STABILITY: in silico 3D simulation studies toward the patient-specific intervention for specific forms of spinal instability (OTKA FK 123884)

Final Report

During the project, we have studied specific forms of spinal instability applying in silico 3D simulation research technologies to better understand the nature and risk factors of biomechanical failure of spinal segments. By the clarification of the development of specific spinal instability scenarios and the exploration of the underlying factors, different surgical and non-surgical strategies can be developed to avoid this possibly debilitating condition. In this 4.5-year long project, we focused on forms of iatrogenic spinal instability such as *adjacent segment degeneration* (ASD) and *proximal junctional kyphosis/failure* (PJK) as well as the *advanced degeneration-related spinal instability* (ADSI) and its minimally invasive surgical treatment the percutaneous cement discoplasty (PCD). The above mentioned specific forms of SI (ADS, PJK and ADSI) affect an increasing number of patients worldwide causing significant disability, pain, loss of QoL and increased healthcare expenditures. Considering the biomechanical complexity of these conditions and the patient-specific variations in the spinal biomechanics, we mostly used comprehensive in silico methods integrating finite element models, whole-body kinematics data and biomechanics as well as condition- and patient-specific features. The results of the project will be discussed according to the pathologies after the general scientific and technological achievements.

1. Development of general and patient-specific, validated lumbar spine FEA models

In this project two different finite element models of the lumbar spine were developed. The geometries of the vertebrae were made based on segmentation of QCT images (Figure 1.1.). In the first model five parts of the vertebra were separated: the cortical shell, the trabecular core, the bony and the cartilaginous endplate and the posterior elements. In this model the material properties were assigned according to literature (LBM). In the second model the vertebra geometries made by segmentation weren’t separated and the material properties were assigned based on the Hounsfield Units, which represent the density of a tissue (patient-specific model (PSM)). Ligaments were defined as spring elements with non-linear characteristics. The intervertebral discs consisted an incompressible nucleus pulposus, an annulus fibrosus ground substance and fibers. The facet joints were modelled as hyperelastic solids. (Figure 1.2.)

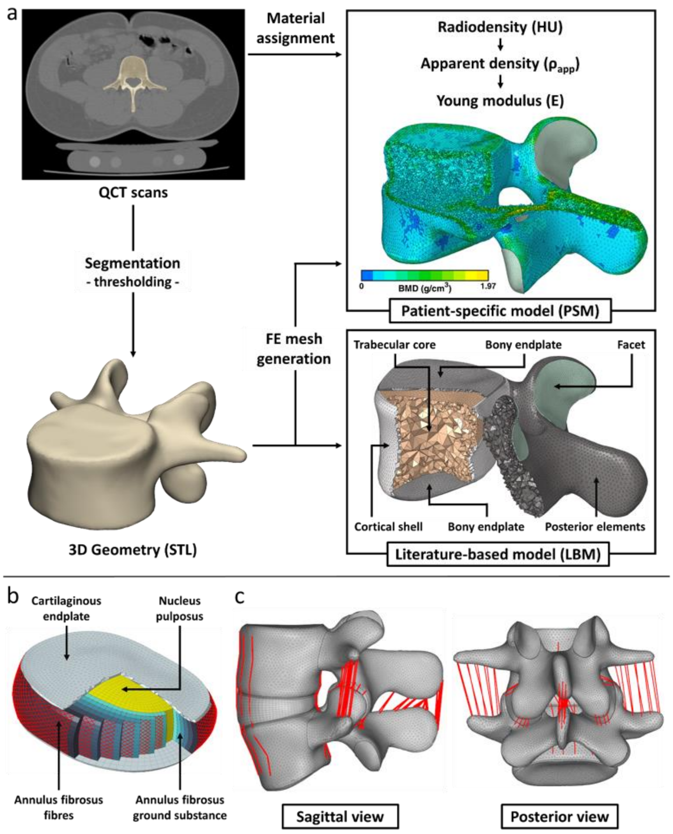

Figure 1.1. Workflow of the FE model development. (**a**) The geometry of the LBM and PSM was defined by segmentation based on QCT scans. The smoothed and remeshed surface mesh was used for the volume meshing. For LBM, the applied material properties were taken from the literature, while for PSM, the material was assigned according to the HUs, using multiple sets of equations. (**b**) The FE model of the intervertebral disc includes the cartilaginous endplate, the nucleus pulposus, the annulus fibrosus ground substance and the collagen fibres. (**c**) Ligaments are illustrated on the L4-L5 FE model in sagittal and posterior views.

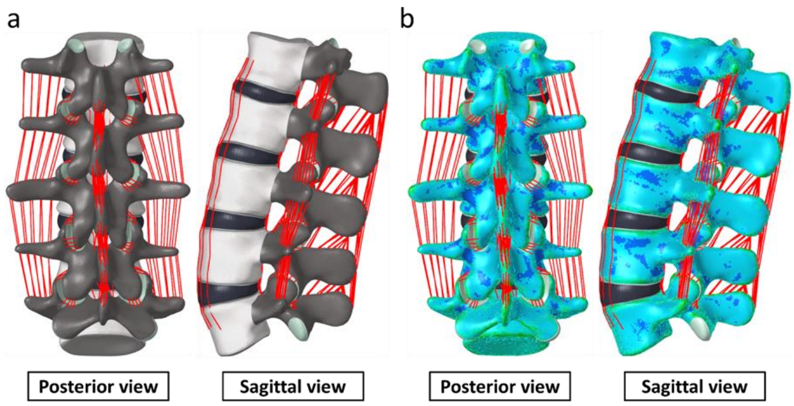

Figure 1.2. Finite element models of the lumbar spine: (**a**) the literature-based model and (**b**) the patient-specific model.

13 different load cases were investigated for both models. The literature and the QCT models were successfully validated to both in silico (Dreischarf et al., 2014) and in vitro (Rohlmann et al. 2001) results and compared to each other based on four parameters: facet joint force (FJF), intervertebral rotation (IVR), range of motion (ROM), intradiscal pressure (IDP). Various biomechanical parameters were investigated to validate the models. The total range of motion of the LBM in pure flexion-extension, lateral bending and axial rotation were 30.9°, 29° and 13.7°, respectively, while for the PSM, it was 31.6°, 28.6° and 14.1°. (Figure 1.3.)

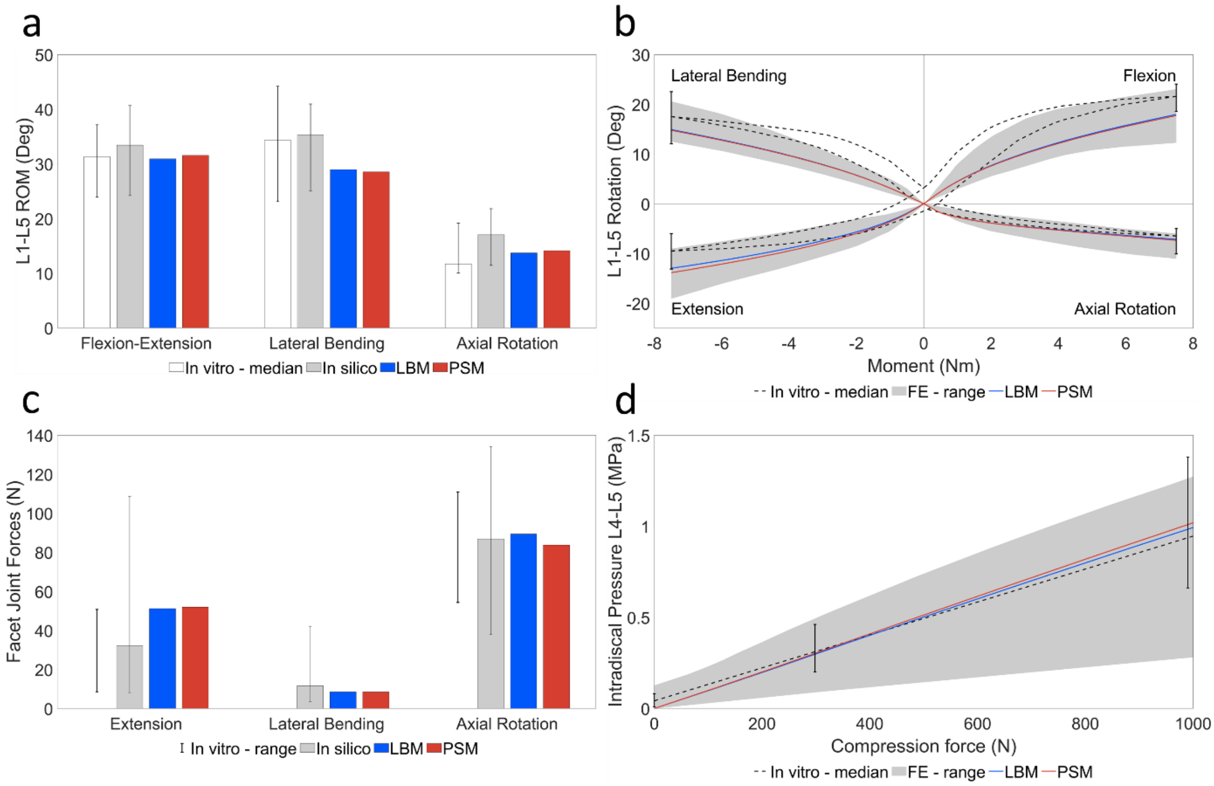

Figure 1.3. Results of the FE models against pure bending of 7.5 Nm. (**a**) Predicted total ROM values in flexion-extension, lateral bending and axial rotation for the LBM and LSP models. The white bars and their ranges correspond to the median and the range of an in vitro measurement. The grey bars and their range represent the median and the range of multiple published FE result. (**b**) Load-deflection curves of the LBM and PSM models. The median results of an in vitro experiment are shown with black dashed line, while the black error bars represent the range of results at 7.5 Nm. The minimum and maximum values of the in silico results are shown as a grey band. (**c**) The mean FJF values at all spinal levels for the LBM and the LSP models. The black error bars correspond to the range of facet joint forces measured in vitro. The grey bars and their ranges show the median, the minimum and maximum values of the in silico results. (**d**) IDP values of the nucleus pulposus at L4-L5 against compressive follower load for both FE models. The black dashed line shows the median result of an in vitro measurement, while the black error bars represent the minimum and maximum values for 0 N, 300 N and 1000 N. The range of validated FE results is shown as a grey band.

The required computational time of the PSM to complete against pure and combined loads were 12.1 and 16.6 times higher on average compared to the LBM.

The current study aimed to present two commonly used modelling techniques to develop a finite element model of the healthy human lumbar spine. Mesh resolution was investigated for both models based on von Mises stress in vertebrae to ensure the accuracy of model

predictions. The results of the models with the converged mesh resolution were compared with in vivo, in vitro, and well-accepted in silico data from the literature to validate them. Validation was performed considering ROM, IVR, IDP, and FJF variables against pure bending and pure compression load, and combined compression and bending load. **Based on the parameters and loads investigated, both the LBM and PSM can be used to model the biomechanical properties, such as ROM, IVR, FJF, and IDP of the lumbar spine, as they are in good agreement with the previously published results in most investigated variables.** However, substantial differences in computational time were observed between the literature-based and the patient-specific models. We plan to use the presented FE models in the future for in silico investigations to develop new medical devices, to evaluate currently used surgical reconstruction, or to test patient-specific solutions.
The modelling process and the scientific results are described in details in a journal paper submitted to the Nature: Scientific Reports[1].

During the development and validation process of the full lumbar spine FEA models, significant sub-studies were successfully implemented focusing on different aspects of in silico biomechanics and 3D technologies.

A ***study about the biomechanical aspects of the surgical solution of a more specific form of spinal instability*** was resulted in the development of a novel 3D method for the assessment of rod contour deformation and bony fusion in lumbopelvic reconstruction after en-bloc sacrectomy (Figure 1.3.).

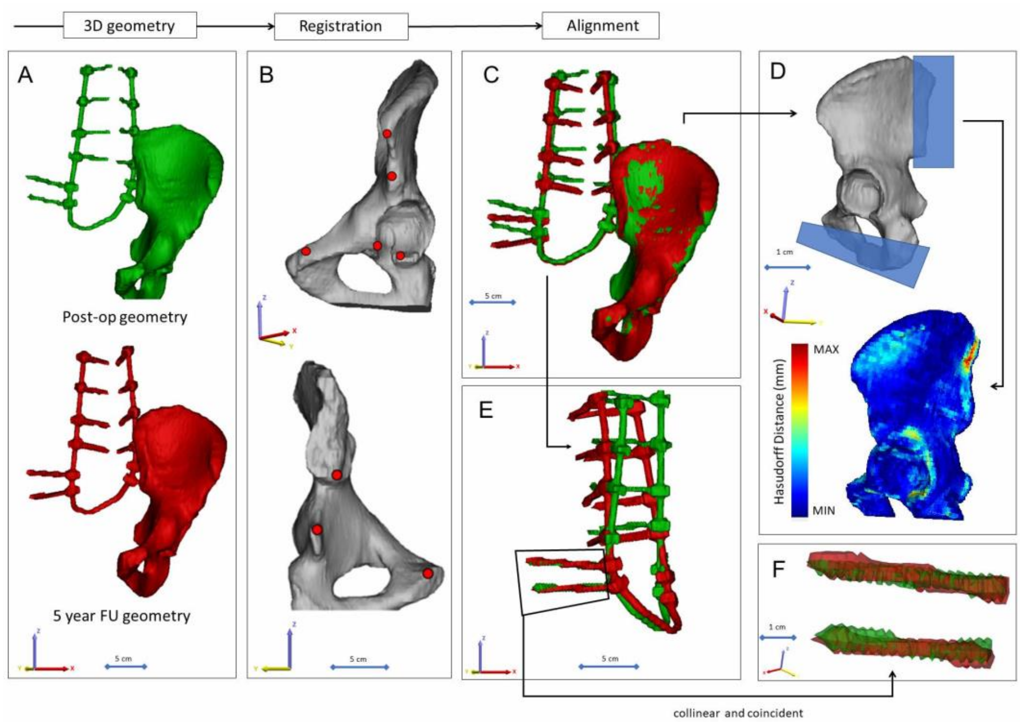

Figure 1.3. Postop CT scan-based geometry definition and alignment. **A** Thresholding based segmentation was performed on the postop CT scan in order to define the left pelvic bone and the implant construct. **B** 8 landmarks corresponding to anatomical landmarks were used for the

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[1] **Development and validation of two intact lumbar spine finite element models for in silico investigations: comparison of the modelling approaches.** Mate Turbucz, Agoston Jakab Pokorni, György Szőke, Zoltan Hoffer, Rita Kiss, Aron Lazary, Peter Endre Eltes. *Submitted to: Nature: Scientific Reports 5ad177c4-3a91-4d9b-a9b1-aa4813a54815 | v.1.1*

simultaneous registration of the pelvic bone and implant construct geometry. **C** Every postop pelvic bone + implant construct geometry was registered to the first postop geometry. **D** The Hausdorff Distance was used as a metrics for the alignment accuracy evaluation. Geometrical reduction of the caudal and posterior part of the registered pelvic bones was performed. **E** The trans-iliac screw bodies geometry overlapped after the pelvic bone registration. The axes of the iliac screws were considered collinear and coincident.

The developed clinical image analysis-based computational method (segmentation, rigid registration, BMD assessment at the voxel level based on HU values) provide accurate information about the implant construct's deformation after sacrectomy, following reconstruction with the closed-loop technique. We can recommend the application of our measurement method for the scientific and clinical analysis of other surgical procedures as well, and other clinical scenarios where large constructs are needed, such as idiopathic or degenerative deformity corrections, growing rods systems, etc. The BMD mapping at the fusion site may help in the future to evaluate the effect of the implant's (rod) diameter, or material, (titanium vs cobalt-chromium) on the fusion process (Figure 1.4.). The identification of regions where the constructs undergo the highest deformation may be useful in the surgical planning and in implant-related failure prevention. *Results of this substudy was published in Frontiers in Surgery*[2]

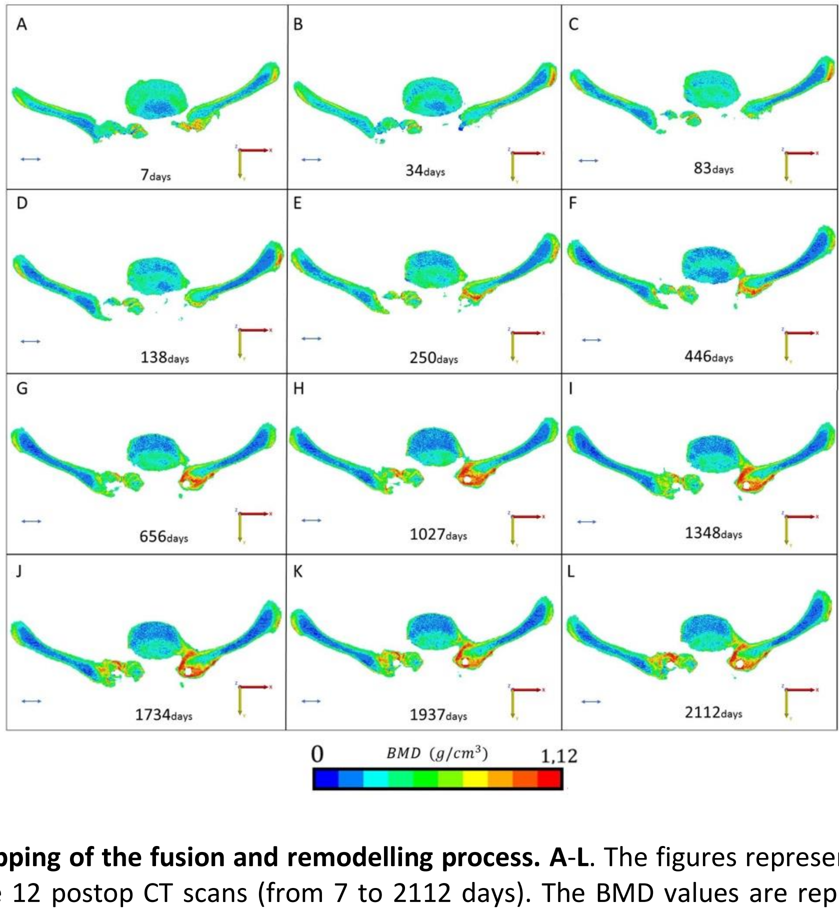

Figure 1.4. Mapping of the fusion and remodelling process. A-L. The figures represent the region of interest for the 12 postop CT scans (from 7 to 2112 days). The BMD values are represented in ten

[2] **A Novel Three-Dimensional Computational Method to Assess Rod Contour Deformation and to Map Bony Fusion in a Lumbopelvic Reconstruction After En-Bloc Sacrectomy.** Peter Endre Eltes, Mate Turbucz, Jennifer Fayad, Ferenc Bereczki, György Szőke, Tamás Terebessy, Damien Lacroix, Peter Pal Varga, Aron Lazary. *Front Surg. 2021; 8: 698179. Published online 2022 Jan 5. doi: 10.3389/fsurg.2021.698179 (IF: 2.718)*

colour codes from 0 to 1.12 g/cm^3 in an RGB scale. Red colour represents the strongest bone tissue, scale bar 2 cm.

Two another sub-studies were conducted to investigate the clinical application of 3D and in silico biomechanics technologies. 3D printing is the only option to have physical patient specific 3D models and the advantages of this technology are absolutely clear in spine surgery. We investigated the ***differences of two distinct 3D printing technologies especially focusing on the feasibility and applicability in a hospital environment***. Based on our results we could conclude that a more cost-effective technology is sufficiently precise in case of 3D printed physical models of the spine (Figure 1.5.). If other **less expensive technologies can similarly be proven to be adequate for several purposes,** then the cost of 3D printing technologies can be reduced to a level that is not only acceptable for healthcare systems but will promote their widespread use. *To demonstrate the feasibility and applicability of the 3D printing in spine surgical care, we have published our scientific results including a clinical case-report (Figure 1.6.) in Journal of Clinical Neuroscience[3].*

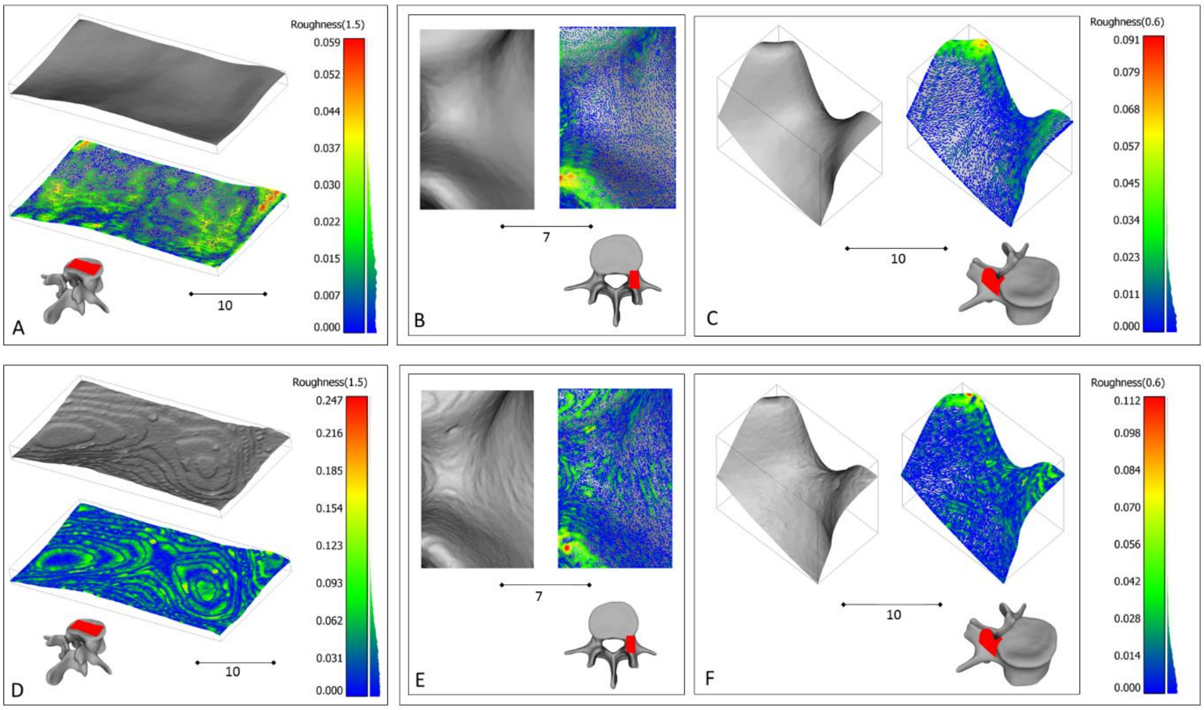

Figure 1.5. **The surface roughness of the two 3D printed models is different. A-F** Roughness of FDM-sup (D, E,F) is greater compared to DLP-sup (A, B, C; Two-sample Kolmogorov–Smirnov test, $p \leq 0.01$) for the endplate (A, D; kernel set to 1.5 mm) and pedicle (B,E; C,F different views respectively; kernel set to 0.6 mm) surface geometries (vertebra, view orientation; red, ROI). Scale bar A, C, D, F 10mm; B, E 7mm.

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[3] **Geometrical accuracy evaluation of an affordable 3D printing technology for spine physical models.** Peter Endre Eltes, Laszlo Kiss, Marton Bartos, Zoltan Magor Gyorgy, Tibor Csakany, Ferenc Bereczki, Vivien Lesko, Maria Puhl, Peter Pal Varga, Aron Lazary. *Journal of Clinical Neuroscience 72 (2020) 438–446, 2020 (IF: 1.760)*

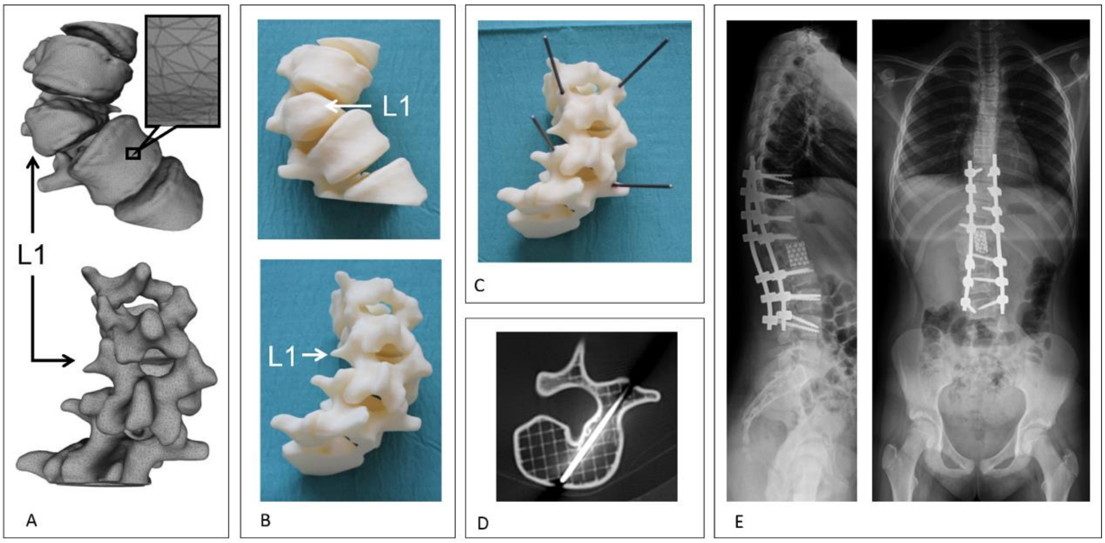

Figure 1.6. Application of the FDM 3D printed model in the surgical planning process in congenital scoliosis. A, The segmented 3D geometry (triangulated surface mesh) of the thoraco-lumbar junction (L.1 hemivertebra) in anterior and posterior view. **B,** 3D printed physical model of the same thoraco-lumbar section as in A. **C** Titanium rods were introduced in the pedicle, in the optimal axis of the screw insertion, as planned for the surgery. **D** Internal grid structure of the FDM model with the inserted titanium rod (axial CT scan). **E** Post-operative standing X-rays shows the screws (correction and stabilization from T9 to L4 with Mesh cage) inserted in the correct position, helped by the visual guidance provided by the rods inserted in the physical model.

We have also implemented the in silico 3D methods and 3D printing to ***develop a new technology for surgical navigation in musculoskeletal surgery***. A surgical guide for the replacement of a revision screw in the lumbo-sacral segment has been designed and manufactured based on the scientific analysis of the patient-specific bone condition (Figure 1.7.). **Different screw trajectories were analyzed in patient-specific FE model to provide the best biomechanical scenario to support the surgical decision-making process** (Figure 1.8.). *The technological innovation and the scientific results were published in Frontiers in Surgery*[4].

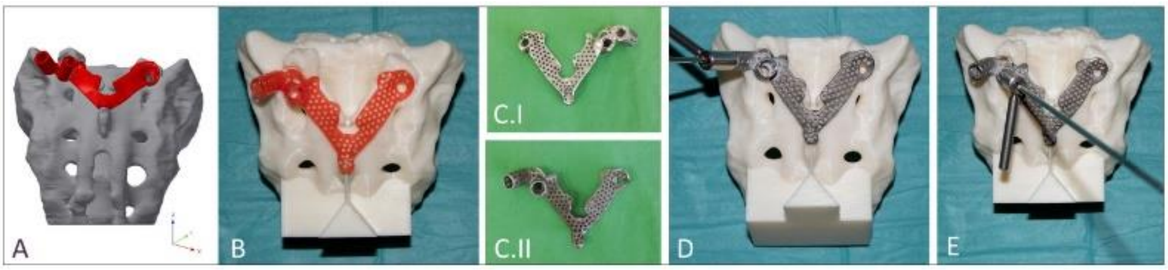

Figure 1.7. Design, manufacturing and accuracy evaluation of the navigation template. (**A**) template's virtual model created via CAD software. (**B**) 3D printed (DLP technology) template (red) fits exactly on the 3D printed (FDM technology) patient specific physical model. (**C.I-II**) final navigation template created via investment casting from cobalt-chrome (**C.I** ventral surface polished, **C.II** dorsal surface).

[4] **Development of a Computer-Aided Design and Finite Element Analysis Combined Method for Affordable Spine Surgical Navigation With 3D-Printed Customized Template.** Peter Endre Eltes, Marton Bartos, Benjamin Hajnal, Agoston Jakab Pokorni, Laszlo Kiss, Damien Lacroix, Peter Pal Varga and Aron Lazary. *Front. Surg., 25 January 2021 | https://doi.org/10.3389/fsurg.2020.583386, 2021 (IF: 2.070)*

Evaluation of the drilling accuracy was performed on the physical model in the (**D**) convergent position (S1) and (**E**) divergent position (ALA).

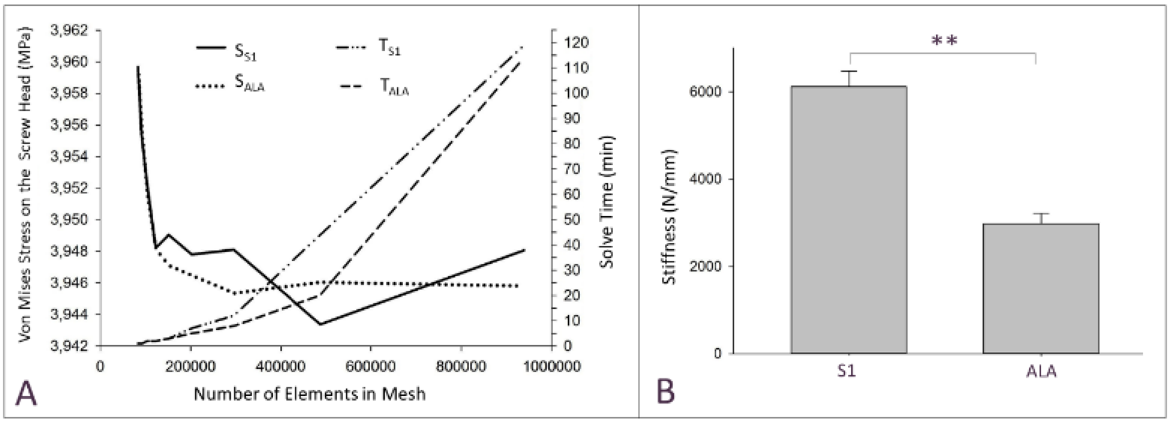

Figure 1.8. FE simulation results. (**A**) Convergence analysis for the average Von Mises stress values (nodes of the middle 1/3 of the screw head) in convergent (S_{S1}) and divergent (S_{ALA}) screw positions at different mesh element numbers. Solve time distribution (right) at different mesh element numbers (convergent (T_{S1}) and divergent (T_{ALA}) screw positions). (**B**) The convergent screw insertion (S1) is significantly ($p<0.01$, Wilcoxon Signed Ranks Test) stiffer compared to the divergent (ALA) insertion.

2. Development of a new method to adapt the lumbar alignment of supine CT-based virtual 3D lumbar spine models to standing position

We also developed a scientific solution for the so called “transfer function” problem. Most of the imaging acquisition used for biomechanical simulations (CT, MR) are done in lying position, however, the physiological loading of the spine is in standing position. Not only the loading conditions but also the segmental and global alignment change when the subject is “standing up”. That is why, a method for “standing-up” the CT/MR based 3D models would be crucial for the simulation of in vivo biomechanics, especially in case of full lumbar and full spine models. Despite of its importance, there is not any scientific method for standing-up the models in the literature. During the project, we have developed and implemented a technical method using the advanced computer tools. 50 full lumbar spine 3D models were created by manual segmentation by two independent researchers and segmental and global alignment parameters were measured on CT models and standing X-rays of the patients. Significant difference was determined in case of most of the parameters. As a last step, the individual 3D CT models were re-aligned using the X-rays of the subjects as a standing-up procedure. (Figure 2.1.) The inter- and intraresearcher reliability of all the steps was determined. (Figure 2.2.)

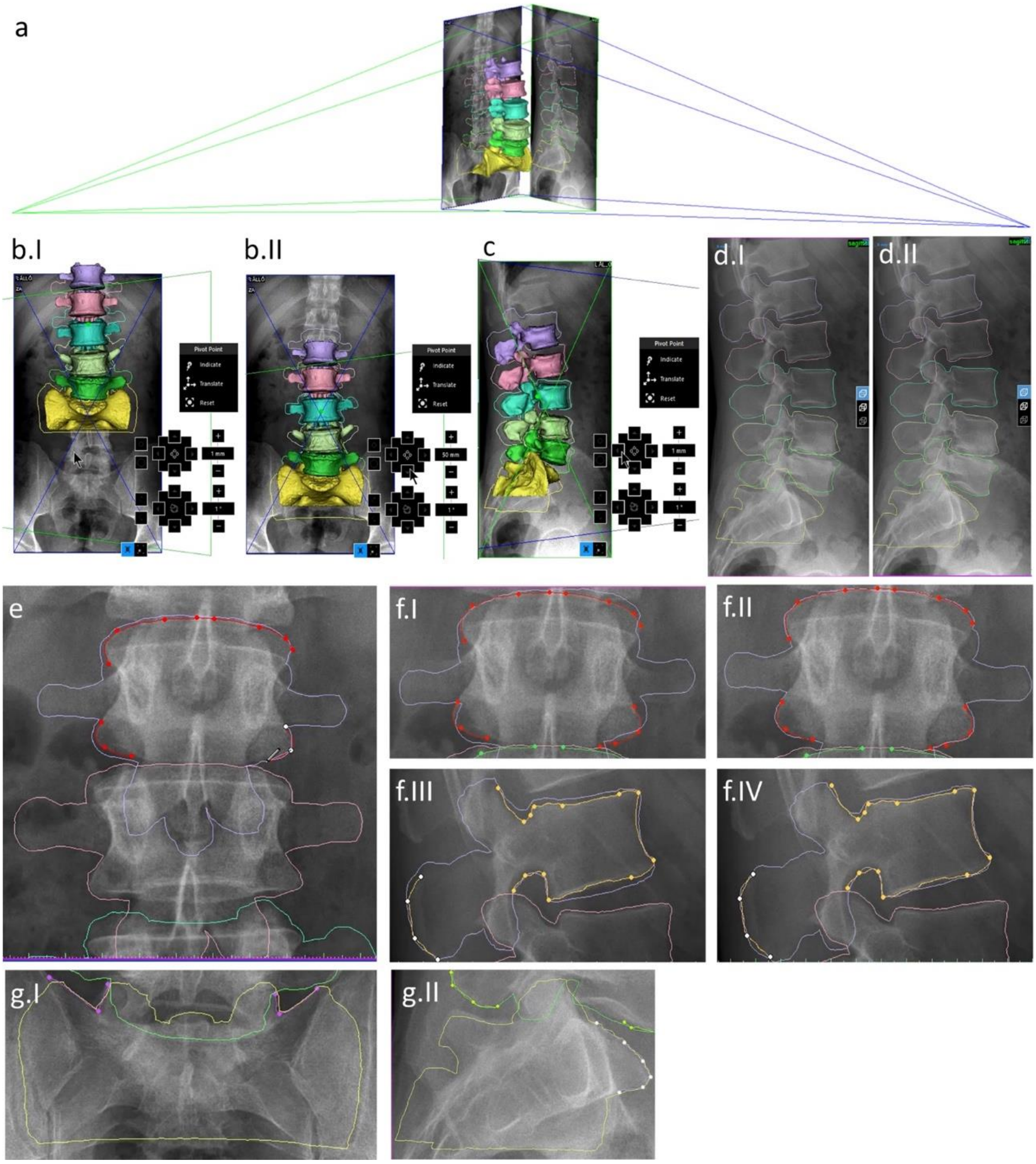

Figure 2.1. Registration of 3D lumbar spine geometry to standing radiographs. **(a)** simulated 3D environment with 3D lumbar spine geometry, radiographs, and radiation sources. **(b.I, II)** manual registration of X-rays, before and after. **(c)** manual registration of vertebrae, 3D viewfinder with manual registration toolbar present. **(d.I, II)** manual registration of vertebrae, before and after **(e)** contour selection, using the contouring tool. **(f)** automatic contour-based registration of a vertebra in the **(f.I, II)** frontal and **(f.III, IV)** sagittal planes before and after. **(g)** contours used for the registration of the sacrum.

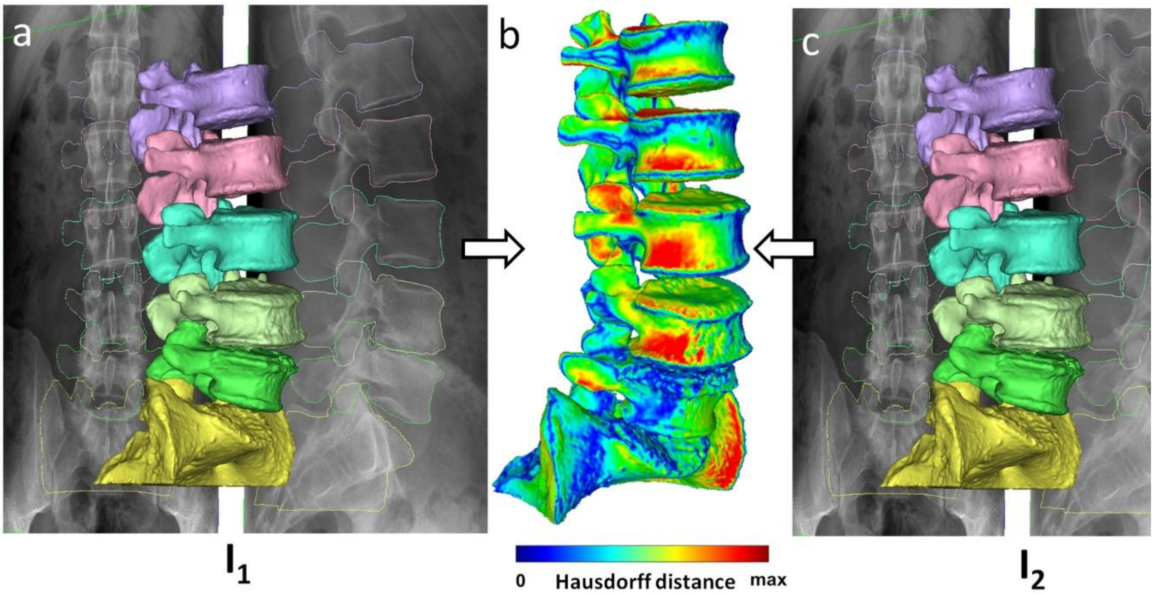

Figure 2.2. Spatial distribution of the distance of identical meshes between independent registrations. **(a and c)** 3D views of lumbar spine geometry registered by I_1 and I_2 respectively. **(b)** 3D heatmap of the spatial distribution of distances between the two meshes.

We found a high accuracy (DSI›0.9) of segmentation work in all cases and excellent (ICC›0.8) intra- and inter-rater reliability of angle measurements characterizing the lumbar alignment in lying and standing position. We found a significant difference in intersegmental and global lordosis angles between supine and standing position of the lumbar spine models (Figure 2.3.)

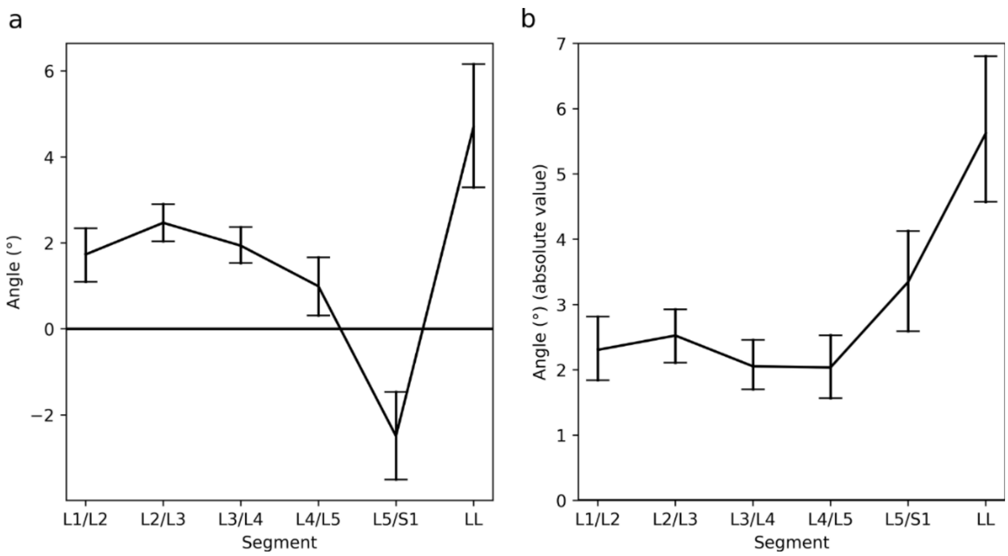

Figure 2.3. (a) Average signed and **(b)** absolute value differences in degrees between intersegmental and LL angles measured in CT scans and standing radiographs. Error bars indicate 95% confidence intervals.

The newly developed method offers an accessible, accurate and reproducible way of producing patient-specific 3D lumbar spine geometries that represent the standing alignment of the spine. This has potential use cases in personalized medicine, as it complements the currently used FEM-based techniques of surgical planning. Our method can

be used with already available radiologic data and has a steep learning curve. The method is perfectly suitable for use in *in silico* studies as it can leverage the potential of retrospective patient data by combining data from CT images with data from X-ray images which are invaluable from a biomechanical perspective. This can lead to the development of more accurate FEMs in research, with all the associated benefits. The results acquired in the process of making this study led to the accumulation of new data that can be used for the development of deep learning-based algorithms to automate the registration process. Additionally, the proposed method can be improved upon by implementing currently published but commercially unavailable automation techniques for spine segmentation and inferring the 3D geometry of the spine from standing biplanar radiographs.
The newly developed modelling method and the corresponding validation results are described in details in a journal paper submitted to the Nature: Scientific Reports[5]

3. Development of full thoraco-lumbo-sacral spine FEA model

In order to develop the full spine multiscale model we combined the full lumbar spine FE model with the generic thoracic spine and pelvis FE model. The different, patient- and condition specific loading conditions are extracted from a large motion analysis cohort study, where complex gait patterns of healthy control subjects (N=25) and patients with different spinal conditions (N=25) before and after short- and long-fusion surgeries have been analyzed. In order to have the best results, we have developed a new gait analysis protocol for spinal measurements, because of the lack of the international standards. Associations of gait parameters, symptoms and quality of life and its changes due to the surgical treatment have been also analyzed. The typical loading conditions parameters are exported from these measurements and can be imported into the FE analysis using the full spine model. Full spine multiscale model was further developed with its calibration in order to achieve agreement with the literature data in the thoracolumbar spine. The following segments were calibrated. T7-T12 compared to Wilke et al. (2017), T12-L1 compared to Germaneau et al. (2016). The load was applied in all 3 anatomical planes with alternating sign to mimic flexion, extension, right and left lateral bending, right and left axial rotation. The material properties of the annulus fibrosus fibers and the ground substance were calibrated. 2 weighting factors (λfiber and λGS) were introduced to achieve agreement with the in vitro data. The weighting factors were limited to remain physiological sensible (Schmidt et al., 2006). Good agreement was achieved with the range of motion data.
The developed full thorco-lumbo-sacral spine FEA model has been used in further scientific application such as PJK-related studies (see below).
As a result of this subproject, a review paper about the different option for spinal kinematic assessments is under preparation. Another scientific paper considering full spine biomechanic analysis and 3D modelling technologies in clinical practice was published in Frontiers in Surgery[6]*.*

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[5] **New method to adapt the lumbar alignment of supine CT-based virtual 3D lumbar spine models to standing position.** Benjamin Hajnal, Peter Endre Eltes, Ferenc Bereczki, Mate Turbucz, Jennifer Fayad, Agoston Jakab Pokorni, Aron Lazary. *Submitted to: Nature: Scientific Reports 15e104c3-2e62-4361-993e-f14ecc6d82ac | v.1.1*
[6] **Complicated Postoperative Flat Back Deformity Correction With the Aid of Virtual and 3D Printed Anatomical Models: Case Report.** Jennifer Fayad, Mate Turbucz, Benjamin Hajnal, Ferenc Bereczki, Marton Bartos, Andras Bank, Aron Lazary, Peter Endre Eltes. *Front Surg. 2021; 8: 662919., 2021 (IF: 2.070)*

4. Risk factors of adjacent segment degeneration and mitigation techniques

To investigate the patient specific risk factors of ASD, an ***ambispective clinical cohort study*** was performed. The PlumDeCo Cohort is focused on the adjacent segment degeneration long-term after routine lumbar stabilization surgeries. Patients underwent 1-2 level lumbar stabilization min. 4 years ago with full clinical and research dataset are included into this cohort and a prospective, 4-5 year FU is performed continuously. Features of the index surgery, degenerative pattern of adjacent segment and clinical outcome will be analyzed to identify the modifiable and non-modifiable risk factors of adjacent segment degeneration. ASD was a clinically signifcant entity in our cohort. Patients with ASD were characterized with high patin and disability due to the development of the condition. Significant risk factors for the development of ASD in univariate analysis was:, PI-LL mismatch (p=0.021) and lower L4-S1 lordosis (p=0.039) as well as presence of disc protrusion/bulging (p=0.007), or significant disc degeneration (p=0.002) ont he preoperative MRI. In a multivariate stepwise backward conditional model, the presence of major degenerative sign in the adjacent disc remained a significant predictor of developing ASD with an OR of 3.85 (CI 95%=1.43-10.37, p= 0.006). Analyzing the casue of reoperations, we found that most of the pathologies were directly related to the failure of the adjacent intervertebral disc. **Based on the results, clinical recommendation has been formulated. According to that, the adjacent disc conditions should be considered carefully during surgical planning even before a short-segment lumbar fusion.** *A manuscript about this study has been submitted to the Clinical Spine Surgery[7]. The manuscript is under review.*

During the ASD related clinical investigations, we realized that the primary stability of the construct in case of lumbar fusion can be also an important factor in the future development of ASD. We implemented two different sub-studies related to different clinical scenarios investigating two different issues. A special form of lumbar fusion surgeries, the ***OLIF (Oblique Lumbar Interbody Fusion) surgery was studied from the stability point-of-view***. Using our previously developed lumbar spine FE model, the FE models of single level OLIF surgery with different additional stabilization constructs were developed and tested in silico (Figure 4.1.). The risk for screw loosening and cage subsidence were analyzed according to the bone quality. A normal and an osteoporotic model were developed. We have found that different stabilization techniques after single-level OLIF had significantly different influence on local mechanical stress and stress distribution, especially in case of compromised bone quality (Figure 4.2.). **Based on our results we have been able to formulate a recommendation for everyday clinical use, namely the addition of OLIF technique with posterior transpedicular screw-rod stabilization system is recommended especially in aged patients** compared to stand-alone, lateral fixations. The results of the study were published in Frontiers in Bioengineering and Biotechnology.[8]

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[7] **Impact of patient-specific factors and spinopelvic alignment on the development of adjacent segment degeneration after short-segment lumbar fusion**. Laszlo Kiss, Zsolt, Szoverfi MD, Ferenc Bereczki, Peter Endre Eltes, Balazs Szollosi, Julia Szita, Zoltan Hoffer, Aron Lazary. *Submitted to Clinical Spine Surgery.*

[8] **Stability Evaluation of Different Oblique Lumbar Interbody Fusion Constructs in Normal and Osteoporotic Condition - A Finite Element Based Study.** Ferenc Bereczki, Mate Turbucz, Rita Kiss, Peter Endre Eltes, Aron Lazary. *Front Bioeng Biotechnol. 2021; 9: 749914. Published online 2021 Nov 5. (IF: 5.890)*

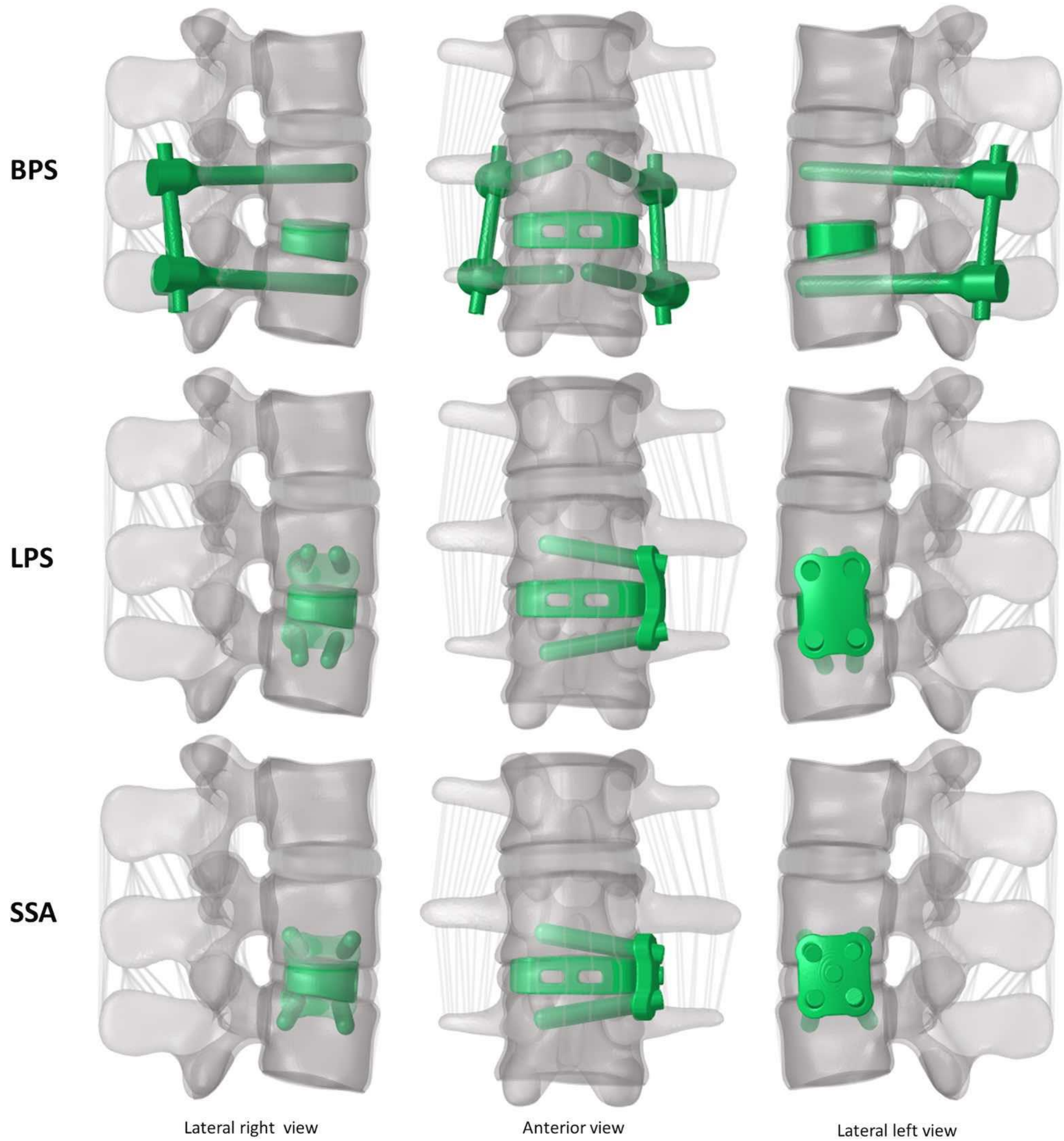


Figure 3. L2-4 spine bi-segment model 3D geometry with the three investigated (OLIF) fixation constructs. (**A**) OLIF cage with bilateral pedicle screw (BPS). (**B**) OLIF cage with lateral plate-screw (LPS). (**C**) self-anchoring stand-alone cage fixation (SSA), lateral left-right and frontal view.

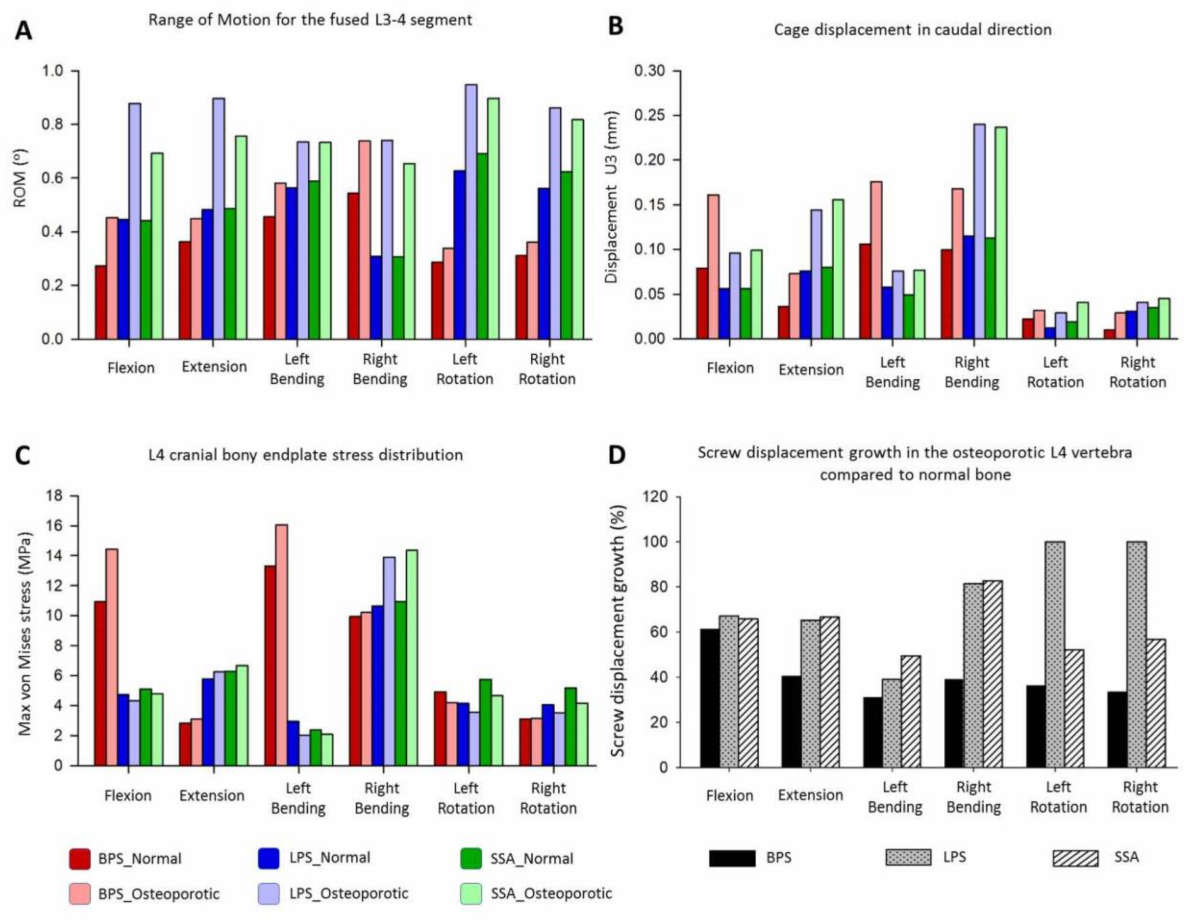
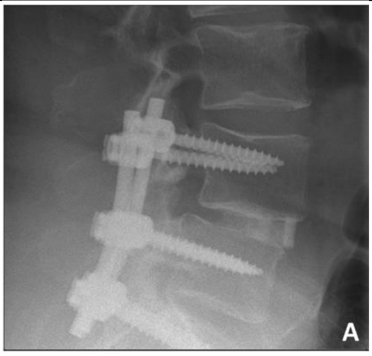
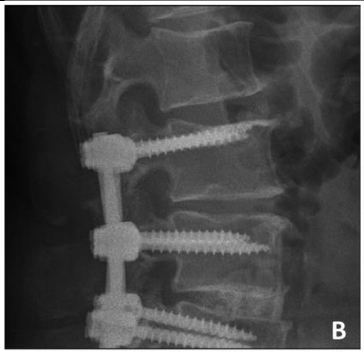


Figure 4.2. Results of the simulations extracted from the surgically reconstructed bi-segmental FEA model according to the six loading scenarios in normal and osteoporotic condition. (**A**) range of motion (ROM) values for the operated L3-4 segment containing the investigated implants constructs (BPS: bilateral pedicle screw, LPS: lateral plate-screw, SSA: self-anchored standalone). (**B**) cage displacement in the caudal direction (U3 in Abaqus). (**C**) Von Mises stress peaks on the L4 cranial bony endplate. (**D**) The measured L4 screw displacement increase (%) caused by osteoporotic bony conditions compared to L4 screw displacements inside normal bone.

A clinical cohort of ›3000 patients underwent lumbar fusion has been analysed to elucidate the association of the ***proximity of the cranial screws to the cranial endplate and the development of biomechanical failure (ASD or PJK) in the cranial segment***. Reoperation because of cranial fusion-extension was deeply analyzed (N=200). We found that the proximity of the cranial pedicle screws to the vertebral endplate can facilitate the failure of the cranial segment (Table 4.1.). Significantly shorter time last from index surgery to reoperation in group of patients was the cranial screw position was suboptimal at the time of the index surgery (p‹0.005).

Table 4.1. Summary of clinical cohorts and time to reoperation because of cranial segment failure

	Neutral positioned screws	Cranially positioned screw
Examples (X-ray)		
Number of patients	28	171
Time to reoperation (days, median)	379.5	974

In parallel of the clinical study, the in silico model of the screw positioning scenarios has been developed using the full lumbar spine FE model. FE analysis under different loading conditions are being performed to describe the effect of the cranial screw position on the local biomechanics. Based on the first experiments we found that the von Misses stress is higher on the cranial endplate if the screw is located closer to the endplate independently from the length of the construct (Figure 4.3.). *The study is under process but the first results are promising. An important clinical recommendation will be formulated supported by clinical and in silico biomechanical evidence.*

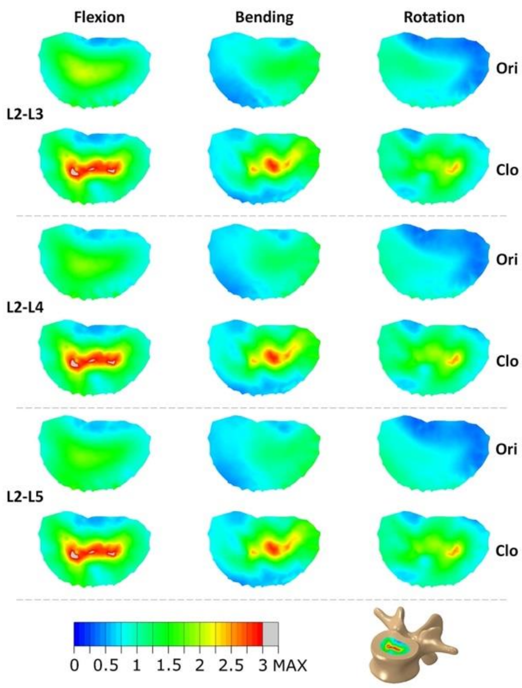


Figure 4.3. von Misses stress distribution on cranial enplate in case of neutrally (Ori) and cranially (Clo) placed pedicle screws in different-long lumbar fusion constructs.

5. Prevention of proximal junctional kyphosis after long thoracolumbar stabilization surgeries

The GAPscore cohort is built to analyze the full body consequences of long spinal stabilization surgeries. Data of 92 patients with mid-term follow up was included into the database and more than 20 radiological parameters are defined and the most recently developed complex analysis on the global proportion of the patient's balance were calculated. Non-radiological features (such as demographic, surgical data, data on implant-construct, etc) were also parameterized in order to perform a multivariate analysis to define the risk factors of adjacent segment failure (degeneration and fracture). Unfortunately, the size of the clinical cohort was not enoughly high to substract strong clinical evidence but a trend-to-significant association between the postoperative GAP score and the risk of PJK was found in our cohort (OR=1.3, p=0.08) supporting the literature data.

Analyzing the variety in the clinical cohort, a hypothesis about the possible influence of the rigidity of the stabilization construct on the risk of development of PJK was formulated by the research group. To analyze this, ***four different scenarios of long thoracolumbar fusion surgeries have been simulated using the full spine FE model*** (Figure 5.1.).

To investigate the biomechanical effect of different spinal fixation techniques on the onset of PJK, in addition to the intact model (Figure 5.1A), one rigid and two semirigid models were developed:

1) PRF – model with Ø5.5 mm PEEK rods between T8 and T9 combined with posterior fusion of the spine from T9 to L5 using bilateral pedicle screws and Ø5.5 mm titanium rods. Rod connector system was placed to connect the titanium and PEEK rods (Figure 5.1B).
2) TRF – model with posterior fusion of the spine from T8 to L5 using bilateral pedicle screws and Ø5.5 mm titanium rods (Figure 5.1C).
3) MRF – model with five Ø1.9 mm titanium rods between T8 and T9 combined with posterior fusion of the spine from T9 to L5 using bilateral pedicle screws and Ø5.5 mm titanium rods. Rod connector system was placed to connect the titanium and the multiple titanium rods (Figure 5.1D).

For all FE models, the loading was applied at the most cranial endplate of T7, while the most caudal endplate of L5 was fixed in all degrees of freedom. For a proper biomechanical evaluation of adjacent segment effects, a modified multidirectional hybrid test protocol has been applied in this study, consisting of two subsequential loading steps. Distribution of the von Mises equivalent stress values at the upper instrumented vertebra were visualized and evaluated through an axial section of the FE models. In general, the largest area with stress higher than 10 MPa was found in the TRF model, while PRF included the least. The stress distributions in flexion and extension show a similar trend, i.e., the TRF technique results in much higher pedicle screw stress in both loading cases. In contrast, MRF gives less, while the PRF technique induces the least stress in both loading directions (Figure 5.2A-B). For right lateral bending, the stress distribution pattern of the MRF model shows similarity with the TRF model in aspect of magnitude and expansion (Figure 5.2C). In contrast, for axial rotation, the peak stress values appeared at the outer edge of the screw bodies in the instrumented models, with TRF model containing notably more area stress above 10 MPa than the MRF and PRF. (Figure 5.2D).

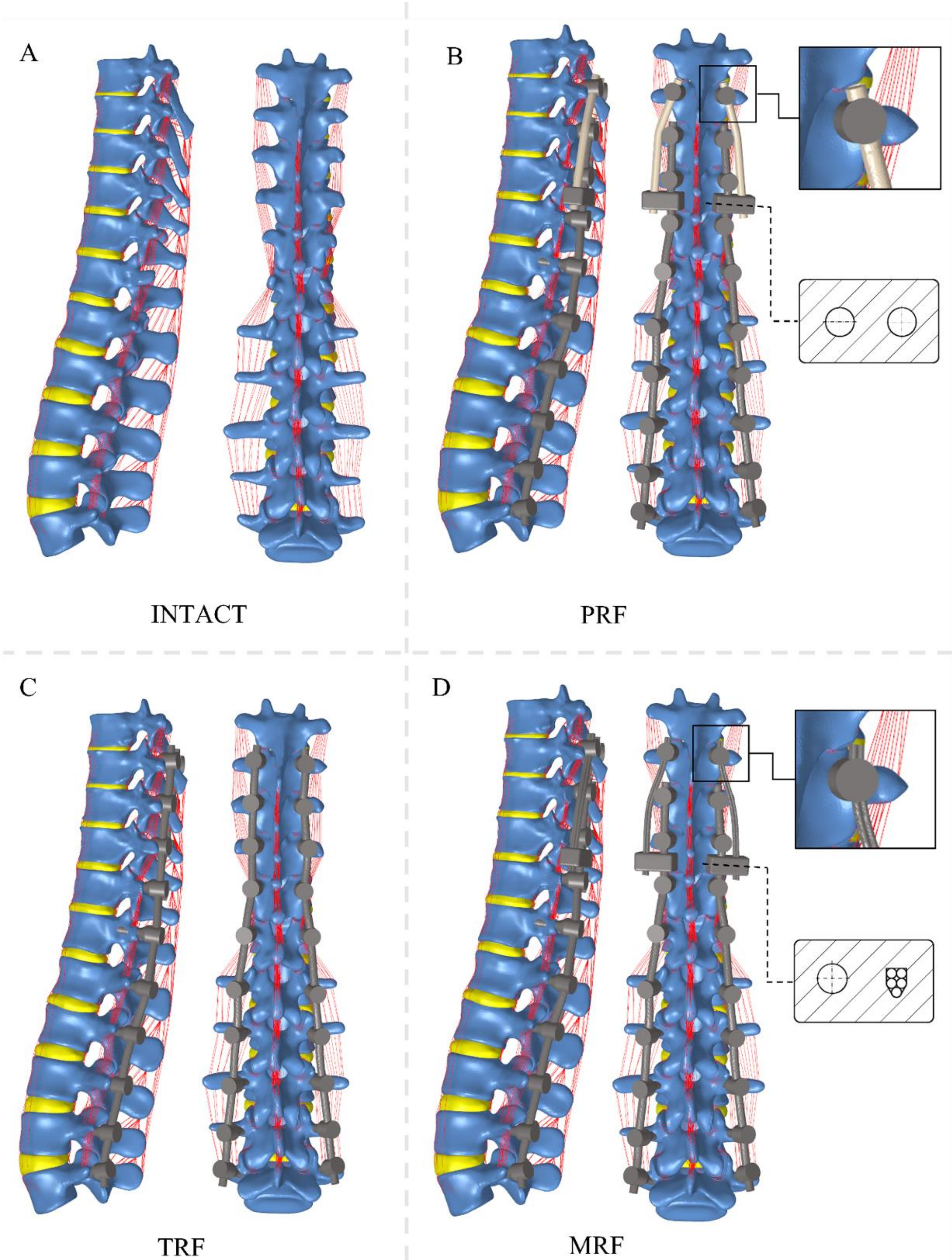


Figure 5.1. The assessed spinal fixation techniques in lateral and posterior views. (A) The intact T7-L5 model, (B) the PRF model, (C) the TRF model, and (D) the MRF model.

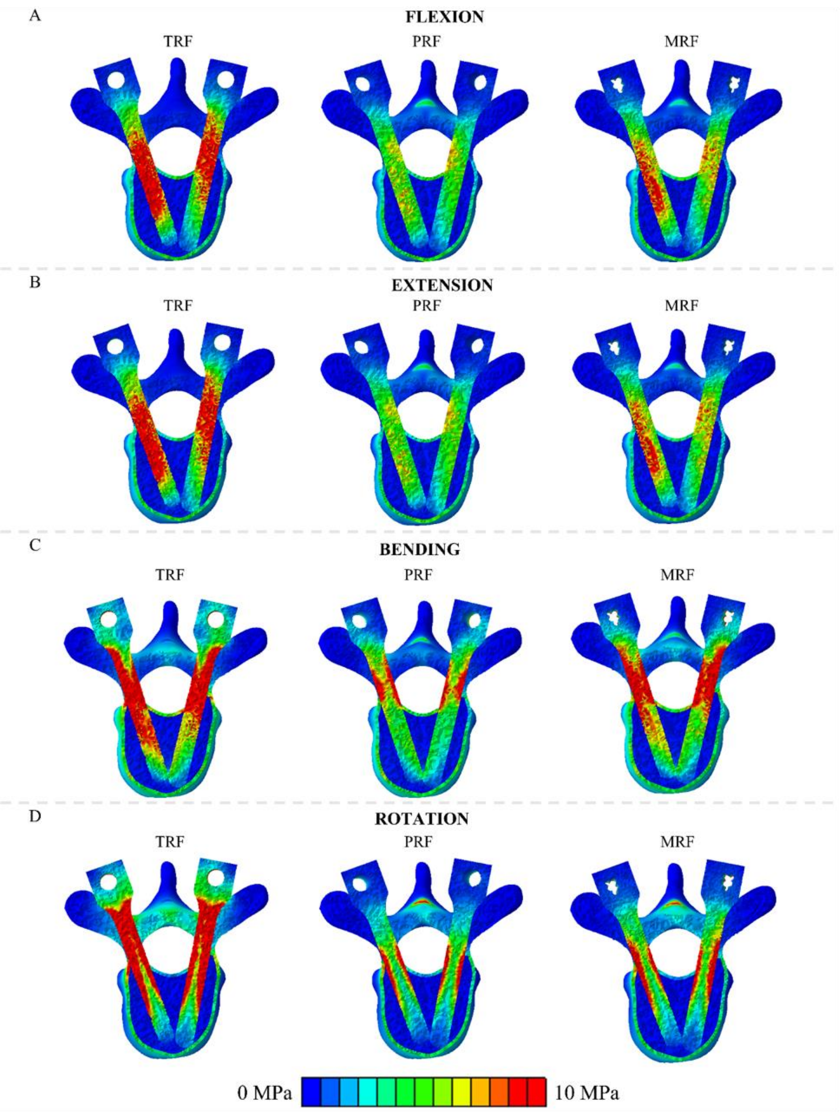


Figure 5.2. The von Mises stress distribution of the three fixation techniques at the UIV level for (A) flexion, (B) extension, (C) right bending, and (D) left rotation with (E) the maximum scale value set to 10 MPa uniformly. Due to the symmetric stress distribution patterns, only one direction is considered for lateral bending and axial rotation

Based on our results, we could conclude that less rigid fixation at the top of the long thoracolumbar construct could allow a more gradual transition in motion between the instrumented and the intact segment of the spine possibly decreasing the load in the pedicle screws at the junctional level; thus, it can help prevent the development of PJK.

A manuscript about the study is under preparation and plane to be submitted into the Journal of Neurosurgery:Spine.

Considering the important of the transition from the rigid caudal and less rigid cranial rod, we have developed a new spinal implant supported by scientific evidence. The in silcio developed new connector allows the proper connection between the rigid 5.5 titanium or chrome-cobalt rod and the semi-rigid multiple rod system. The concept is patented with the aid of our industrial partner (Sanatmetal Kft.).[9]

[9] **Bejelentési kérelem használati mintaoltalom bejegyzése érdekében**: „Sebészeti eszközkészlet csigolyatestek összekapcsolására”. Szellemi Tulkajdon Nemzeti Hivatala 2022. (U2200053)

6. Clinical and biomechanical aspects of percutaneous cement discoplasty

Various aspects of advanced stage disc degeneration-related spinal instability (ADSI) and its minimally invasive surgical (MIS) treatment the percutaneous cement discoplasty (PCD) were studied during the study providing a mass of scientific evidence supporting the clinical use of PCD.

Two clinical cohort studied were conducted to study the clinical outcome of the PCD procedure in relation to its biomechanical aspects. Relationship between the ***segmental and global lumbar alignment and clinical improvement as well as change spino-pelvic paramteres after PCD procedure*** was determined on a subcohort of patients using prospectively collected radiographic, clinical and patient-reported outcome data. We found that **the minimally invasive surgical procedure can increase the area of the neuroforamen, improve the lumbar lordosis and scoliotic deformity too beyond the pain relief**. Some of the alignment changes were significantly related to the improvement of the clinical outcome. The results have been published in the European Spine Journal[10].

Another, large cohort study was conducted to describe the ***complications related to PCD and their risk factors***. Pre-, intra- and postoperative clinical data of 344 patients treated with PCD technique was analyzed in different statistical models. There was not any previous report focusing on the description of the complication pattern and the analysis of risk factors after PCD procedure. Detailed analysis of risk factors for cement leakage (Table 6.1.), length of hospital stay (LOS) (Table 6.2.) and risk for reoperation (Table 6.3.) was performed.

Table 6.1. Multivariate logistic regression analysis of selected factors on index cement leakage ($p<0.01$, Wald=36.551, R^2=0.33, c-index=0.807)

	B (SE)	**Wald**	**OR (CI)**	**p**
Age	0.042 (0.018)	5.368	2.043 (0.925-4.294)	**0.021**
BMI	0.095 (0.032)	8.917	1.100 (0.854-3.968)	**0.003**
First 5-year practice	0.851 (0.367)	5.394	2.341 (1.208-6.876)	**0.020**
Spondylolisthesis	0.093 (0.435)	0.046	0.991 (0.388-2.136)	0.830
SS	0.043 (0.026)	2.637	1.044 (0.991-1.099)	0.104
PI	0.019 (0.016)	1.366	0.981 (0.951-1.013)	0.243
L1-S1 LL	0.011 (0.016)	0.453	1.011 (0.979-1.044)	0.501
L4-S1 LL	0.003 (0.017)	0.026	1.023 (0.970-1.036)	0.873
Lumbar scoliosis	0.007 (0.025)	0.071	0.993 (0.946-1.043)	0.790
Type of cement	2.094 (0.372)	31.623	8.115 (3.912-16.835)	**<0.001**
No of operated levels	1.180 (0.354)	11.118	3.257 (1.638-6.594)	**0.001**
Procedure type	1.139 (0.586)	3.781	3.122 (0.991-9.839)	0.052
OR time	0.008 (0.006)	1.604	0.992 (0.981-1.004)	0.205

[10] **Indirect foraminal decompression and improvement in the lumbar alignment after percutaneous cement discoplasty.** Kiss L, Varga PP, Szoverfi Z, Jakab G, Eltes PE, Lazary A. *Eur Spine J. 2019 Jun;28(6):1441-1447. doi: 10.1007/s00586-019-05966-7. Epub 2019 Apr 20., 2019 (IF: 2.634)*

Table 6.2. Multiple linear regression analysis of certain factors on LOS ($p<0.01$, $R^2=0.41$)

	B(SE)	**T**	**p**
Age	0.000 (0.002)	2.912	0.912
No of operated levels	0.017 (0.035)	0.477	0.634
Procedure type (PCD+)	0.184 (0.045)	4.075	**<0.001**
BMI	0.002 (0.003)	0.610	0.542
Charlson score	0.037 (0.011)	3.374	**0.001**
Reoperation	0.480 (0.115)	4.167	**<0.001**
Postoperative symptoms	0.428 (0.073)	5.857	**<0.001**
Non-surgical adverse event	0.575 (0.084)	6.848	**<0.001**

Table 6.3. Final result of the backward multivariate logistic regression analysis on risk for reoperation ($p<0.01$, $R^2=0.20$ c-index=0.72)

	B (SE)	**Wald**	**OR (CI)**	**p**
First 5-year practice	0.700 (0.328)	4.543	2.013 (1.058-3.830)	**0.033**
PCD+	-0.865 (0.449)	3.705	0.421 (0.175-1.016)	0.054
Cement leakage	1.621 (0.353)	21.093	5.057 (2.532 -10.098)	**<0.001**
BMI	0.056 (0.029)	3.900	1.058 (1.000-1.119)	**0.048**

Beside the previously published good clinical outcome, **we could conclude that PCD could be characterized with a relatively low complication rate and short length of hospital stay (LOS).** Major surgical or non-surgical complications as well as reoperations were rare in this cohort, however, our findings underlined some important variables associated with poorer treatment outcome. 1) Cement leakage is asymptomatic in most cases, but it should be avoided because its association with postoperative symptoms and risk for reoperation. 2) **Use of high-viscosity cement** and surgeon's experience are the non-patient dependent factors helping to avoid cement leakage, reoperation and thus longer LOS. 3) **Obese patients have higher risk for cement leakage as well as for reoperation** and comorbidities are important factors on LOS even in case of this MIS procedure. The results of this study has been submitted to Global Spine Journal and is under first revision after the first, positive review.[11]

In vitro biomechanical studies on animal and human spine specimens were performed analyzing the biomechanical effect of advanced stage disc degeneration (ie. the presence of vacuum inside the disc) and PCD procedure. Experimental work, data acquisition and analysis have been conducted successfully during the project providing **high quality basic scientific evidence on the background and on the biomechnical effect of PCD**. Results of the animal

[11] **Complication pattern following percutaneous cement discoplasty: identification of factors influencing reoperation and length of hospital stay**. Kristof Koch, Zsolt Szoverfi, Gabor Jakab, Peter Pal Varga, Zoltan Hoffer, Aron Lazary. *Global Spine Journal - Revision on Manuscript ID GSJ-22-0049*

study has been published in Medical Engineering and Physics[12] while the results of the human cadaveric study has been submitted to PLOS One.[13]

The ***finite element model of the PCD*** procedure has been built and analyzed from different aspects (e.g. the relationship between the stress distribution in the segment and the features of the injected PMMA, the degree of the indirect decompression via the computational measurement of the 3D change of the spinal canal, etc). One study about the effect of PCD on the 3D dimensional changes of the spinal canal (ie. **the significant indirect decompression effect of PCD**) *has been published in the Journal of Orthopaedic Translation*[14]*.* The paper is also describe a **new method for the in silico measurement of the volumetric change of the spinal canal** characterized by a complicated anatomy. Another, review paper has been also written about the PCD procedure which was submitted to the Frontiers in Surgery.[15]

Summary

The OTKA FK 123884 (STABILITY: in silico 3D simulation studies toward the patient-specific intervention for specific forms of spinal instability) project has been successfully implemented. Minor changes in the scientific methodology and timeline were applied without significantly influencing the original aims, methods and expected results of the project. Significant, high level scientific evidence has been generated and published as well as technological developments have been also resulted by the project. In silico and in vitro biomechanical investigations were successfully combined with clinical research providing recommendations for everyday clinical practice. Based on the research and scientific results, 8 scientific papers have been published in high-rank international journals and 6 further manuscripts have been submitted to international scientific journals. Two additional scientific journal manuscripts related to the project are under preparation, so altogether the project has directly led to 16 international journal papers. The team of the In Silico Biomechanics Laboratory (ISBL) of the National Center for Spinal Disorders has significantly developed during the project. Two successfully defended PhD thesis, and two other ongoing PhD works are directly related to the project. The lab infrastructure has been significantly developed thanks to the OTKA funding. ISBL has become one of the leading in silico musculoskeletal biomechanics laboratory in Europe by the end of the project.

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[12] **Testing the impact of discoplasty on the biomechanics of the intervertebral disc with simulated degeneration: An in vitro study.** Chloé Techens, Marco Palanca, Peter Endre Éltes, Áron Lazáry, Luca Cristofolini. *Medical Engineering & Physics Volume 84, October 2020, Pages 51-59 (IF: 2.242)*

[13] **Biomechanical consequences of cement discoplasty: an in vitro study on human spines.** Chloé Techens, Sara Montanari, FerencBereczki, Peter Endre Eltes, Aron Lazary, Luca Cristofolini. *Submitted to PLOS One*

[14] **A novel three-dimensional volumetric method to measure indirect decompression after percutaneous cement discoplasty.** Peter Endre Eltes, Laszlo Kiss, Ferenc Bereczki, Zsolt Szoverfi, Chloé Techens, Gabor Jakab, Benjamin Hajnal, Peter Pal Varga and Aron Lazary. *Journal of Orthopaedic Translation Volume 28, May 2021, Pages 131-139, 2021. (IF: 5.191)*

[15] **Critical review of the state-of-the-art on lumbar Percutaneous Cement Discoplasty.** Chloé Techens, Peter Endre Eltes, Aron Lazary and Luca Cristofolini. *Submitted to Frontiers in Surgery*.

Most important scientific and technological results of the project:

- Development and validation of full lumbar spine generic and patient-specific finite element models
- Development and validation of a new method to adapt the lumbar FE models to standing position
- Development and application of a new method for the assessment of implant deformation and new bone formation after spinal surgeries
- Scientific evidence on the appropriateness of using a more affordable 3D printing technology in spinal application
- Development and validation of generic full thoraco-lumbo-sacral FE model
- Identification of major degenerative signs at adjacent disc as significant risk factors for adjacent segment degeneration after short lumbar fusions
- Recommendation of using additional transpedicular fixation to improve the stability of OLIF construct especially in case of compromised bone quality
- Scientific evidence on the favorable use of hybrid (rigid+non-rigid) rod constructs to decrease the risk of PJK in long thoracolumbar stabilizations
- Development and patenting a new implant providing the clinical application of hybrid rod constructs
- Scientific evidence on the improvement on lumbar alignment, foraminal height and spinal canal 3D dimensions due to PCD procedure
- New in silico method for the assessment of spinal canal 3D dimensions
- Identification of most common complications and their risk factors related to PCD technique
- In vitro and in silico evidence on the influence of advanced stage disc degeneration and its PCD treatment on segmental biomechanics

Aron Lazary MD PhD
principal investigator

Budapest, 15 Apr 2022