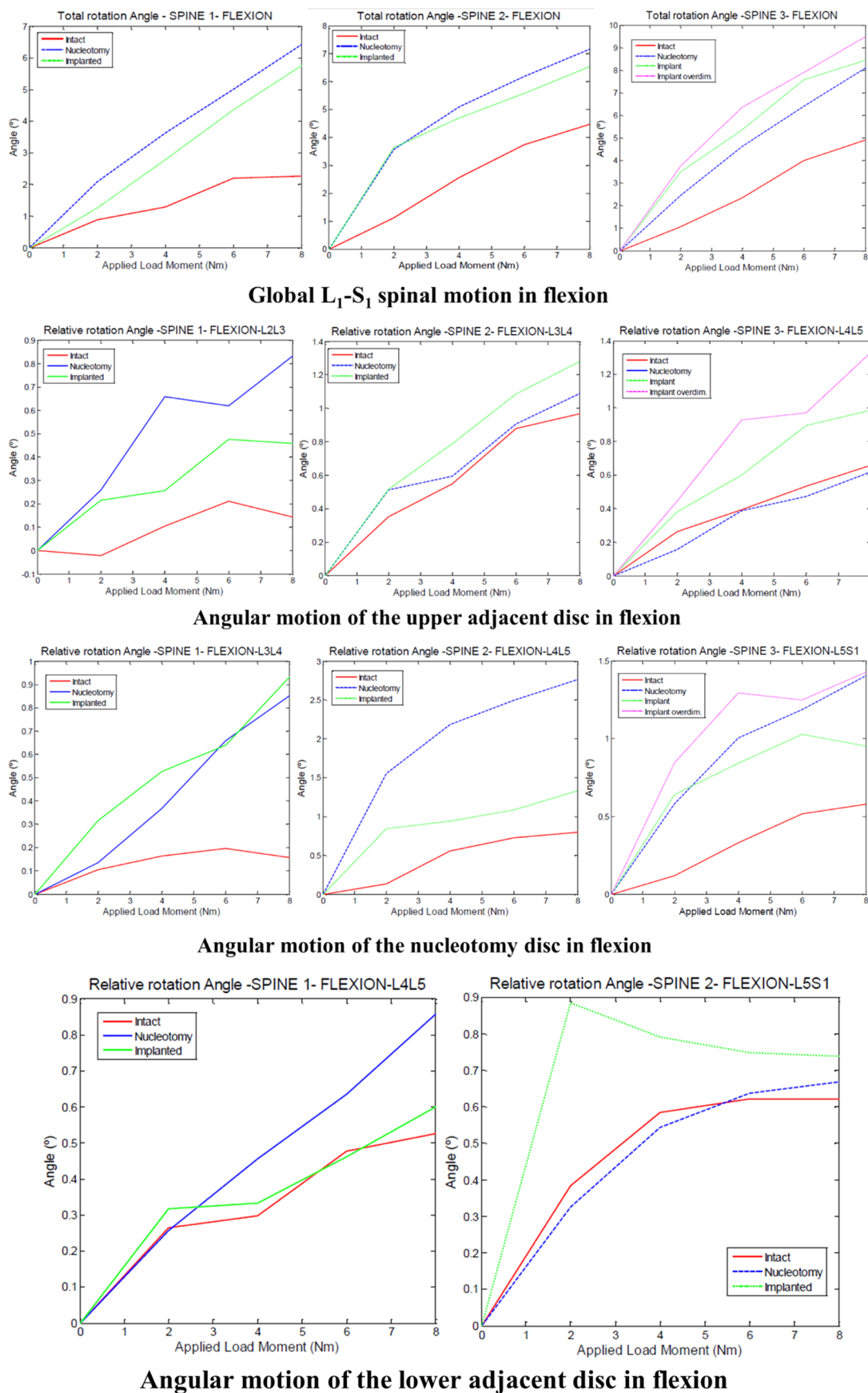
Figure 6. Spinal motion in flexion.

Global L₁-S₁ spinal motion in extension

Angular motion of the nucleotomy disc in extension

Angular motion of the upper adjacent disc in extension

Angular motion of the lower adjacent disc in extension
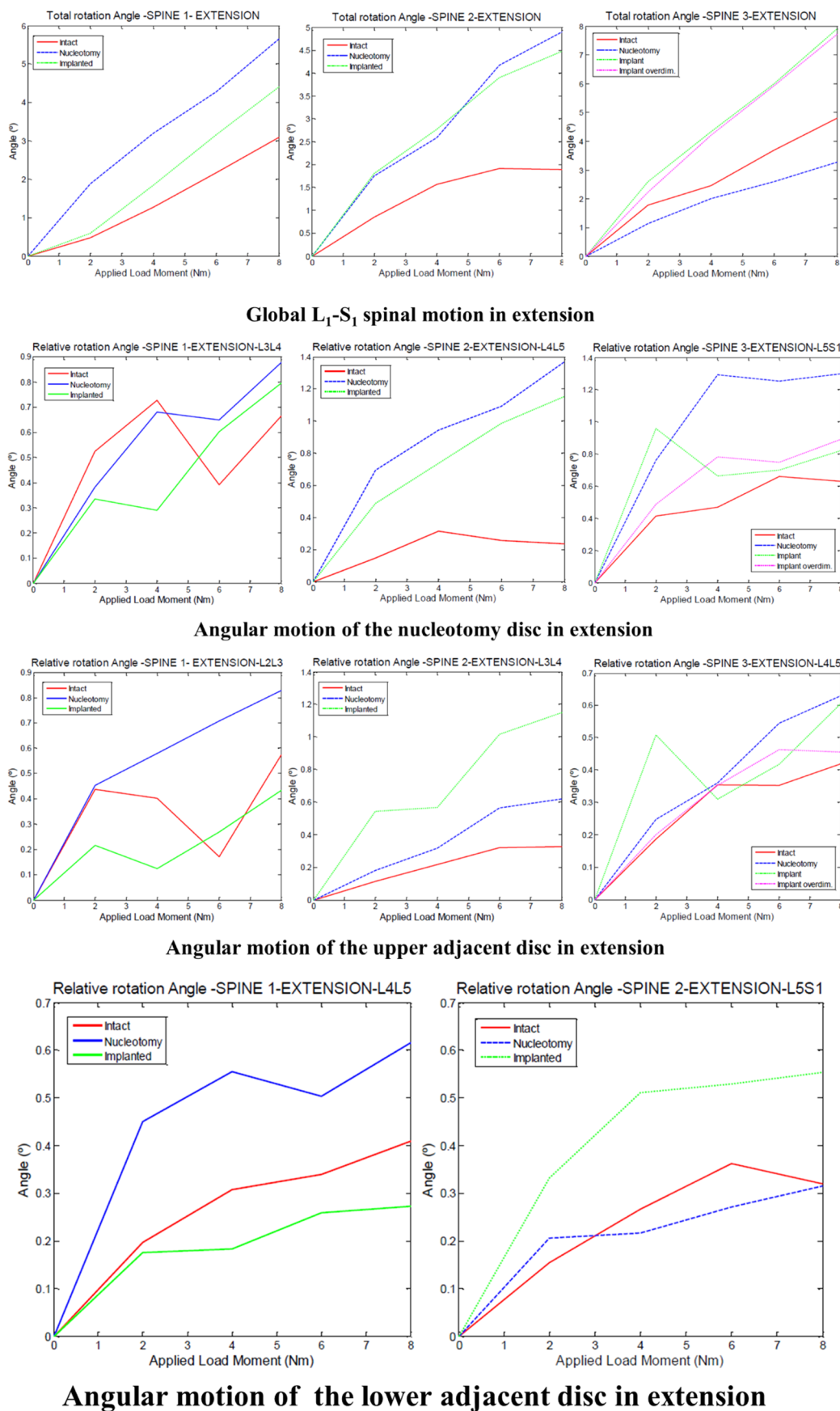
Figure 7. Spinal motion in extension.

Global L₁-S₁ spinal motion in right lateral bending

Angular motion of the operated disc in right lateral bending

Angular motion of the upper adjacent disc in right lateral bending

Angular motion of the lower adjacent disc in right lateral bending

Figure 8. Spinal motion in right lateral bending.

Global L_1-S_1 spinal motion in left lateral bending

Angular motion of the nucleotomy disc in left lateral bending

Angular motion of the upper adjacent disc in left lateral bending

Angular motion of the lower adjacent disc in left lateral bending
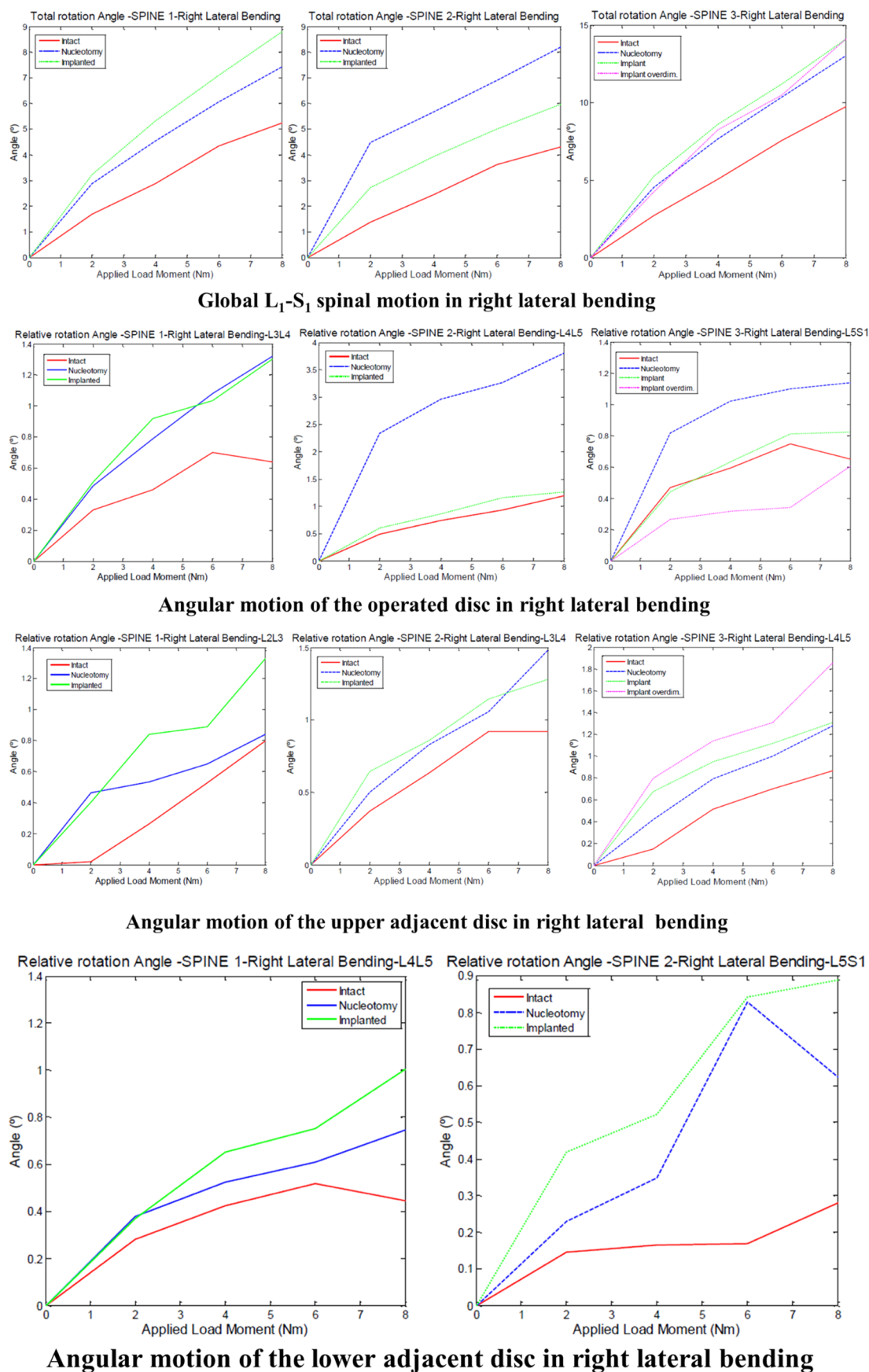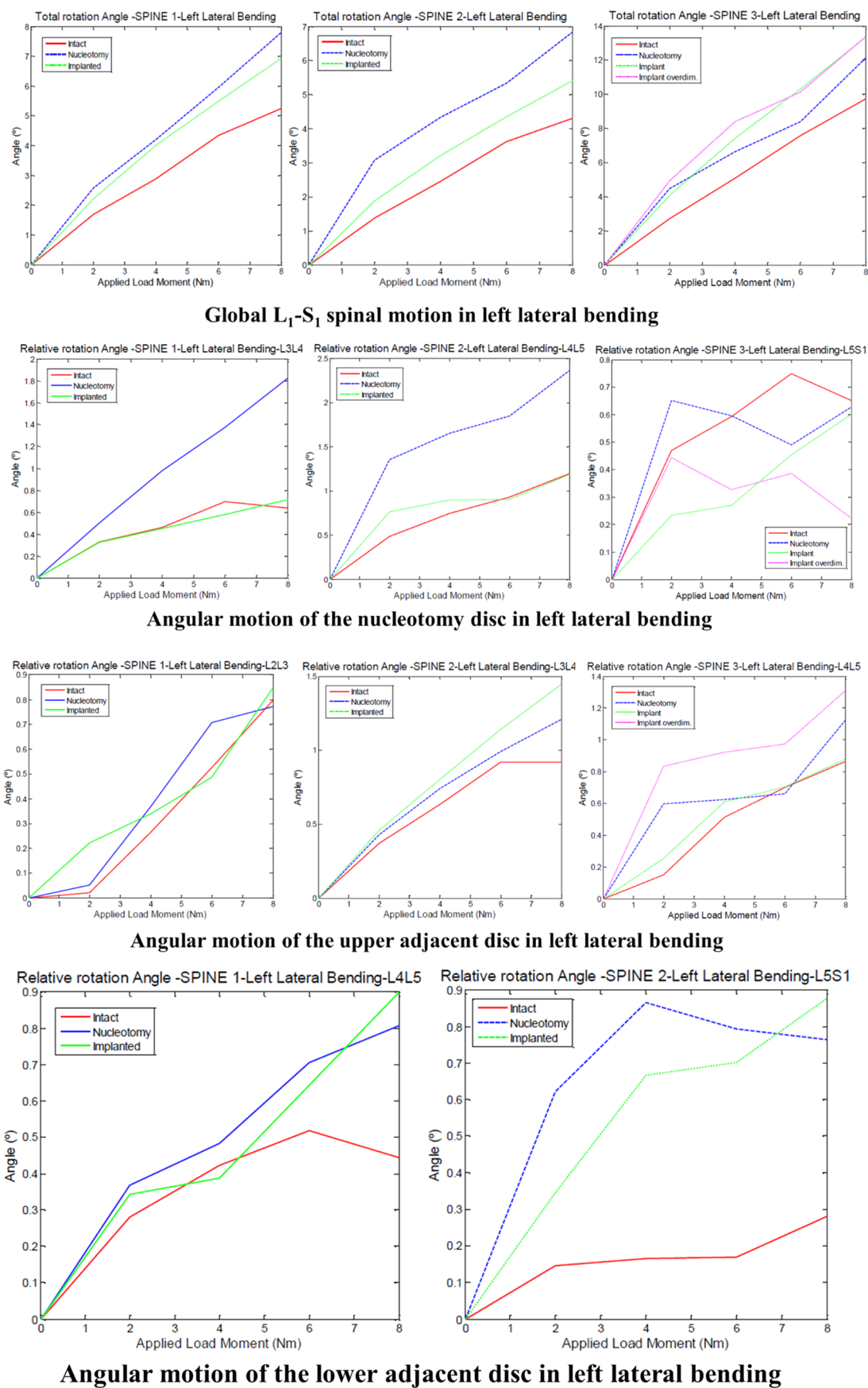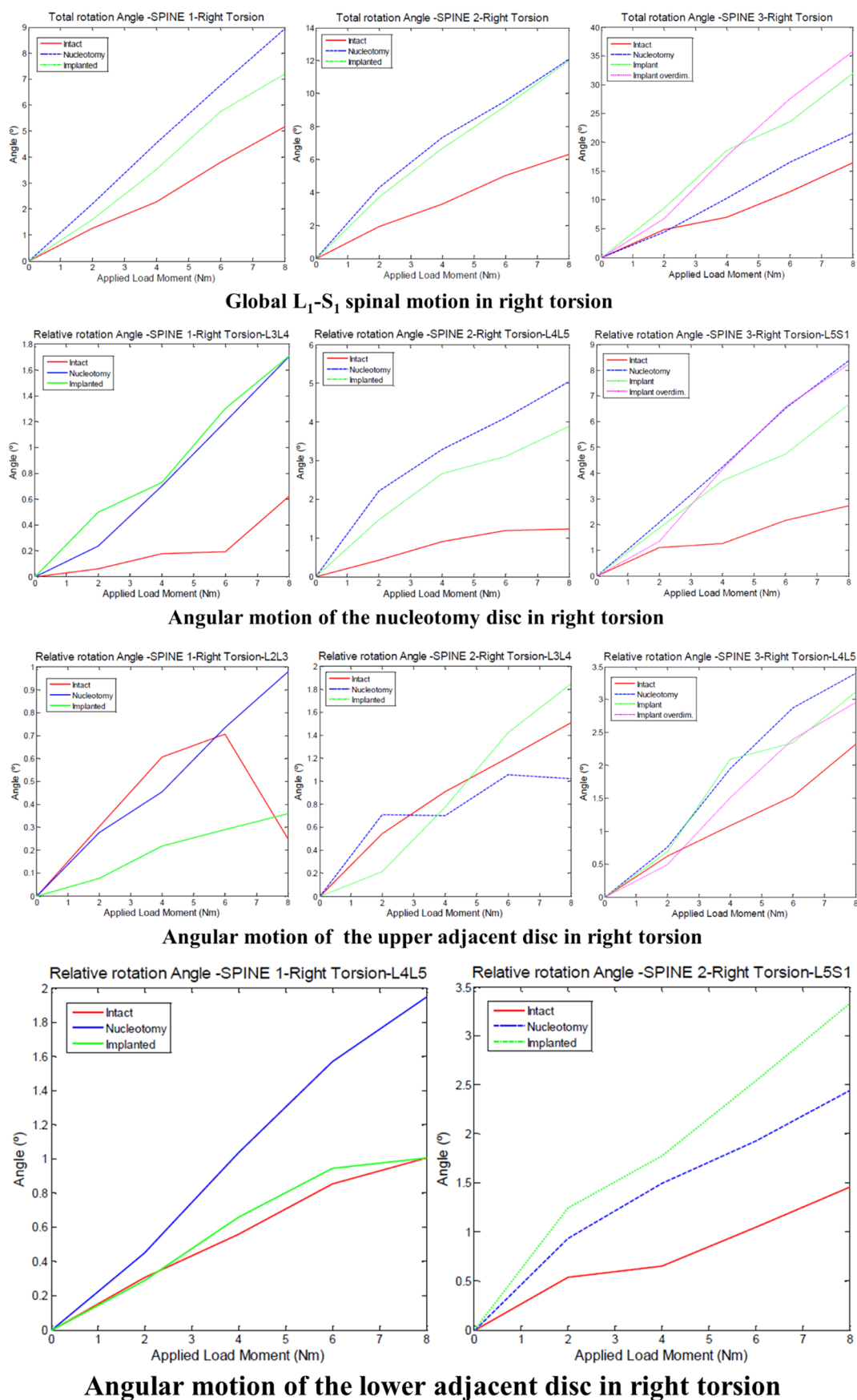
Figure 9. Spinal motion in left lateral bending.

Figure 10. Spinal motion in right torsion.

We divided the results according to the type of motion: flexion, extension, right and left lateral bending, and right and left torsion. For each movement, we will depict different scenarios' flexibility separately for each specimen. These results will be presented on graphs with the angular motion average curves concerning the applied bending moment. The maximum measurement technique associated error was $\pm 0.2°$.

In flexion, global L_1-S_1 flexibility was increased by nucleotomy in all cadaveric spines. Although nucleus implantation yielded lower flexibility than nucleotomy, this reduction was not statistically significant and did not restore intact spine flexibility ranges in any specimen. An over-dimensioned implant induced a higher flexion range than a customized implant (Figure 6).

Disc angular motion flexion range was increased by nucleotomy in all specimens. Nucleus implantation reduced the flexibility compared to nucleotomy in spines 2 and 3, but the original intact flexibility was almost restored only in spine 2 but not in spine 3. The overdimensioned implant, compared to the customized implant, yielded a higher flexion (Figure 6).

Upper adjacent segment flexibility was not affected by nucleotomy except in spine 1, which increased it. Nucleus implantation did not affect upper segment flexibility, except in spine 1, which showed a reduction compared to nucleotomy. In spines 2 and 3, there were no statistically significant differences between the intact spine, nucleotomy, and implanted states. The overdimensioned implant, compared to the customized implant, did not yield substantial flexibility changes (Figure 6).

Lower adjacent disc flexibility showed no significant differences between intact spine, nucleotomy, and nucleus implant (Figure 6).

In extension, nucleotomy increased global L_1-S_1 lumbar spine mobility in specimens 1 and 2 but with statistically nonsignificant differences. Nucleus implantation did not entirely recover intact spine flexibility. In spine 3, the nucleus implantation yielded even higher spinal mobility than nucleotomy or an intact spine (Figure 7).

The disc angular motion extension range was increased by nucleotomy, particularly in spines 2 and 3. Nucleus implantation retained or slightly reduced mobility compared to nucleotomy. No differences existed between customized and overdimensioned implants (Figure 7).

The upper spinal segment motion in extension was not significantly affected by nucleotomy . In specimen 1, nucleus implantation reduced flexibility; in specimen 2, it increased it; and in specimen 3, it showed no differences than nucleotomy. However, customized and overdimensioned implants showed significant differences (Figure 7).

The extension's lower adjacent disc angular motion showed no significant differences between the intact disc, nucleotomy, and nucleus implant (Figure 7).

Global L_1-S_1 spine mobility in right lateral bending was increased by nucleotomy in all specimens. Nucleus implantation reduced flexibility only in spine 2, without restoring the intact spine flexibility in any specimen. There were no differences between overdimensioned and customized implants (Figure 8).

Disc angular motion in right lateral bending was increased by nucleotomy in all spines. Nucleus implantation restored intact spine initial flexibility in specimens 2 and 3, whereas, in specimen 1, there was no improvement compared to

nucleotomy. Overdimensioned and customized implants showed no statistically significant differences (Figure 8).

Upper segment flexibility in right lateral bending was not affected by nucleotomy in spine 1, but nucleus implantation increased it. In spines 2 and 3, nucleotomy increased the mobility slightly, but it was not significantly changed by nucleus implantation. In all specimens, nucleus implantation flexibility differed from the intact disc. The overdimensioned implant, compared to the customized implant, increased the upper adjacent segment flexibility (Figure 8).

The lower adjacent disc angular motion in right bending was similar between nucleotomy and intact disc in spine 1. In spine 2, nucleotomy increased the downward segment mobility. There were no significant differences between nucleotomy and nucleus implantation (Figure 8).

In left lateral bending, global L_1-S_1 flexibility was increased by nucleotomy. Nucleus implantation slightly decreased flexibility compared to nucleotomy in specimens 1 and 2 (more in 2) but not in specimen 3. In any case, nucleus implantation recovered the intact disc global flexibility ranges. There were no statistically significant differences between overdimensioned and customized implants (Figure 9).

In left lateral bending, flexibility was increased by nucleotomy, and nucleus implantation restored it in specimens 1 and 2, with no significant differences among different states for specimen 3 (Figure 9).

Upper adjacent disc angular motion flexibility in left lateral bending was similar among the intact disc, nucleotomy, and nucleus implant in all specimens. However, the overdimensioned implant, compared to the customized implant, increased the upper segment flexibility (Figure 9).

Lower adjacent disc angular flexibility in left lateral bending was slightly increased in spine 1. Nucleus implantation produced the same behavior as nucleotomy (Figure 9).

Global L_1-S_1 mobility in right torsion was increased considerably by nucleotomy in all specimens, partly because some bone structures—part of the lamina and facet joints—were removed to perform the nucleotomy, and these structures played an essential role in limiting lumbar spine torsion movements. Nucleus implantation reduced it only in spine 1, not in spine 2 or 3. Indeed, in spine 3, flexibility with nucleus implantation was significantly higher. In addition, the over-dimensioned implant, compared to the customized implant, produced higher global mobility (Figure 10).

Angular disc mobility in the right torsion was increased by nucleotomy. Nucleus implantation reduced the nucleotomy disc mobility in specimens 2 and 3 without restoring the intact spine values. The overdimensioned implant, compared to the customized implant, increased the mobility (Figure 10).

Upper segment mobility in right torsion values was similar among intact disc, nucleotomy, and nucleus implantation. Nucleus implantation reduced the mobility in spine 1, increased it in spine 2, and was identical to nucleotomy in spine 3. The overdimensioned implant, compared to the customized implant, showed no significant differences (Figure 10).

Lower adjacent disc angular mobility in right torsion was increased by nucleotomy. Nucleus implantation restored the initial mobility in spine 1, but in spine 2 it had the opposite effect (Figure 10).

Global L_1-S_1 flexibility in left torsion was increased by nucleotomy in all specimens, especially in spine 3 ($10°$ increase). Nucleus implantation, compared to nucleotomy, did

Global L$_1$-S$_1$ spinal motion in left torsion

Angular motion of the nucleotomy disc in left torsion

Angular motion of the upper adjacent disc in left torsion

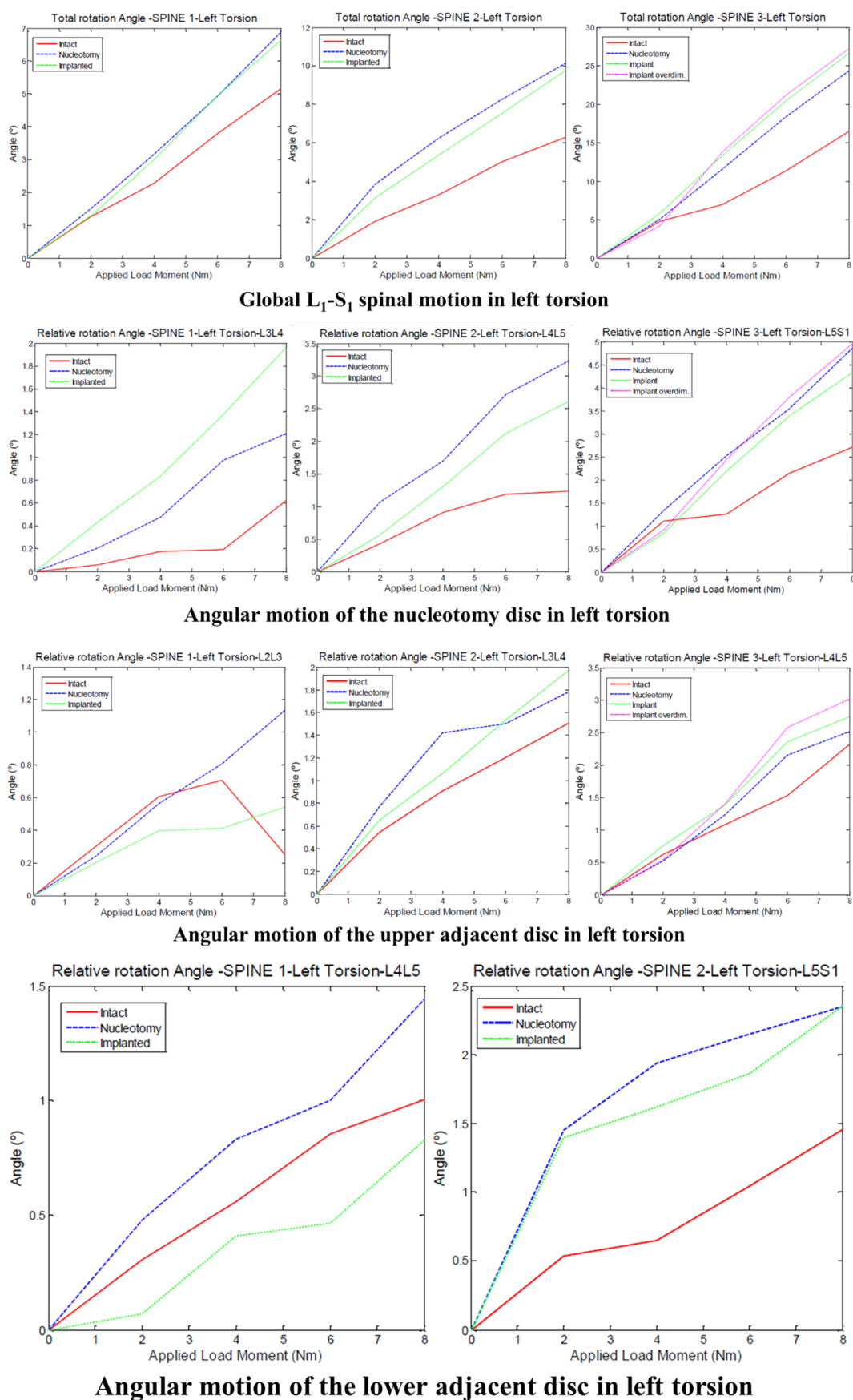**Angular motion of the lower adjacent disc in left torsion**

Figure 11. Spinal motion in left torsion.

not reduce the global flexibility in any specimen. The overdimensioned implant, compared to the customized implant, showed no significant differences (Figure 11).

In left axial torsion, flexibility was increased by nucleotomy. Nucleus implantation, compared to nucleotomy, reduced the segment mobility in spines 2 and 3. In all cases, the nucleus implant restored original intact disc mobility. The overdimensioned implant, compared to the customized implant, increased the mobility of the nucleotomy disc (Figure 11).

Upper disc flexibility in left torsion was not significantly affected by nucleotomy. Nucleus implantation, as nucleotomy and intact disc, yielded similar flexibility, especially in spines 2 and 3. There was no significant difference between overdimensioned and customized implants (Figure 11).

Lower-level flexibility in left torsion was increased by nucleotomy. Nucleus implantation reduced mobility only in spine 1 (Figure 11).

4.2. Flexibility Test Conclusions. Nucleotomy increased the L_1-S_1 spine global mobility for all degrees of freedom, and, in most movements, the disc mobility was increased. However, it induced minor changes in upper adjacent disc mobility, in most cases leading to a status similar to that of the intact spine, and it had a more significant impact on the lower adjoining disc, mainly in the lateral bending and torsion movements, where mobility of this segment was increased compared to the intact spine.

Nucleus implantation, compared to nucleotomy, did not reduce the L_1-S_1 global mobility to any degree of freedom, with few exceptions. In the nucleotomy disc, nucleus implantation reducesd disc flexibility compared to nucleotomy in most cases. However, intact disc flexibility ranges were no longer recovered with nucleus implantation in flexion-extension and torsion movements. In most movements, nucleus implantation did not affect upper adjacent disc mobility. In all cases, mobility with nucleus implantation was equivalent to that with the nucleotomy state.

In most cases, nucleus implantation, compared to nucleotomy, did not modify lower adjacent segment mobility. The overdimensioned implant, compared to the customized implant, had the same or sometimes even higher flexibility.

Nucleus implantation did not restore the intact L_1-S_1 spine's initial flexibility, yielding a biomechanical behavior like the nucleotomy status.

Partial lamina, facet joint, and annulus removal during nucleotomy had a higher damaging effect on the operated disc and adjacent vertebral level biomechanics than the mechanical restoration achieved by nucleus implantation.

The main conclusion from the flexibility tests is that the customized nucleus implantation achieved a limited improvement in lumbar disc biomechanics compared to nucleotomy.

4.3. Expulsion Test Results. In dynamic testing, no specimens suffered nucleus implant expulsion or change in implant position or orientation inside the disc.

In static tests, the maximum compression load was 1068 N (>40 Nm flexion moment) for spine 1, 854 N (32 Nm) for spine 2, and 925 N for spine 3 (35 Nm). We stopped the static tests when discs or ligaments tore or lumbar spine deformation was excessive.

These results are positive as no specimen suffered nucleus implant expulsion, and in static tests, spinal anatomical structures would collapse before it. Therefore, implant expulsion risk under loads typical for daily activities is relatively low.

4.4. Subsidence Test Results. Maximum compression loads applied were 6697.8 N for spine 1, 6776.9 N for spine 2, and 6812.3 N for spine 3, and the maximum average lumbar vertebra resistance value was above 6000 N.[18] These results are positive since any specimen had no subsidence or vertebral body fracture. Implant subsidence risk into adjacent endplates was shallow under loads typical of daily activities.

5. DISCUSSION

Nucleotomy relieves nerve root impingement[21] but creates biomechanical destabilization[22] due to disc height loss,[23,24] intradiscal pressure reduction,[25] and motion range increase.[24,26] These changes accelerate disc degeneration[27,28] and induce zygapophyseal joint overload[29] with arthritic changes.[30,31]

Nucleus replacement technology, available since the 90' (PDN, Raymedica Inc., Minneapolis, USA),[9] had good clinical results initially, followed by complications related to subsidence and extrusion.[32−35] As a result, many other implants have been created,[7,8,36−44] only a few reaching the market,[10,45−50] and most are no longer in use. The reason is that although they achieve biomechanical restoration close to but not equal to an intact intervertebral disc,[24,26,36,51−56] extrusion and subsidence are not fully solved yet.[32,33,45,57,58]

Annulus functional restoration is paramount to recovering intervertebral disc biomechanics[12] as this keeps intradiscal pressure within normal ranges and minimizes extrusion risk.[12,59−61]

Different ways have been attempted.[62] Some researchers used materials that allow cellular seeding and, thus, disc regeneration.[63,64] The materials tried are many, and some, like silicones,[65] hydrogels,[44,55,66] polyurethane,[50] polycarbonate urethane,[10] or carboxymethylcellulose,[38] have biomechanical properties similar to the intact disc. However, problems are still commonplace. Hydrogels, for example, do not restore intact intervertebral disc biomechanics because they fail to correct the disc height and intradiscal pressure.[55] In addition, some of these materials fracture or break under cycling loading.[45] Some designs have an outside bag that prevents the spillage of implant debris, but the injected core-curing process poses another challenge.[51,53]

Implants with an uneven load distribution have a higher subsidence risk,[56] which is minimized in those with a central void cavity.[65] Without this space, implants are stiffer and apply higher stresses on the adjacent endplates.[65] The hole works as a dampening mechanism, improving load transmission and minimizing extrusion and subsidence. Our implant was based on this idea and has proven to be safe from the extrusion and subsidence points of view.

After nucleotomy, compared to the intact nucleus, motion range recovery is not complete in our nucleus replacement, as reported with other nucleus implant devices.[24,26,36,51−56] The most significant improvement is in lateral bending, axial torsion, and flexion-extension,[24] as in our nucleus replacement. Therefore, in this area, there is still room for improvement.

Another critical issue is how the nucleus implant fits the nucleotomy cavity, as filling below 85% leads to insufficient disc biomechanics recovery.[13,26,67,68] On-site self-curing implants seem logical,[53,69] but the *in situ* polymerization process is uncontrollable,[70] sometimes takes several hours,[41] and the risk of tissue damage induced by polymerizing agents or byproducts makes this option unpredictable. Manufacturing a nucleus implant outside the human body is more reliable but

needs a bigger annulotomy. We opted for this last option but selected a material and implant design that allowed a reasonable annulotomy. We did not see an increased extrusion risk that could be related to our strategy.

Nucleus implant size also matters, as 25% oversizing yields biomechanical results resembling the intact intervertebral disc and 25% undersizing reproduces the nucleotomy.[67,71] Therefore, a customized implant provides the best situation because oversizing makes the implant stiffer and increases the extrusion and subsidence risks.[13,67,71] Our data support this assumption.

Our study shows that nucleus replacement returns the adjacent level loads to the situation before nucleotomy. As far as we know, our research group is the first to report these data.

6. LIMITATIONS

The number of specimens is small, and we have not done long-term studies. The amount of disc nucleus removal might not be as complete as expected, and in some specimens, perhaps some nucleus material was unwantedly left inside the disc. The necessary lamina and facet joint partial removal must have influenced the results. A completely percutaneous procedure (*e.g.*, chemonucleolysis) with a percutaneously injected self-curing implant would provide more accurate data. We do not present clinical studies.

7. STRENGTHS

We have repeatedly tested the intact cadaveric spine, nucleotomy, and nucleus implantation statuses and compared overdimensioned and customized implants' biomechanical behaviors. Each specimen served as the control. In addition, we performed extrusion and subsidence tests under most stringent conditions.

8. CONCLUSIONS

The nucleus replacement design and material showed excellent mechanical strength and endurance under dynamic loading conditions. On cadaveric spines, compared to the intact specimens operated on the spinal segment and L_1-S_1 spine, global mobility increased after implanting our nucleus replacement. This motion increase is acceptable from the functional performance perspective and is partly related to the necessary alteration of anatomical structures to perform nucleotomy and nucleus implantation. However, the new customized nucleus implant had shallow expulsion and subsidence risks. Therefore, we can say that overdimensioning the implant does not provide additional advantages.

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A.V., conception and design of the study, methodology, drafting the article, revising it critically for crucial intellectual content, and final approval of the version to be submitted. **V.V.**, conception and design of the study, methodology, drafting of the article, revising it critically for crucial intellectual content, and final approval of the version to be submitted. **C.M.A.**, conception and design of the study, methodology, drafting the article, revising it critically for crucial intellectual content, and final approval of the version to be submitted. **P.C.**, acquisition of data, analysis and interpretation of data, data curation, formal analysis, and final approval of the version to be submitted. **P.J.-G.**, acquisition of data, analysis and interpretation of data, data curation, formal analysis, and final approval of the version to be submitted. **C.B.**, analysis and interpretation of data, software, supervision, validation, visualization, and final approval of the version to be submitted. **N.S.-S.**, acquisition of data, analysis and interpretation of data, data curation, formal analysis, and final approval of the version to be submitted. **L.V.**, drafting the article, writing—original draft, writing—review and editing, and final approval of the version to be submitted. All authors reviewed the manuscript.

Notes

The authors declare no competing financial interest.

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