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◆ **Methodology**

◆ **In Vitro Investigation of Lumbar Disk Implants (SINUX)**

Degenerative changes to the spinal column and disk-related disorders of human beings were described in antiquity by Hippocrates (460–377B.C.) as hip pain. Even before the age of 30 people begin to suffer degenerative changes of the intervertebral disks, and four out of five people suffer from back pain at some time in their lives. However, 80 to 90% of all cases of acute backache clear up within 6 weeks regardless of whether they are treated or of the type of therapy received. The disk is the largest unvascularized structure in the body. In children, disks have a water content of up to 90%, but as age increases, this figure falls to less than 70%. The solid constituents of the disk, such as proteoglycans, form up to 50% of its dry weight. The water is not free, rather being bound to structural components of the macromolecules. In vivo, the pressure in the nucleus pulposus is generated via the osmotic gradients of the proteoglycans and the water-binding molecule hyaluronic acid. With the exception of organ pain, pain syndrome in the lumbar spine region is generally due to premature disk deterioration, particularly at L4–L5 and L5–S1. Atrophy and compression of the disk lead to loosening of the vertebral motor segments. Degeneration involves the disturbance of fluid transfer due to sclerosis of the end plates and basal plates. As a result, the disk loses more and more water and the intradiskal pressure falls, leading to reduction in the intervertebral space. Kolditz et al¹ were able to show that the disk loses water under increasing strain, and in consequence the osmotic gradient increases until equilibrium between osmotic and mechanical pressure is reached. When the strain on the disk is relieved there is a corresponding influx of fluid. The normal intradiskal pressure (L5–S1), without any additional external load, has been put at up to 5 atm (500 kPa).² In their paper, Wilke et al³ showed that, under unfavorable load when lifting heavy weights, the intradiskal pressure in segment L4–L5 can rise as high as 2300 kPa.

In an intact segment the outer fibers are aligned with the longitudinal ligaments, whereas the fibers in internal layers are arranged at a 60 degree angle.⁴ This orientation is the principal factor producing torsional strength.⁵ An important element in the degenerative process is the microsystem for transporting matter via the end plates. As the disk becomes drier, the end plates transform into a sclerotic barrier. The

◆ **Conclusion**

segment reduces in height, with attendant parallelization of the type I collagen fibers in the region of the external annulus fibrosus. This parallelization causes the segment to lose torsion resistance.

This process may be regarded as a vicious circle. The degeneration of the nucleus pulposus leads to reduction in segmental height and accompanying loss of torsion resistance. This, in turn, entails an increase in the segment's physiological mobility and accelerated degeneration. Degeneration involving radial fissures in the annulus fibrosus can lead to a prolapsed disk and a subsequent need for nucleotomy. In this vicious circle the segmental degeneration and the nucleotomy are intimately linked because the nucleotomy has a similar effect to the degeneration just described. However, unlike that process, the changes after nucleotomy can proceed at a significantly faster rate, so that mobility compensation mechanisms such as osteophytic bone spurs, which produce a secondary reduction in mobility, do not cut in until later. The removal of disk tissue reduces the intradiskal pressure and the intervertebral space, thus increasing segmental mobility. This process causes considerable wear of the vertebral arch joints, which can lead in turn to significant symptoms. The pain caused by these degenerative symptoms, such as narrowing of the spinal canal, is often difficult to distinguish from pain resulting from disk problems. Furthermore, if age leads to a natural stiffening of the segment the symptoms will rapidly diminish. However, all too often this process takes many years and is not complete until advanced old age, or indeed it may not occur at all. Meanwhile, as long as mobility is retained the accompanying pain can be expected to persist.

In the presence of the relevant indications, lumbar nucleotomy may be performed. However, the procedure is associated with a significant rate of postoperative problems. A meta-analysis of the literature conducted by Schulitz et al,⁶ involving a total of 20,148 patients, found rates of poor postoperative outcomes ranging from 7 to 27%. These postoperative problems in connection with disk surgery are often described either as postdiscectomy syndrome (PDS) or as failed back surgery syndrome (FBSS). Two major causes of these problems are postoperative instability and postoperative recidivism, although they may also be due to

narrowness of the recessus lateralis, epidural fibrosis, arachnoiditis, facet syndrome, operating on the wrong segment, or poor surgical technique. The changed postoperative mobility of the vertebral motor segment is a significant causative factor for the occurrence of postoperative pain.⁷ Increasingly, discectomy was found to lead to decreased height of the intervertebral space and reduced intradiskal pressure. White and Panjabi⁸ describe a variable pivot in the dorsal region of the segment. Increasing instability can lead to a displacement and widening of this pivot, which means in turn that this increase causes complex changes in the overall biomechanical structure. Because there is no precise definition of the term *instability* in relation to the vertebral motor segment, this state of affairs is better described as “abnormal mobility” or “increasing mobility,” and most closely resembles the situation after a nucleotomy. Others, though, describe the postnucleotomy situation as an increased range of motion (ROM) between adjacent vertebral bodies.

The field of spinal surgery, and in particular the surgical treatment of degenerative disease of the lumbar spine, is currently undergoing a paradigm shift. Both disk operations in their technical variants and fusion methods are being viewed in an increasingly critical light. In a leading article for *Scientific American* entitled “New Thinking about Back Pain,” the author notes the minimal correlation of pathological findings and imaging techniques, of the simultaneous frequency of back pain syndrome and the consequent problems in determining whether surgical or conservative therapy is indicated.⁹ A new “old” concept involves the development of a flexible disk implant, which aims to stabilize the affected segment while also reconstructing the physiological mobility of the vertebral motor segment. The principal requirements of a disk implant are well-functioning biomechanical reconstruction of the intervertebral space, good biocompatibility, and long-term load resistance coupled with ease of handling conducive to implantation via minimally invasive methods of surgical access.

◆ Methodology

The three-dimensional (3D) study was performed under the leadership of Professor F. Lavaste in connection with a cooperation agreement with ENSAM (Ecole Nationale Supérieure d'Arts et Métiers), University of Paris, and also the biomechanics laboratory located there [Laboratoire de biomécanique (LBM)]. The research setup developed there¹⁰ allowed us to conduct a 3D study of the lumbar motor segments. Two segments plus three vertebrae were required to conduct each study. The adjacent musculature was removed but the bony and ligament structures were retained. The vertebral motor segment under investigation, together with its lower vertebral body, was fixed to a special metal with a low boiling point (70°C) to avoid damaging the bony and ligamentous structures (Fig. 18-1).

The test receptacle was attached to the adjacent, central vertebral body, and to ensure that it interfered as little as possible with the application of force, the force transducer was attached to the upper vertebral body. As a result it was possible to take measurements of even large ranges of

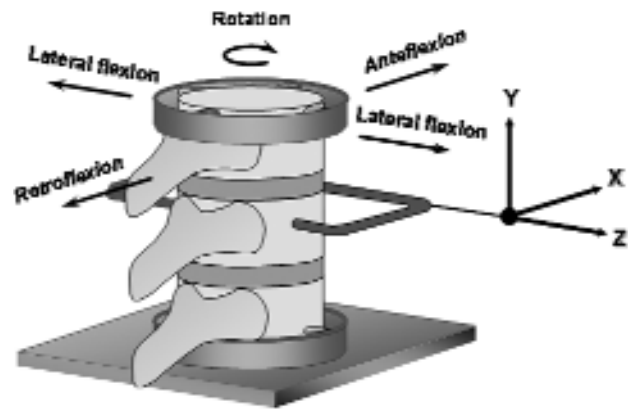


Figure 18-1 Three-dimensional experimental setup.

motion. The force applied was limited to a physiologically nondestructive 7 Nm. In investigating anteflexion, retroflexion, lateral flexion, and torsion in the three directions of movement (Fig. 18-2), rotation was measured in degrees and translation in millimeters over each of the three spatial axes (X, Y, Z). The rotation and translation could be directly recorded and processed digitally via the electromechanical resistors (Fig. 18-2). Test values were always recorded from maximum amplitude to maximum amplitude and back, thus ruling out errors in determining the neutral point or neutral zone.

To evaluate the stability of the motor segment, the degree of movement relative to the force applied was calculated, and the value for the maximum experimental force of 7 Nm was used as the measure of maximum segmental stability. The results were then shown as percentage increases or decreases in the ROM as compared with the zero measurement for the intact disk segment (the relative extent of motion). For anteflexion and retroflexion the rotation A_z and translation D_x were recorded, whereas for lateral flexion A_x and D_z were calculated and for torsion A_y and D_y (Fig. 18-3).

Human spinal segments L2-L3 and L3-L4 were selected for experimental purposes because these are subject to less degenerative changes than the lower segments of the lumbar spine. The mean time of removal was 12 hours (9-16 hours) postmortem. Immediately after removal, the segments were frozen to -20°C, and the maximum preservation duration was limited to 3 months.^{11,12} The exclusion criteria applied were bone-destroying processes or injury to the annulus fibrosus, and in particular a prolapsed disk.

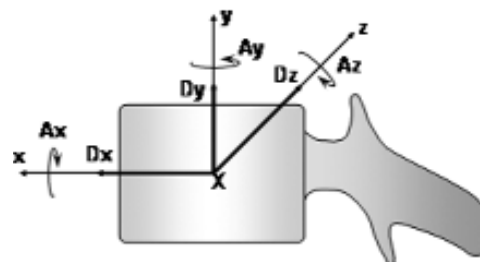


Figure 18-2 Three-dimensional measurement axes. D_x , D_y , and D_z directions of translation. A_x , A_y , and A_z directions of rotation.

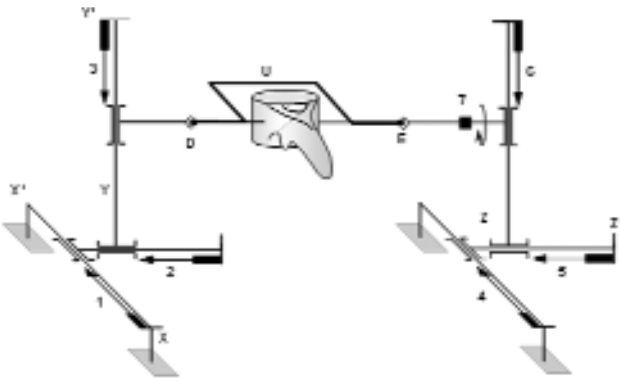


Figure 18-3 Recording and spatial layout of the electromechanical resistors.

◆ In Vitro Investigation of Lumbar Disk Implants (SINUX)

Apart from their biomechanical and toxicological properties, the most important criteria for disk implants are their intraoperative manageability and the size of the surgical access route. The suitability of a variety of different autopolymerizing plastics has been tested. Aryl- and vinyl-based compounds were found to be unsuitable because the chemical softeners that are added to these materials lead to severe wear and breakage under long-term load. Accordingly, the only option was to use a silicon-based plastic because its strength is controlled by intramolecular cross-linking. The plastic chosen was a polymethylsiloxane polymer. This was processed using a twin-cartridge system and applied using a mixing attachment. The polymer is initially a viscous liquid, but within 15 minutes it hardens without heat treatment into a dimensionally stable and permanently elastic solid.

Before testing the material's biomechanical suitability any possible tissue incompatibility had to be ruled out. Sterilization with both ultraviolet (UV) and gamma radiation led to material destruction, and the only possible means of sterilizing the polymer was through the use of ethylene oxide gas. It was found that sterilization did not lead to any changes in the plastic's physical properties because a variety of experimental setups uncovered no differences compared with the unsterilized material. Cytotoxicity was investigated in accordance with the International Standards Organization (ISO) 10993-5 standard. An important finding was that both the fully polymerized plastic and the two individual components did not cause any incompatibility reactions. Both the polymer and its two components were tested in direct and indirect contact. The tests were performed using HeLa cells, a line of human carcinoma cells. Tissue culture polystyrene (TCPS) was used as the negatively cytotoxic material and the metals tin and nickel as positively cytotoxic materials. In direct cell contact, the morphology, cell count, proliferation were investigated microscopically. None of these tests revealed any cytotoxic reactions under direct cell contact. The morphology was then examined microscopically in indirect (extract) contact. The metabolism after the MTT test, proliferation after the K_1 -67 test, and cell count after crystal violet

[DE4]

[DE5]

dyeing were recorded using an enzyme-linked immunosorbent assay (ELISA) reader, and no cytotoxic reactions were found under indirect contact either. [DE6]

Finally, long-term stress testing was performed. Using sterile materials, six elliptical test pieces were manufactured, each with a diameter of 31–20 mm and 3.5 mm thick. These dimensions represent those of an idealized nucleus pulposus. In an experimental setup using glass ceramic contact surfaces, the test pieces were subjected to long-term load at 37°C in a culture medium with an antibiotic additive. The components were then either autoclaved at 131°C for 20 minutes or disinfected using a 70% alcohol solution in the case of non-heat-resistant parts. Over the planned ~6-day period for the long-term load test, the medium in which each test piece was immersed was changed each day to examine the fluid for abrasion particles and possible cytotoxic reactions. The load profile was determined following a recent paper by Wilke et al.¹³ This involved a self-experiment conducted by a colleague in orthopedics who had a pressure sensor implanted in his L4–L5 intervertebral space to measure the pressure exerted under a variety of different load situations. The figures recorded were compared with those from the seminal study,¹⁴ to a large extent confirming these earlier findings. In our experimental setup the lowest pressure was fixed at 0.1 MPa (1 bar), equivalent to lying on one's back, and the maximum long-term load was set at 0.8 MPa, which is equivalent to the load exerted when jogging, and thus covering any normal load likely to be exerted during everyday life. Coughing, for instance, increases intradiscal pressure to only 0.38 MPa. Each test piece was subjected to a total of 5 million load cycles (LCs) at a frequency of 10 Hz. After each million LCs the load was raised to 1.7 MPa for 1000 LCs, a load equivalent to lifting 20 kg from the knees following back school recommendations. This load pattern was designed to test the demands placed on an implant over a 5-year lifetime. The varying load profile produced five load blocks for each of the six test pieces.

First, the dynamic modulus (**Fig. 18-4**) was evaluated. In the first block there was a significant increase in the modulus and thus of the test piece's rigidity, but in each subsequent block the rigidity leveled out at a stable value.

The mean plastic strain changed in similar fashion (**Fig. 18-5**). Initially, the load caused pronounced creep in the test piece, leading to reduced mean strain, but subsequently this leveled out at a stable value.

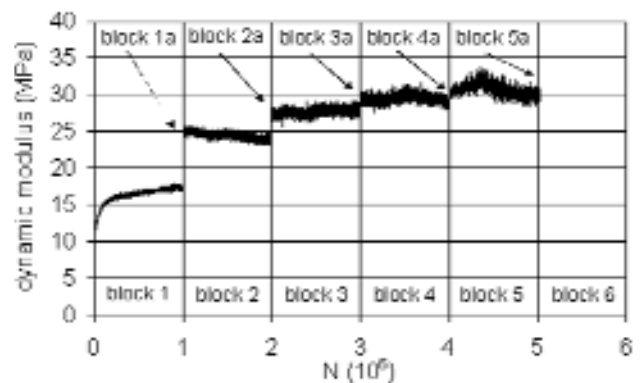


Figure 18-4 Dynamic modulus changes during the experiment.

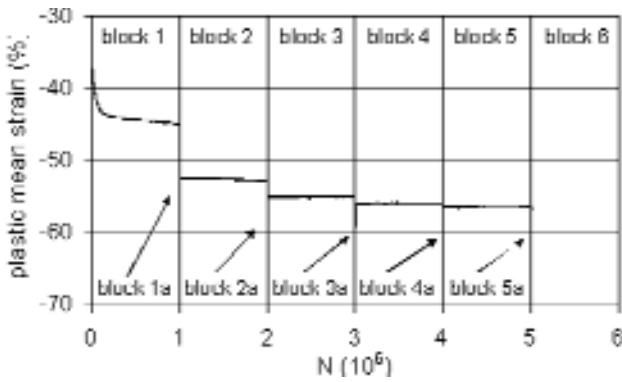


Figure 18-5 Mean plastic strain changes during the experiment.



Figure 18-7 Application of the polymer in line with standard nucleotomy with left mediolateral access.

Tests of damping (Fig. 18-6) as both a measure of work performed and of plastic damage to the test piece showed stable readings with little change throughout the load cycle. All three parameters indicate that the test pieces withstood the load cycle undamaged, and there is no reason to expect material failure under further sustained load.

In a second experimental approach, one test piece was subjected to a high long-term load of 1.7 MPa for 3.6 million LCs with just five brief respites of 0.1 MPa for 1000 LCs. In this test the dynamic modulus and plastic mean strain both approximated constant values, and all in all the readings confirmed the polymer's good long-term load capabilities. Meanwhile, initial research findings on the culture medium have revealed no significant abrasion particles or indications of cytotoxicity.

The aim next was to reproduce these findings in the 3D experiment described earlier. To this end seven human L3-L4 vertebral segments were investigated. The ages of the vertebral segments ranged from 66 to 78 years with a mean age of 72 years; four were female and three male. First, the intact motor segment was measured again. Then, after virtually complete removal of the nucleus pulposus (mean wet weight 6 g) via a left mediolateral access point in line with standard nucleotomy, new readings were taken. Final readings were then taken after inserting the implant (Fig. 18-7).

The polymer was inserted in the intervertebral space using the mixer attachment. The pre-load pressure applied by the mixing gun is sustained by a locking ring for a period of

15 minutes until the material hardens to a dimensionally stable and permanently elastic form. After removal of the mixer attachment, no dislocation of the material was observed. There was no significant increase ($p = .0156$) in segmental mobility, as compared with an intact vertebral motor segment, in terms either of translation or of rotation ($p = .0156$ to $p = .0313$) of the measuring point in any of the planes examined. Furthermore, despite the nucleotomy, no significant loss of height along Dy was observed ($p = .3281$). After implantation of the polymer, mobility was reconstructed for all parameters tested with no significant difference ($p = .1563$ to $p = 1.0$). The only reduction in mobility as compared with the intact segment was found in the flexion-extension, yielding a difference here of $p = .0156$. The 3D research thus confirmed the good stabilization of the entire motor segment for all directions of motion investigated.

◆ Conclusion

In conclusion, the 3D research setup revealed good stabilization of the motor segment after implantation of the SINUX in both the human and calf lumbar spine models. After dorsal insertion good alignment of the segment was observed. Without any suturing of the annulus fibrosus, the plastic's dimensionally stable polymerization meant that no tendency to dislocation was found during the experiment.

In collaboration with an independent test laboratory (RCC Cytotest Cell Research GmbH), corresponding tests of acute cytotoxicity were performed. Among the tests conducted were the Ames test of genetic toxicity, tests of acute systemic toxicity, and experimental implantations in six rabbits. The overall assessment in accordance with ISO 10993 is that the polymer displays neither cytotoxicity, genetic toxicity, nor acute systemic toxicity, and there were no negative findings impacting on the requirements for CE licensing as laid down in the ISO standard.

The first clinical study began in November 2000, and a license for use in the CE followed in January 2004. Currently the implant is being used in Europe in an extended study entitled "A multi-centre, prospective, non-comparative, open, post-marketing surveillance study to obtain clinical outcome data on the use of the SINUX Nucleus Replacement device for degenerative disk disease."

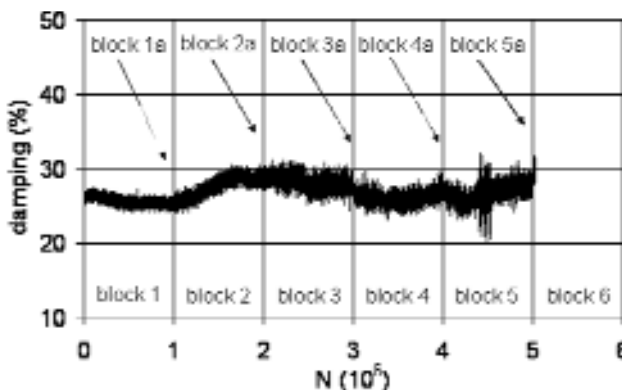


Figure 18-6 Damping changes during the experiment.

References

- [DE10]
1. Kolditz D, Krämer J, Gowin R. Water and electrolyte content of human intervertebral disc under variable load. *Spine* 1985;10:69–71
 2. Ghosh P. *The Biology of the Intervertebral Disc*. Vols 1 and 2. Boca Raton, FL: CRC Press; 1989:152–161
 3. Wilke HJ, Neef P, Caimi M, Hoogland T, Claes LE. New in vivo measurements of pressures in the intervertebral disc in daily life. *Spine* 1999;24:755–762
 4. Marchand F, Ahmed AM. Investigation of the laminate structure of lumbar disc anulus fibrosus. *Spine* 1990;15:402–410
 5. Krismer M, Haid C, Rabl W. The contribution of anulus fibers to torque resistance. *Spine* 1996;21:2551–2557
 6. Schulitz K-P, Abel R, Schöppe K, Assheuer J. Der Bandscheibenvorfall. *Dt Ärztebl* 1999;96:B424–B428
 7. Krämer J. *Bandscheibenbedingte Erkrankungen*. Stuttgart; New York: Georg Thieme Verlag; 1994, 1997
 8. White AA, Panjabi MM. *Clinical Biomechanics of the Spine*. 2nd ed. Philadelphia: Lippincott; 1990
 9. Deyo RA. Low back pain. *Sci Am* 1998;279:48–53
 10. Lavaste F, Asselineau A, Diop A, et al. Experimental procedure for mechanical evaluation of dorso-lumbar segments and osteosynthesis devices. *Rachis* 1990;6:435–446
 11. Panjabi MM, Krug MH, Summers D, Videmann T. Biomechanical time tolerance of fresh cadaveric human spine specimens. *J Orthop Res* 1985;3:292–296
 12. Flynn JC, Rudert MJ, Olsen E, Baratz M, Hanley E. The effects of freezing or freeze-drying on biomechanical properties of the canine intervertebral disc. *Spine* 1990;15:113–117
 13. Klein CL, Wagner M, Kirkpatrick CJ, van Kooten TG. A new quantitative test method for cell proliferation based on the detection of the Ki-67 protein. *J Mater Sci Mater Med* 2000;11:125–132
 14. Nachemson A. The load on lumbar disks in different positions of the body. *Clin Orthop Relat Res* 1966;45:107–122
- [DE11]

[DE1] Au: There is no mention of Sinitec in the article; please mention or define if possible.

[DE2] Au: Sense? do you mean minimal correlation of....with the simultaneous frequency...? Please clarify.

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