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CONTENTS

ORIGINAL ARTICLES

REVIEW

JOURNAL OF TURKISH SPINAL SURGERY

EDITORIAL

Dear Colleagues,

Once again, it is my honor to publish this, the 2nd issue, of our professional journal this year. The Journal of Turkish Spinal Surgery (www.jtss.org), is the official publication of the Turkish Spine Society, and it's made possible because of the contributions of the authors, reviewers, assistant editors, secretaries, and the Galenos Publishing Team. Once again, my sincere thanks to them for their help in getting this issue out to you. In addition, we are very happy to announce that we will be accepting new reviewers for our journal. Please apply to us, as soon as possible, if you are interested. I hope you will review this issue carefully, and incorporate the information and insights into your practices.

In this issue, there are six clinical research studies and one review article. The first study is a clinical one about scoliosis. It's titled, "Scoliosis Screening from Plain Radiographs Including Chest and Abdominal X-rays by Using the Deep Learning Method: is it Worth it?". The second study is a clinical study about "The Turkish Validity and Reliability of Hospitals for Special Surgery-Lumbar Spine Surgery Expectations Survey". The third is a clinical study, "Comparison of Cervical Cage and Cervical Disc Prosthesis in Cervical Disc Herniation: A Single Center Study". The fourth one is about "Clinical Outcomes of En-Bloc Cervical Laminoplasty for Cervical Spondylotic Myelopathy". The authors of the fifth study examined relationships. "Relationship of Lumbar Spinal Anatomical Structures with Lumbar Disk Hernia and Spinal Stenosis". The sixth study is entitled "Vertebroplasty Combined with Transpedicular Fixation for the Management of Non-Traumatic Osteoporotic Vertebral Fractures Associated with Pedicle Fractures" while the seventh is a review article entitled, "Could Pharmacological Targeting Mitophagic or Lysophagic Signaling Pathways be a New Hope in the Treatment of Intervertebral Disc Degeneration?".

I hope you will all appreciate the contributions that were made to bring this issue to you, and that you will attempt to apply the suggestions in it to your practices. As always, our goal is to provide you with the most current research available on practices and methodologies to guarantee that we remain at the forefront of all the latest developments.

With kindest regards,

Editor in Chief
Metin Özalay, M.D., Prof.

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SCOLIOSIS SCREENING FROM PLAIN RADIOGRAPHS INCLUDING CHEST AND ABDOMINAL X RAYS BY USING THE DEEP LEARNING METHOD: IS IT WORTH?

Alim Can Baymurat[1], Kemal Üreten[2], Tolga Tolunay[1], Gökhan Koray Gültekin[3], Muhammed Furkan Tosun[1], Muhammed Şakir Çalta[1], Alpaslan Şenköylü[1], Hakan Atalar[1]

[1]*Gazi University Faculty of Medicine, Department of Orthopaedics and Traumatology, Ankara, Turkey*
[2]*Ufuk University Faculty of Medicine, Department of Rheumatology, Ankara, Turkey*
[3]*Ankara Yıldırım Beyazıt University Faculty of Engineering and Natural Sciences, Department of Electrical and Electronics Engineering, Ankara, Turkey*

ABSTRACT

Objective: This study aimed to use deep learning techniques to discriminate different degrees of scoliosis on plain radiographs.

Materials and Methods: The study was performed on 1006 standing plain abdominal and chest radiographs (age range 10-18 years) obtained from the archive of our institution. The radiographs were divided into three groups according to the degree of scoliosis: normal (0-9°), mild (10-29°), and moderate/advanced (30° and above). The data were randomly selected and 15% were used for testing, 15% for validation, and the remaining 70% for training. Due to the limited data, the transfer learning (TL) method was used. Pre-trained VGG-16, ResNet-101, and GoogLeNet networks were used for TL. The original classifier was replaced with a new one. Geometric transformations of the radiographs were used for data augmentation. Rotation (-30, 30 degrees), translation (-30, 30 pixels), and scaling (0.9, 1.1 pixels) were applied to the images. The performance of the networks was evaluated using the performance parameters of accuracy, sensitivity, specificity, precision, and F1 score.

Results: Overall accuracy after testing the models was determined to be 90.1% for VGG-16, 86.1% for ResNet-101, and 85.5% for GoogLeNet. The accuracy, sensitivity, specificity, precision, and F1 score were 90.1%, 90.7%, 95.0%, 89.9%, and 90.1% for VGG-16, respectively. The VGG-16 values were determined to be higher than those of the ResNet-101 and GoogLeNet networks.

Conclusion: The results showed favorable results for deep TL methods in the assessment of normal, mild, and moderate/advanced scoliosis.

Keywords: Adolescent idiopathic scoliosis, deep learning method, pre-trained network.

INTRODUCTION

With advances in technology, artificial intelligence methods are now being applied in the field of medicine and in many areas of human life. Artificial intelligence studies are developing with increasing momentum. Recently, there have been many successful studies using convolutional neural networks (CNN), which is a deep learning (DL) method, especially in the field of image processing in medicine[1-3]. The layers in the CNN hidden layer mainly consist of the convolution layer, pooling layer, and fully connected layer. Feature extraction is performed in the convolution layers of the image transferred to the network operation through the input layer. In the pooling layer, the diversity of inputs is reduced. It is typically used as a fully connected layer classifier, and a softmax classifier is added to the output layer to calculate the prediction probability.

There are studies that have been conducted on different imaging methods of CNN in the field of medicine. CNNs are excellent at feature extraction, object detection, and classification, but a large amount of data is required to train the CNN model from the start. When there are not enough data, transfer learning (TL) is used to prevent overfitting and improve the performance of the model. For TL, some pre-trained networks developed from the imagent dataset are used. Some of these are AlexNet, VGG-16, GoogLeNet, ResNet-50, DenseNet, Inception, and MobileNet[4-6]. Another method applied to improve the performance of the model in DL methods is the data augmentation method. With this method, the number of data is artificially increased by

Address for Correspondence: Alim Can Baymurat, Gazi University Faculty of Medicine, Department of Orthopaedics and Traumatology, Ankara, Turkey
Phone: +90 312 202 22 33 **E-mail:** alimcanbaymurat@yahoo.com **Received:** 21.02.2024 **Accepted:** 21.03.2024
ORCID ID: orcid.org/0000-0002-0062-621X

cropping, scaling, translating, and rotating the data, and these data are used for training the network[7].

Generally, scoliosis patients are referred to the orthopedist during school health screenings by chance or after the child's parents notice the patient's shoulder and trunk asymmetry. Sometimes, patients are referred to an orthopedist or spine surgeon after a curve in the spine is observed on the chest and outpatient abdominal radiographs taken in the hospital or health centers because of other complaints. While adolescent idiopathic scoliosis (AIS) patients who are diagnosed early with mild curvatures of the spine and start appropriate treatment are followed up and treated with conservative methods, surgical intervention is required in severe spinal curvatures that are overlooked or noticed late for any reason[8,9].

The application of DL methods has been extensively investigated across various medical disciplines. In addition, there have been studies on scoliotic deformities of the spine[10,11]. There have also been studies on the classification of scoliosis according to its degree[12-14]. DL studies of scoliosis in the literature have generally been conducted using computed tomography or scoliosis radiographs of the entire spine. There is no study in the literature on the effectiveness of the DL method in scoliosis screening from other plain radiographs including the spine, such as chest and/or standing abdominal radiographs, and grading the degree of curvature from these radiographs.

The aim of this study was to evaluate the effectiveness of DL methods in discriminating normal and scoliotic spines from chest and standing plain abdominal radiographs. To assess the ability of these methods to accurately classify scoliotic spines according to the degree of curvature.

MATERIALS AND METHODS

Approval for the study was obtained from the Gazi University Clinical Research Ethics (approval number: 02, date: 17.01.2023). In this retrospective study, posterior anterior chest radiographs and standing direct abdominal radiographs of patients aged 10-18 years who presented at our institution with any complaint between January 2021 and December 2022 were obtained from the picture archiving and communication systems (PACS) of our institution. A total of 20264 radiographs obtained from PACS were screened by four investigators. T1 and L1 vertebrae on chest radiography and T10 and L5 vertebrae on standing direct abdominal radiography were included in the study. Those who underwent spine surgery, rib cage surgery, implant-detected radiography, or radiography with incomplete spine images were excluded from the study. On the X-ray images used in the study, any identification such as hospital name, patient names, age, and date was removed, and the images were recorded as jpg files. The study included 1006 radiographs, which underwent assessment by four investigators for Cobb's measurement angles representing spinal curvatures. Subsequently, the precision of the measured Cobb angles was verified by an experienced spinal surgeon. The images were divided into three groups according to the degree of Cobb angles. Group 1 included cases with Cobb angles between 0° and 9°, Group 2 included Cobb angles between 10° and 29°, and Group 3 included cases with spinal deformity of 30° or more. There were 372 radiographs with Cobb angles between 0° and 9° (Group 1), 332 radiographs between 10° and 29° (Group 2), and 302 radiographs with Cobb angles of 30° or more (Group 3). Because the data used in the study was limited, the TL method was used. Pre-trained VGG-16, ResNet-101, and GoogLeNet networks were used for TL.

Data Processing Environment

The width and height of the PACS images were of different sizes and in jpg format. This study was conducted on a computer with a GeForce RTX2060 graphics processing unit, using MATLAB and Image Processing Toolbox. Each graph in the raw dataset was cropped using the rectangular area MATLAB® image cropping function, which includes the entire spine image. The hyperparameters used in the study were Optimizer; Stocastic gradient descent with momentum, mini batch size 16, dropout 0.5, initial learning rate 3e-4, and L2 regularization 0.004.

Data Preprocessing and Splitting

The data in this study were randomly selected and 15% were used for testing, 15% for validation, and the remaining 70% for training. Adjustment of parameters was made using validation data. Thus, the test and training data were not used during validation. No data augmentation was performed on the test and validation data. The number of images used in the splits, training, verification, and testing is shown in Table 1.

Transfer Learning, Data Augmentation

DL methods require a large amount of data for training. When there is insufficient data, data augmentation and the TL method are used. The data enhancement process is achieved by copying or converting images, such as sharpness, brightness, contrast change, and mirror symmetry. To improve the performance of the CNN model, online data augmentation by randomly flipping and rotating images was used. TL is the use of networks trained with ImageNet data, which contains many natural object images, for a new task. In this study, pre-trained VGG-16[12], ResNet-101[14], and GoogLeNet networks were used for TL. Therefore, the original classifier was replaced with a new classifier. Geometric transformations of radiographs were used for data augmentation, with rotation (-30, 30 degrees), translation (-30, 30 pixels), and scaling (0.9, 1.1 pixels) applied to the images.

Table 1. The number of images used for training, validation and testing

Cobb angle	Train	Validation	Test	Total
0-9 (normal)	261	54	57	372
10-29 (mild)	234	48	50	332
30 and above (moderate/severe)	213	44	45	302

Statistical Analysis

Because of the classification, the performances of the networks were evaluated with respect to accuracy, sensitivity, specificity, precision, and F1 score performance parameters. These performance measures were calculated using macroaverages from the confusion matrix obtained during the testing of the models.

$$accuracy=\frac{(TP+TN)}{(TP+TN+FP+FN)}$$

$$sensitivity\ (recall)=\frac{TP}{TP+FN}$$

$$specificity=\frac{TN}{TN+FP}$$

$$precision=\frac{TP}{TP+FP}$$

$$F1\ score=\frac{2*(precision*recall)}{(precision+recall)}=\frac{2TP}{2TP+FP+FN}$$

TP: True positive; FP: False positive; TN: True negative; FN: False negative

RESULTS

The patients comprised 651 (64.7%) females and 355 (35.3%) males with a mean age of 14.61±3.89 years. Cobb angle values were within normal limits (0-9º) in 372 patients, mild scoliosis (10-29º) in 332 patients, and moderate/severe scoliosis (30º and above) in 302 patients (Table 2).

Three distinct groups of datasets were constructed based on the magnitude of the curves observed in the images: normal (Group 1), mild (Group 2), and moderate/severe (Group 3) (Table 1). The efficacy of the models was assessed by employing performance metrics, including accuracy, sensitivity, specificity, and precision. These metrics were computed using confusion matrices. The training process was repeated five times for each model. A summary of the performance of the pre-trained models is presented in Table 3. The overall accuracy of the VGG-16, ResNet-101, and GoogLeNet models tested was 90.1%, 86.1%, and 85.5%, respectively. The accuracy, sensitivity, specificity, precision, and F1 score results were 90.1%, 90.7%, 95.0%, 89.9%, and 90.1% in VGG-16, respectively, and were higher than the ResNet-101 and GoogLeNet results (Table 3). The confusion matrices obtained by testing the models are shown in Figure 1. Figure 2 shows the prediction results of six randomly selected samples during testing with VGG-16, first showing which classification was predicted, and then showing the percentage probability at which the predicted classification was predicted.

Table 2. Demographic characteristics and basic information of the patients

Mean age (year)	14.61±3.89
Gender F/M n (%)	651 (64.7%)/355 (35.3%)
Number of images (n)	1006
Cobb angle values	
Normal limits (0-9º)	372
Mild scoliosis (10-29º)	332
Moderate/severe scoliosis (30º and above)	302

F: Female; M: Male

DISCUSSION

The objective of this study was to assess the efficacy of DL techniques in detecting scoliosis from chest and standing plain abdominal radiographs, as well as accurately distinguishing various degrees of scoliosis based on the severity of spinal curvature. In addition, this study aims to gauge the potential of DL methods for scoliosis screening using chest and upright abdominal radiographs stored within healthcare institution image archives. TL was employed to implement the DL models using pre-trained VGG-16, ResNet-101, and GoogLeNet networks. These models were applied to the lung and standing abdominal radiographs used in the study. In the present study, the accuracy, sensitivity, specificity, precision, and F1 score results of VGG-16 with the DL method were 90.1%, 90.7%, 95.0%, 89.9%, and 90.1%, respectively, and it was found to be successful in both scoliosis detection and classification according to the degree of curvature.

Spine radiography is the first-line imaging method for the evaluation of patients with scoliosis. This study was conducted using radiographs with DL methods for the diagnosis and grading of scoliosis. Scoliotic deformities may be missed on chest or abdominal radiographs for any reason, especially in non-orthopaedic departments, because the physicians performing the evaluation do not have sufficient experience with scoliotic deformities. The success in scoliosis detection and grading with the DLmethod will help in scoliosis detection, grading, and referral to a specialist by physicians with limited knowledge of scoliosis disease. Previous studies have been conducted on DL methods in the diagnostic of musculoskeletal diseases. Successful results were obtained in radiological imaging studies where TL was applied with previously trained networks[15,16].

Table 3. Performance results obtained by testing the models

	VGG-16 (%)	ResNet-101 (%)	GoogLeNet (%)
Accuracy	90.1	86.1	85.5
Sensitivity	90.7	86.1	85.7
Specificity	95.0	93.0	92.6
Precision	89.9	86.1	85.6
F1 score	90.1	86.1	85.6

There are studies in the literature that have measured and predicted the Cobb angle of the scoliotic spine with the DL method using plain radiographs and computed tomography images[10,17,18]. Huang et al.[19] conducted a comparative analysis of CNNs and manual measurement of the Cobb angle in AIS. The findings revealed that the fully automated framework not only accurately identified vertebral borders, vertebral sequences, superior/inferior end vertebrae, and apical vertebrae but also successfully evaluated the Cobb angle for Proximal Thoracic, Main Thoracic (MT), and Thoracolumbar/Lumbar curves. In this study, the measurement of Cobb angle pain was excluded as a parameter for assessing spinal curvatures. Instead, the focus was on investigating the efficacy of DL methods in the detection of scoliosis and discrimination of the magnitude of curvature[19]. Fraiwan et al.[18] used deep TL to detect scoliosis and spondylolisthesis from patient X-ray images. In the study

Figure 1. Confusion matrices of the pretrained models, A) VGG-16 model, B) ResNet-101 model, C) GoogLeNet model

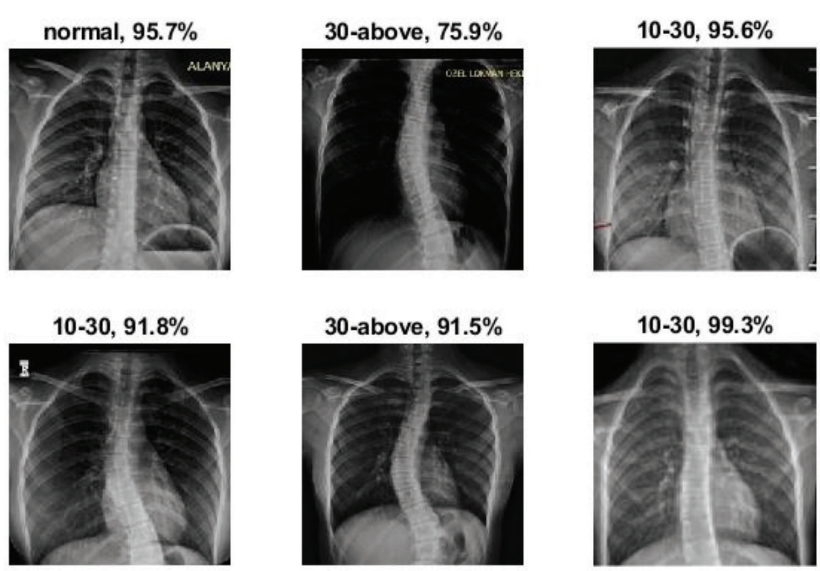

Figure 2. The prediction results of randomly selected six images during testing of the VGG-16 model

conducted on 188 scoliosis patients aged 5-35 years, successful results were obtained with an accuracy rate of 96.73% and 98.02%[18]. The current study is the first to focus on radiographs of adolescent patients aged 10-18 years, a population in which scoliosis commonly occurs. Furthermore, a substantial dataset of 1006 plain radiography images was analyzed, indicating a relatively extensive sample size. To mitigate the risk of overfitting, TL techniques were employed. The images were categorized into distinct groups based on the severity of curvature, as shown in Table 1. The evaluation of the VGG-16 model yielded promising results, with accuracy, sensitivity, specificity, precision, and F1 score values of 90.1%, 90.7%, 95.0%, 89.9%, and 90.1%, respectively.

Tavana et al.[20] performed a comparative analysis between a DL approach and a classical method for classifying the shape of spinal curvatures using a dataset of 1000 anterior-posterior spine radiographs. The study findings revealed that the pre-trained Xception model exhibited superior performance compared with the pre-trained MobileNetV2 network and the classical K nearest neighbors and support vector machine methods, specifically in discriminating between C- and S-shaped curvatures of the spine[20].

In a faster R-CNN and ResNet-based computer-aided scoliosis diagnosis study by Chen et al.[12], X-rays of the spine with normal, mild, moderate, and severe scoliosis were studied. For verification and analysis, the results were compared with the measurement results of the orthopedic surgeon. It has been reported that faster R-CNN and ResNet-based computer-assisted scoliosis diagnosis achieved successful results[12]. Chen et al.[12] used scoliosis radiographs including the entire vertebral column in their study. In the current study, using chest and standing abdominal radiographs, there were similar results, and it was seen that the DL method was successful in recognizing normal, mild, and moderate/severe scoliosis. However, chest and standing abdominal radiographs were not used in our study.

In this study, the reason for separating the images into three groups according to the degree of scoliotic curvatures of the spine was primarily because the treatment of patients with scoliosis varies depending on the size of the spinal curvature. While scoliotic curvature of the spine up to 10° is considered normal and does not require any follow-up and treatment, careful follow-up and appropriate treatment should be performed for errors where bone maturity has not been completed and in cases of spine curvatures of 10° and above. In this study, Cobb angles were considered normal at 0-9 degrees (Group 1) and did not require follow-up and treatment. Mild curvatures of 10-29 degrees (Group 2) are usually followed up radiologically. For curvatures of 30° and above (Group 3), brace treatment is applied, and surgical treatment is required in curvatures of 45°.

One of the key contributions of this study lies in the capacity of DL methods to discern different degrees of spinal curvature. The ability to classify scoliosis into normal, mild, moderate, and severe categories using DL techniques has significant implications for healthcare professionals. It allows for the provision of preliminary information to patients regarding their condition, guiding them toward appropriate treatment options, and facilitating referrals to specialists.

As a limitation of this study, due to limited number of radiological images, the radiographs were divided into only three groups (0-9 degrees: 1st group; 10-30 degrees: 2nd group and 30 degrees and above: 3rd group): 3rd group. In addition, not using the DL method in scoliosis measurements and the retrospective design of the study can also be considered limitations.

CONCLUSION

In conclusion, the results of this study show that DL methods are effective in detecting scoliosis in chest and standing plain abdominal radiographs and in classifying spinal curvature according to its magnitude. Also, the results of this study showed that deep TL methods may be useful in the evaluation of normal, mild and moderate/advanced scoliosis. The spine on X-ray images can be labeled and separated with DL methods as normal, mild, and moderate/advanced scoliosis. Thus, scoliosis patients requiring follow-up and treatment can be referred to orthopedics or spinal surgery. Furthermore, this study provides non-orthopedic physicians with limited expertise in spinal disorders with the opportunity to accurately assess the detection of scoliosis in a patient and the severity of spinal curvature. Thus, it offers the possibility of early detection of scoliosis and referral to the appropriate specialist, enabling early treatment. We also believe that this study will shed light on advanced scoliosis screening and statistical studies.

Ethics

Ethics Committee Approval: Approval for the study was obtained from the Gazi University Clinical Research Ethics (approval number: 02, date: 17.01.2023).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: A.C.B., T.T., A.Ş., H.A., Concept: A.C.B., T.T., H.A., Design: M.F.T., A.Ş., Data Collection or Processing: K.Ü., G.K.G., M.F.T., M.Ş.Ç., Analysis or Interpretation: A.C.B., K.Ü., G.K.G., Literature Search: A.C.B., M.F.T., M.Ş.Ç., Writing: A.C.B., M.Ş.Ç.

Conflict of Interest: The authors have no conflicts of interest to declare.

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THE TURKISH VALIDITY AND RELIABILITY OF HOSPITAL FOR SPECIAL SURGERY-LUMBAR SPINE SURGERY EXPECTATIONS SURVEY

Aydın Sinan Apaydın[1], Musa Güneş[2], Metehan Yana[2], Cihan Caner Aksoy[3], İsmail Saraçoğlu[3], Cevat Akıncı[1]

[1]Karabük University Faculty of Medicine, Department of Neurosurgery, Karabük, Turkey
[2]Karabük University Faculty of Medicine, Department of Physiotherapy and Rehabilitation, Karabük, Turkey
[3]Kütahya University of Health Sciences Faculty of Medicine, Department of Physiotherapy and Rehabilitation, Kütahya, Turkey

ABSTRACT

Objective: The postoperative recovery expectations of patients are important for surgical decisions. The Hospital for Special Surgery-Lumbar Spine Surgery Expectations Survey (HSS-LSSES) is a questionnaire evaluating expectations from lumbar surgery. This study aims to adapt the HSS-LSSES to Turkish and to assess its validity and reliability.

Materials and Methods: The methodology of this study was based on the COSMIN guideline. The Turkish version of the HSS-LSSES created with the double-back translation procedure and the Turkish version of the Quebec Back Pain Disability Scale (QBPDS) were administered to the participants who were scheduled for surgery with the diagnosis of lumbar radiculopathy, respectively. Cronbach's alpha coefficient and item analysis were used to assess internal consistency. Also, intraclass correlation coefficient (ICC) was used to determine test-retest reliability.

Results: The study included 180 participants (54.4% male) with a mean age of 50.96±13.42 years at scheduled lumbar spine surgery. HSS-LSSES had good internal consistency (Cronbach's α=0.87) and excellent test-retest reliability [ICC (2.1)=0.99; p<0.01]. A strong negative correlation was found between HSS-LSSES-TR and QBPDS-TR (r=-0.71, p<0.01). It was observed that there was no ceiling and floor effect in the scale.

Conclusion: HSS-LSSES-TR is a practical, valid, and reliable measurement method that can be used in clinical and research settings to evaluate the expectations of individuals planning for lumbar spine surgery and to examine how well these expectations are met after surgery.

Keywords: Cross-cultural adaptation, expectation, radiculopathy, lumbar surgery

INTRODUCTION

Lumbar spine disorders are among the important health problems that can cause physical and psychological disability, especially pain, severe symptoms that often coexist, job loss, and high health expenditures. Moreover, the number of patients who are operated on to treat pain and disability due to lumbar spine disorders is increasing daily[1]. Deciding on surgical methods for the spine and their potential impact on the degenerative process and patients' symptoms remains an important research topic[2,3]. It has been revealed in many studies that one of the most important determinants is the patients' expectations, both for deciding on surgical procedures and for examining the effects of surgical methods[4-6].

From the past to the present, patients' expectations from spine surgery for the lumbar area have been evaluated with various methods, including standard questions to individuals before extensive surgery[7-10]. However, when these methods are examined, it has been observed that "ad hoc surveys" developed by the researchers specifically for the study, which have no validity and reliability and cannot be adapted to different languages, are used. For this reason, the Hospital for Special Surgery-Lumbar Spine Surgery Expectations Survey (HSS-LSSES) was developed in 2013[11]. This scale thoroughly evaluates the patient's recovery expectations for physical and social functions following lumbar spine surgery. When the literature is examined, no version of HSS-LSSES has been found in languages other than Russian[12]. Evaluating the expectations of individuals from lumbar spine surgery in a patient-centered framework and reporting that it is valid and reliable in the original and other published versions are among the advantages of this scale.

HSS-LSSES may help evaluate the expectations of Turkish-speaking patients and provide additional benefits for physicians in deciding on surgical procedures and achieving better clinical

Address for Correspondence: Aydın Sinan Apaydın, Karabük University Faculty of Medicine, Department of Neurosurgery, Karabük, Turkey
Phone: +90 506 589 76 13 **E-mail:** dr.sinanapaydin@yahoo.com **Received:** 01.03.2024 **Accepted:** 21.03.2024
ORCID ID: orcid.org/0000-0002-2916-9550

results. In addition, creating versions of the scales in different languages may contribute to the development of a general procedure for the results obtained from studies on lumbar spine surgery. Therefore, this study aims to use the Turkish version of the HSS-LSSES by making a linguistic and cultural translation and examining the validity and reliability of this scale.

MATERIALS AND METHODS

The methods used in this study were determined and reported according to the COSMIN guidelines[13,14].

Participants

Individuals who were referred to the neurosurgery department with symptoms of low back pain and decided to undergo lumbar radiculopathy (LR) surgery by a neurosurgeon were invited to participate in the study. Inclusion criteria were (1) being between 18 and 70 years of age, (2) meeting the indications for LR surgery, (3) giving consent and consent for surgical treatment, and (4) volunteering to participate in the study. The exclusion criteria were (1) planned spine surgery other than LR (spinal fusion, arthroplasty, etc.), (2) scheduled revision surgery for LR, and (3) illiteracy in Turkish. Patients who met the inclusion criteria were informed, and written and verbal consent was obtained.

The study was approved by the Karabük University Rectorship Non-interventional Clinical Research Ethics Committee (approval number: 2022/772, date: 20.01.2022) and was conducted at Karabük University Education and Training and Research Hospital between February 2022 and January 2023. This study was conducted according to the Declaration of Helsinki criteria. According to the COSMIN guideline, 7-10 times the number of items in the scale and a minimum of 100 people are required to assess construct validity[14]. Since the scale has 21 items and considering the 15% loss rate, it was decided to include at least 170 people in the study. Submitted to ClinicalTrials: NCT04547075.

Outcome Measures

Hospital for Special Surgery Lumbar Spine Surgery Expectation Survey

It is a self-report measure developed by Mancuso et al.[11] and is used to evaluate patient expectations from lumbar surgeries. The original version of the scale, published in English, consists of 21 items and addresses pain, function, employment status, mental health, and expected future spinal conditions. The patient's expectations were evaluated using a 5-point Likert scale ranging between 1 and 5 points. The total score from the scale is between 25 and 100, and an increase in the score indicates high expectations.

The Quebec Back Pain Disability Scale (QBPDS)

It is a scale developed by Kopec et al.[15] that evaluates how much difficulty back problems cause a person during 20 different activities. Individuals were evaluated with a score ranging from 0 to 5. A score of zero indicates no difficulty during the activity, whereas a score of 5 indicates that the activity could not be performed. The total score from the scale varies between 0 and 100. A higher score indicates greater involvement at the functional level. The Turkish validity and reliability of the scale was conducted by Melikoglu et al.[16] in individuals with low back pain.

Translation Procedure

The following procedure was followed to develop and validate the Turkish version of HSS-LSESS[14].

Preparation of the Turkish Version of the Scale: The original scale was translated into Turkish by three native speakers, and a preliminary version was created by comparing them. This version has been analyzed by a linguist for narrative purposes and revised accordingly. This version was applied to 10 participants who met the inclusion criteria but were not included in the data collection sample. Participants were asked to read the revised scale and rate the items as easy to understand, understandable, or difficult to understand. Items that were considered difficult to understand were reviewed and revised.

Back Translation of the Scale into English and Ensuring Consistency with the Original: The scale items were translated into English by a native English speaker who knows Turkish well. The reverse-translated scale was sent to Professor Mancuso, the scale developer, and asked to verify its consistency with the original scale.

First Test of Scales: HSS-LSSES-TR and QBPDS-TR were administered by face-to-face interview to all participants who met the inclusion criteria and agreed to participate in the study.

Second HSS-LSSES-TR Test (Retest): HSS-LSSES-TR was administered to the participants who agreed to repeat the assessment one week later by face-to-face interview method. Test-retest reliability was assessed using data from these participants. The scale was not applied a second time to patients who underwent surgery or gave up on surgery within a week after the first interview.

Statistical Analysis

The study data were analyzed using IBM SPSS 22.0 (IBM Corp., Armonk, NY) package program. Descriptive variables were given using the mean, minimum and maximum, and standard deviation (SD). Percentage values were used for category data.

Whether the data showed a normal distribution was examined by considering the skewness, kurtosis values, and histograms. Data with skewness and kurtosis values between +1.0 and -1.0 were considered normal distributions[17]. Standard Error of Measurements (SEM) and Minimal Detectable Changes (MDC) were calculated using the following formulas.

$$SEM = SD \times \sqrt{(1-r)}$$

$$MDC = SEM \times 1.96 \times \sqrt{2}$$

The test-retest method was used to determine reliability. The relationship between the first and second measures was examined using the intraclass correlation coefficient [ICC (2.1)]. An ICC value of <0.5 was accepted as poor, between 0.5 and 0.75 as moderate, between 0.75 and 0.9 as good, and greater than 0.90 as excellent reliability(18).

Hypothesis testing was used to determine the structural validity of the HSS-LSSES scale. In the established hypothesis, it was accepted that there should be a medium-high ($0.4 \leq r \leq 0.89$) relationship between HSS-LSSES-TR and QBPDS-TR results. In correlation analyses, the correlation coefficient was considered negligible if it was between 0.00-0.10, weak if 0.10-0.39, medium between 0.40-0.69, high between 0.70-0.89, and very high between 0.90-1.00(19).

In determining whether there is a ceiling and floor effect in the scale scores, 15% was accepted as the threshold value, as is widely accepted in the literature(20-22). The minimum score obtained from the Lumbar Spine Surgery Expectations scale is 20, and the maximum score is 100. The ceiling and floor effects were evaluated according to these minimum and maximum values.

RESULTS

Two hundred and fifty-one people were initially invited to this study, but 71 were excluded because they did not meet the inclusion criteria, and data from 180 participants were analyzed at the end of the study. The mean age of the participants was 50.96±13.42 years, and 54.4% were male. 36.7% of the participants had an additional chronic disease. Detailed information about the physical characteristics, gender, marital status, education level, and diseases of the participants is given in Table 1. For the test-retest analysis, one week after the first application, the HSS-LSSES-TR was questioned again with a face-to-face interview method with 165 participants who still had not undergone surgery, reaching a 90.9% response rate (Figure 1).

Reliability

Cronbach's alpha (Cronbach's α) coefficient was used to determine internal consistency. While this value is expected to be at least 0.7 and above, values above 0.8 indicate good internal consistency(23). Cronbach's α coefficient of the 21-item HSS-LSSES-TR scale was found to be 0.87. When deleted, we investigated whether the overall scale was the item that increased the Cronbach's α coefficient. In the case of deletion, no item was found that increased the Cronbach's α coefficient of the scale. Item-total correlations were item 18, the only item with a minimal value of >0.20. When this item was examined in detail, it was thought that the relatively small number of participants who answered this question may have caused this situation. Participants who work in any job on the scale should mark item 17, and those who do not work in any job should mark item 18. Considering that the statistical data of the 18th item was low for this reason, it was decided that the relevant item should not be removed from the scale. Test-retest reliability was excellent [ICC (2.1)=0.994, 95% confidence interval [(CI) 0.992-0.996, p<0.001]. The SEM value was 0.954 (2.27% of the mean). The MDC was 2.64 (6.3% of the mean). The mean and SD of the items and item-total correlations are shown in Table 2.

Validity

The minimum and maximum scores obtained because of the answers given by the participants to the scale are shown in

Table 1. Sociodemographic Information of the Participants

Variables	X	SD
Age (year)	50.96	13.42
Height (cm)	170.67	9.03
Weight (kg)	77.97	12.65
Body mass index (kg/m^2)	26.67	3.02
	n	**%**
Sex		
Female	82	45.6
Male	98	54.4
Marital status		
Married	139	77.2
Single/Widowed	41	22.8
Work status		
Housewife	63	35
Officer	30	16.7
Employee	61	33.9
Retired	23	14.4
Dominant side		
Right	161	89.4
Female	19	10.6
Education status		
Not literate	13	7.2
Elementary school	65	36.1
Middle/High school	69	38.3
College or higher	33	18.3
Chronic disease		
Yes	66	36.7
No	114	63.3
Diseases		
Diabetes	48	26.7
Cardiac diseases	22	12.2
Hypertension	43	23.9
Pulmonary diseases	12	6.7
Disc herniation		
L_2-L_3	8	4.4
L_3-L_4	23	12.8
L_4-L_5	86	47.8
L_5-S_1	63	35

X: Mean, SD: Standard deviation, cm: Centimeters, kg: Kilograms, L: Lumbal, S: Sacral, n: number of cases, %: Percent

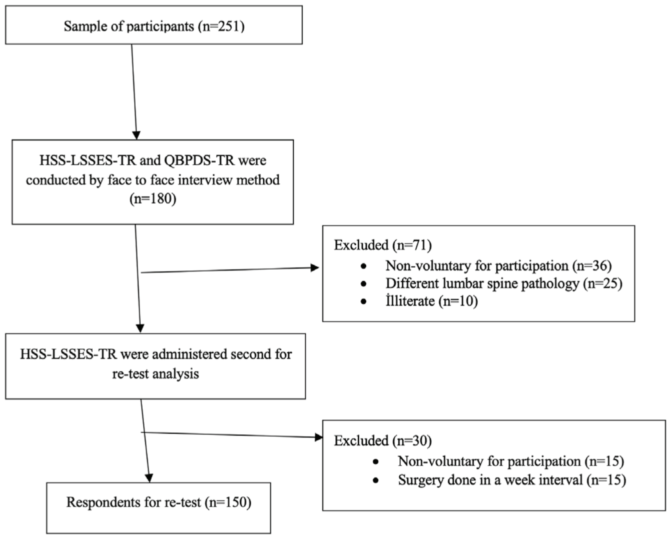

Figure 1. Flowchart
HSS-LSSES: Hospital for Special Surgery-Lumbar Spine Surgery Expectations Survey, QBPDS: Quebec Back Pain Disability Scale

Table 3. It was determined that only 1.67% of the participants achieved a base score.

When the relationship between HSS-LSSES-TR and QBPDS was examined, it was determined that there was a high negative correlation between the scores of both scales (r=-0.71, p<0.001) (Table 4).

DISCUSSION

The aim of this study was to evaluate the validity and reliability of the HSS-LSSES by adapting it to the Turkish language. During the intercultural translation and adaptation process, it was concluded that all items, except one, were suitable for Turkish culture. It was observed that the patients could easily understand the scale. In addition, it was concluded that the HSS-LSSES-TR items evaluated a single basic structure, had good internal consistency, excellent test-retest reliability, no ceiling and floor effects, and showed a high correlation with QBPDS-TR in individuals with LR.

While evaluating the internal consistency, one of the important parameters used to determine the reliability of a scale, it was stated that if the scale has a Likert structure, Cronbach's α value

Table 2. Lumbar spine surgery expectations scale item analysis

	X ± SS	Item-total correlation	Cronbach's α if item is deleted
Relieve pain	3.57±0.76	0.41	0.84
Relieve symptoms that interfere with sleep	3.15±1.21	0.48	0.84
Improve ability to walk more than several blocks	3.24±0.85	0.55	0.84
Improve ability to sit for more than half an hour	3.14±0.87	0.6	0.84
Improve ability to stand for more than half an hour	3.08±0.9	0.64	0.84
Regain strength in the legs	3.01±1.09	0.51	0.84
Improve balance	2.32±1.57	0.21	0.85
Improve ability to go up and down stairs	3.12±0.9	0.54	0.84
Improve the ability to manage personal care (such as dressing and bathing)	3.51±0.76	0.43	0.84
Improved ability to drive	1.94±1.94	0.58	0.83
Remove the need for pain medications	2.54±1.4	0.49	0.84
Improve ability to interact with others (such as social and family activities)	3.14±1.05	0.41	0.84
Improved sexual activity	2.41±1.67	0.3	0.85
Improve the ability to perform daily activities (such as chores, shopping, errands)	3.14±0.98	0.48	0.84
Improve the ability to exercise for general health	1.64±1.29	0.62	0.83
Remove restrictions in activities (such as be more mobile, not have to rest every few minutes)	2.69±1.06	0.55	0.84
If currently employed, fulfill job responsibilities (such as work required hours complete expected tasks)	1.18±1.69	0.38	0.85
If currently work-disabled or unemployed because of spine, return to work for salaried employment.	0.79±1.44	0.05	0.86
Reduce emotional stress and sad feelings	2.28±1.51	0.33	0.85
Stop the spine condition from getting worse	3.28±0.82	0.53	0.84
Remove the control that the spine condition has on my life	3.17±0.96	0.50	0.84

X: Median, SD: Standard deviation, Cronbach's α: Cronbach's alpha

Table 3. Lumbar spine surgery expectations scale ceiling and floor effect

Scale	X ± SD	Lowest score	Lowest scoring participant n (%)	Highest score	Highest scoring participant n (%)
LSSE	42.28±12.3	20	3 (1.67%)	-	-

X: Median, SD: Standard deviation, LSSE: Lumbar spine surgery expectations

Table 4. Lumbar spine surgery expectations and the Quebec back disability questionnaire correlation

Variable		
Lumbar spine surgery expectations: Quebec back disability questionnaire	r	-0.71
	p	0.00

should be above 0.70[24]. In this study, the HSS-LSSES-TR was shown to have a good internal consistency (Cronbach α=0.87). This result showed that the Turkish version of the scale had similar internal consistency with the Russian version (α=0.94)[12] and the original version (α=0.90)[11]. According to the good internal consistency results found in the studies conducted in all three versions, participants generally thought carefully about each of the items and took the necessary time to give a valid answer to each question. In addition, in the item analysis for HSS-LSSES-TR, although the correlation value between the 18th item and the total score scores was below 0.2, Cronbach's α value of the scale did not change when the relevant item was deleted. To allow generalizability and comparison of the HSS-LSSES results, item 18 was not removed from the scale in the Turkish version either. In the original version of the scale, participants who are still active are expected to mark item 17, and those who previously worked in a paid job but did not work because of low back pain are expected to check item 18. However, regardless of low back pain, it is thought that individuals who do not work in a salaried job (such as housewives) have more difficulty choosing between these two items by answering item 17. Therefore, the item-total correlation for item 18 remains low.

Another method used to determine the reliability of a scale is the test-retest. HSS-LSSES-TR has also been shown to have excellent test-retest reliability (ICC=0.99). Similarly, high ICC values in the Russian version (ICC=0.89)[12] and original version (ICC=0.86)[11] of the scale are an indication that consistent responses can be obtained and reliable in all versions of the HSS-LSSES.

Construct validity is another important concept in adapting assessment tools to different languages[25]. Construct validity was examined with patient-reported functional scales because no other similar scale with validation and reliability was established to evaluate the expectations of patients scheduled for lumbar spine surgery. While the Oswestry Disability Index (ODI) was used in the Russian version of the study[12], a similar scale to the ODI, QBPDS-TR, was used in our study. A high level of negative correlation (r=-0.71) was observed between HSS-LSSES-TR and QBPDS-TR, and the construct validity of HSS-LSSES was supported by hypothesis testing. In the Russian version, there was a weak negative correlation (r=-0.36) with HSS-LSSES and ODI scores[12]. Unlike the Russian version, we believe that the higher correlation may be due to QPBDS interrogating more functional activity status than ODI. However, both versions of the study revealed that individuals with worse functional performance had higher expectations. These results are also consistent with those of Mancuso et al.[26], who reported that individuals with worse functional scores had higher expectations.

Using a scale developed for individuals scheduled for lumbar spine surgery, such as the HSS-LSSES, which has been shown to be valid and reliable in English, Russian, and Turkish, where the expectations most expressed by patients are questioned, may provide significant clinical benefits. In particular, it may improve communication and collaborative decision making by promoting discussions among physicians before clinical decision-making[10,27]. In addition, it may contribute to patient-surgeon harmony by enabling patients and surgeons to meet in line with the same goals and expectations. Moreover, such scales can also be used to examine the patient-centered efficacy of the surgical intervention in question, as it would potentially allow a comparison of the expected amount of healing and recovery achieved before surgery.

Study Limitations

There are some limitations to this study. Unlike the original version of the HSS-LSSES, the participants in this study consisted only of individuals who were scheduled for surgery with a diagnosis of LR. Although this was planned to reduce heterogeneity and increase the internal validity of our study, it may negatively affect the generalizability of the study results for patients scheduled for surgery due to other spinal pathologies. In addition, responsiveness and minimal clinically important difference (MCID) values, which are not found in other versions of the scale, could not be examined in our study. Future studies may examine other psychometric properties of HSS-LSSES, such as responsiveness and MCID, in individuals scheduled for different lumbar spinal surgeries.

CONCLUSION

This study revealed that in addition to the Russian version of the HSS-LSSES, it could be adapted to the Turkish language by cross-cultural adaptation, and this adapted version has good internal consistency, excellent test-retest reliability, and no ceiling and floor effects. Therefore, HSS-LSSES-TR can be a practical, valid, and reliable measurement method that can be used in clinical and research settings to evaluate the expectations of individuals planning for lumbar spine surgery and to examine how well these expectations are met after surgery.

Ethics

Ethics Committee Approval: The study was approved by the Karabük University Rectorship Non-interventional Clinical Research Ethics Committee (approval number: 2022/772, date: 20.01.2022) and was conducted at Karabük University Training and Research Hospital between February 2022 and January 2023.

Informed Consent: Patients who met the inclusion criteria were informed, and written and verbal consent was obtained.

Authorship Contributions

Surgical and Medical Practices: A.S.A, M.G., C.C.A., C.A., Concept: A.S.A, M.G., C.C.A., C.A., Design: A.S.A, M.G., M.Y., İ.S., Data Collection or Processing: A.S.A, M.Y., C.C.A., C.A., Analysis or Interpretation: A.S.A, M.G., M.Y., C.C.A., Literature Search: A.S.A, M.G., M.Y., C.C.A., İ.S., C.A., Writing: A.S.A, M.G., C.C.A., İ.S.

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COMPARISON OF CERVICAL CAGE AND CERVICAL DISC PROSTHESIS IN CERVICAL DISC HERNIATION: A SINGLE-CENTER STUDY

Faruk Altınel[1], Bora Limnili[2], Gözde Özcan Söylev[3], Yonca Özvardar Pekcan[4]

[1]Başkent University Zübeyde Hanım Application and Research Centre, Clinic of Neurosurgery, İzmir, Turkey
[2]Başkent University Zübeyde Hanım Application and Research Centre, Clinic of Orthopedics and Traumatology, İzmir, Turkey
[3]Başkent University Zübeyde Hanım Application and Research Centre, Clinic of Physical Therapy and Rehabilitation, İzmir, Turkey
[4]Başkent University Zübeyde Hanım Application and Research Centre, Clinic of Anaesthesiology and Reanimation, İzmir, Turkey

ABSTRACT

Objective: Anterior cervical discectomy (ACD) and fusion is the standard surgical treatment for cervical radiculopathy. The cervical disc prosthesis is designed to prevent complications such as pseudoarthrosis and adjacent segment degeneration and to preserve spinal motion.

Materials and Methods: In this retrospective study, 57 patients who underwent microsurgical ACD between 2015 and 2020 were included. Patients were divided into four groups: I group cervical cage (CC), II group cervical disc prosthesis (CDP) at one level, III group and CDP, and IV group CC+CC at two levels. For cage application, 1 cc of canceled bone graft was used in each case. In our study, the clinical outcomes, operations, and complications of patients who underwent CC and CDP and those who underwent double-level hybrid CC and CDP were evaluated during the 2-year follow-up period.

Results: When the groups were compared according to the localization of patient complaints (p=0.235) and neurological findings such as preoperative brachial neuropathy, upper extremity paresis, and cord compression (p=0.781), there was no statistically significant difference (p>0.05). In preoperative cervical magnetic resonance imaging (MRI) reports; In the CDP group, protrusion and extrusion were reported in the midline in 13 (22.8%) patients and in the lateral location in 17 (29.8%) patients. Osteophyte formation was more frequently encountered in the midline and lateral locations in the CC group (17.5%). Osteophyte formation was not observed in the CDP group. A significant difference was found in the preoperative cervical MRI results (p=0.006) and postoperative cervical spinal alignment averages (p=0.021). In all groups, C 5/6 (64.9%) and C 6/7 (40.4%) were the frequently affected disc spaces. In those who underwent CDP, soft disc was observed in 24 (80.0%) patients, and hard disc, CC, CDP+CC, was observed in 6 (20%) cases. A hard disc was detected in the entire group with CC (two distances). There was a statistically significant difference according to the affected disc nature and spacing (p<0.001). When all groups were compared according to operation times, operation results, and complications, there was no significant difference between the groups (p=0.074).

Conclusion: Microsurgical ACD is an effective and reliable method preferred in cervical disc herniations. Although autologous or heterologous bone grafts and cages are used to ensure fusion, CDP, which reduces adjacent segment disease and provides spinal mobility, has been preferred more frequently in recent years.

Keywords: Anterior, cervical discectomy, cage, disc prosthesis

INTRODUCTION

Cervical intervertebral disc herniations occur when a part of the nucleus pulpous or annulus fibrosus occupies space within the spinal canal and are an important pathology that causes neck pain, radiculopathy, and myelopathy. It may limit working life and daily activities, and cervical spine surgery is effective when conservative treatment is not sufficient to reduce pain[1,2]. The most appropriate method for treating symptomatic cervical disc herniation is microsurgical anterior cervical discectomy.

In recent years, with the introduction of the microscope, non-fusion or fusion techniques have been used[1,3]. Discectomy with fusion relieves the pressure on the spinal cord and nerve roots, and autologous or heterologous bone grafting and cervical cage (CC) are applied to achieve appropriate cervical vertebra alignment and solid arthrodesis with minimal risk[4-6]. Although there are many surgical options for cervical disc herniation, cervical disc prosthesis (CDP) is now an established and validated option that has demonstrated its safety and effectiveness with good clinical results[4]. In the posterior approach, posterior cervical foraminotomy (PCF) can be performed openly or endoscopically[7-9].

In this study, in 57 patients with single- and double-level cervical disc herniation who were operated on using a microscope with an anterior approach in our clinic, posterior longitudinal ligament excision was performed and cage and/or CDP were used instead of bone graft. In cases of double-level

Address for Correspondence: Faruk Altınel, Başkent University Zübeyde Hanım Application and Research Centre, Clinic of Neurosurgery, İzmir, Turkey
Phone: +90 532 215 42 36 **E-mail:** farukaltinel@gmail.com **Received:** 23.12.2023 **Accepted:** 02.04.2024
ORCID ID: orcid.org/0000-0002-8326-3900

degenerative disc herniation, a hybrid cage or cage and CDP were used together.

MATERIALS AND METHODS

The information of 57 patients who underwent surgery with a diagnosis of cervical disc herniation in our clinic between 2015 and 2020 was collected from the nucleus database. In patient groups, age, gender, motor and sensitive deficits, disc nature (hard, soft), osteophyte formation, the most common disc level, two or more affected levels, the relationship of the disc with the posterior longitudinal ligament and postoperative cervical vertebra curvature, early and postoperative 6^{th}-month Visual Analogue Scale (VAS) results, healing status according to Odom's criteria, reoperation, and developing complications were evaluated. It was questioned whether there might be other reasons for symptoms such as neck pain, pain radiating to the arm, and shoulder pain. Preoperative plain radiographs, cervical magnetic resonance imaging (MRI), and computer tomography were examined in all patients. Cervical lordosis changes, intervertebral level stenosis, and osteophyte formation in the posterior vertebra were recorded. Patients with fractures, infections, deformities, tumors, and chronic systemic illnesses, such as rheumatoid arthritis and neurodegenerative diseases, were not included in this study. Postoperative cervical vertebral sagittal alignment was compared between the groups (Figure 1). The number of patients meeting the criteria was 29 males (50.9%) and 28 females (49.1%), and the follow-up period was 2 years.
Patients according to the type and level of fusion; were divided into 4 groups: group I, CC; group II, CDP at one level; group III, CC+CDP; and group IV, CC+CC at two levels. In cases with CC, 1 cc canceled bone allograft was placed inside the cage and placed at the level to achieve better fusion. Patients with cervical trauma, neoplasm, infection, bleeding tendency, and chronic systemic disease were not included in the study. The patients had neck pain before and after surgery. Severity was evaluated using VAS results, and postoperative quality of life was evaluated using Odom's criteria.

This study was approved by the Başkent University Medicine and Health Sciences Research Board (approval number: KA23/267, date: 22.08.2023) and supported by the Başkent University Research Fund.

Statistical Analysis

Statistical Package for Social Sciences for Windows 11.0 program (SPSS Inc., Chicago) was used. While evaluating the data, descriptive statistics were given as mean, standard deviation, and n (%). Categorical variables were compared using the chi-square (X^2-test). If the alpha value was less than 0.05 ($p<0.05$), the data were considered statistically significant.

RESULTS

When the groups were evaluated, the average age of the group I cases was 46.5 years, 20 (66.7%) of whom were female, and in the II, III, and IV group cases, the average age was over 55 years, 19 (70.3%) of whom were male. In preoperative cases, brachial neuropathy (pain radiating to the arm) in group I was found in 10 (33.3%), reflex disorders in 7 (23.3%), paresis in the upper extremity in 12 (40.0%), and Brown-Séquard findings in 1 (3.3%). In groups II and IV, brachial neuropathy and paresis were more frequent. It was determined that cord compression findings (clonus) developed in 2 (6.7%) cases. Because of the comparisons, there was no statistically significant difference ($p>0.05$) (Table 1).
In operated cases, in all groups, the affected disc space was frequently C 5/6 in 37 cases (64.9%) and C 6/7 in 23 cases (40.4%). In those who underwent CDP, soft disc was observed in 24 (80.0%) patients and hard discs in 6 (20%) cases. Hardness was detected in the entire group with CC, CDP+CC, and CC (two distances). There was a statistically significant difference according to the affected disc nature and spacing ($p<0.001$) (Table 2).
In the preoperative cervical MRI reports of the cases; In the CDP group, protrusion and extrusion were reported in the midline in 13 (22.8%) patients and in the lateral location in

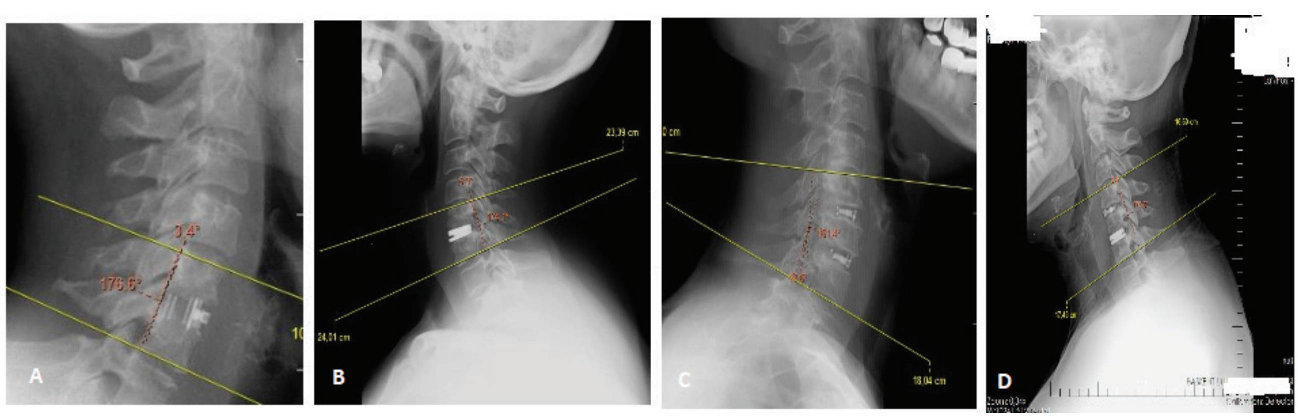

Figure 1. Post operative cervical sagittal alignment of the cases in cervical lateral radiograph, A) C5-6 cervical cage, B) C5-6 cervical disc prosthesis, C) hybrid C5-6 and C6-7 cage (CC+CC), D) hybrid C4-5 cage and C5-6 disc prosthesis (CDP+C)
CDP: Cervical disc prosthesis, CC: Cervical cage

17 (29.8%) patients. Osteophyte formation was more frequently encountered in the midline and lateral locations in the CC group (17.5%). Osteophyte formation and autofusion were not observed in the CDP group. Due to restrictions set by the Social Security Institution in Turkey, patient selection for CDP was limited to those who met certain criteria. However, if used in a single distance, at C3/4, C4/5, C5/6, and C6/7 disc distances, over the age of 18, it can be used in patients with no degenerative changes in the posterior elements (such as facet arthropathy, osteoporosis), no listhesis, no infection, and traumatic disc herniation. CDP was applied to patients who met all the criteria, such as having no cervical kyphosis or cervical lordotic, and showing on MRI that the height of the disc space to be applied was at least half of the height of the healthy adjacent disc. There was a statistically significant difference between the preoperative cervical MRI results (p=0.006) and the postoperative cervical spinal alignment averages (p=0.021) was determined to be 4.28°-5.84° on average in the single-level CDP and CC groups and 4.66°-7.22° in those who underwent two-level CDP+CC and CC hybrid surgery (Table 3).

Although the operation time was performed at an average of 115.50-141.60 min in all 4 groups, postoperative VAS results showed a significant decrease and excellent improvement was detected in 47 (82.45%) cases. As a result of the surgeries in all cases, temporary dysphagia was observed in 2 (3.50%) cases, and only 1 patient (1.75%) who underwent hybrid CC was re-

Table 1. Demography, symptoms, and neurological findings of preoperative cases

Operation	n	Age	Sex	Arm pain				Neurological findings					
			W/M	R	L	Bilateral		Radicular			Cord compression		
								B/N	Reflex disorder	Paresis	Br-Sq	clonus	
CDP	30	46.5	20/10	14	12	4	x^2=8.037 p=0.235	10	7	12	1	-	x^2=5.574 p=0.781
CC	10	58.2	4/6	2	8	-		5	-	4	-	1	
CDP+CC	5	51.2	1/4	2	3	-		2	2	1	-	-	
CC+CC	12	55.5	3/9	5	4	3		4	2	5	-	1	
Total	57												

x^2: Chi-squard test statistic, W: Woman, M: Male, R: Right, L: Left, B/N: Brachial neuropathy, Br-Sq: Brown-sequard, CDP: Cervical disc prosthesis, CC: Cervical cage, n: Number

Table 2. Intervertebral disc levels and disc nature characteristics of operated patients

Operation	Disc levels					Disc nature			
	C3/4	C4/5	C5/6	C6/7		Hard	Soft	n	
CDP	1	3	19	7	x^2=5.684 p=0.771	6	24	30	x^2=46.981 p<0.001
CC	1	1	4	4		8	-	10	
CDP+CC	- 2	1 -	4 -	3 -		5 5	- -	5 -	
CC+CC	2 -	3 -	10 -	9 -		24	- -	12 -	
Total	6	8	37	23		49	24	-	
								57	

x^2: Chi-squard test statistic, CDP: Cervical disc prosthesis, CC: Cervical cage, SDP: n: Number

Table 3. Preoperative cervical MRI results and postoperative CSA averages

Operation	Cervical MRI								Postop CSA	
	n	Midline				Lateral				
		Protruded	Extrusion	Osteophyte		Protruded	Extrusion	Osteophyte		
CDP	30	6	7	-	x^2=17.918 p=0.006	10	7	-	4.28	x^2=14.898 p=0.021
CC	10	2	2	3		2		1	5.84	
CDP+CC	5	2	1	1		2	2	2	4.66	
CC+CC	12	14	-	2		4	-	4	7.22	
	57									

x^2: Chi-squard test statistic, CDP: Cervical disc prosthesis, CC: Cervical cage, MRI: Magnetic resonance imaging, CSA: Cervical spinal alignment, n: Number operated because of cage displacement (CD). When all groups are compared according to operation times, operation results, and complications, there is no statistically significant difference between the groups (p=0.074) (Table 4).

DISCUSSION

Cervical intervertebral disc herniations occur when part of the nucleus pulposus or annulus fibrosus occupies space within the spinal canal. Disc degeneration can lead to symptoms such as osteophyte formation, disc narrowing, subluxation, instability of one cervical vertebra relative to another, or disc protrusion, i.e., pathological changes. Symptoms such as neck pain, radicular, motor, and sensory disorders, and signs of cord compression may occur, whereas MRI shows signs of radicular and cord compression. C3-4, C4-5, and often C5-6, C6-7 levels are affected[3,10].

In surgical treatment, discectomy without fusion with the anterior approach or cervical discectomy with fusion (mACDF), in which different bone grafts and devices are used to obtain good bone fusion, and PCF with the posterior approach are the preferred surgical techniques[1,2,10]. Anterior contralateral microdiscectomy without fusion is a minimally invasive technique that can be recommended in foraminal or lateral disc lesions, ventral osteophytes, and instability of the affected disc space[11]. Although titanium cages, carbon fiber-reinforced polymer cages, polyetheretherketone, and polymethylmethacrylate cages are frequently used in mASDF surgery to provide mechanical support to the spine, preserve disc height, and restore sagittal lordosis, negative results have also been reported in some studies[1]. In recent years, microsurgical cervical surgery with anterior intervention has been reported. CDP surgeries were preferred over mACDF, and good results were obtained[4].

It has also been reported that there is an increase in the number of hybrid surgeries in which mACDF and CDP are used together in patients with multilevel cervical degenerative disc disease[12,13]. Such hybrid surgeries are performed because the degree of degeneration at each level is different and fusion or arthroplasty is applied equally to all levels. It is recommended in cases where application is difficult. Such hybrid surgeries limit the hypermobility of adjacent segments while preserving the segmental motion of each segment. In patients with multilevel cervical degenerative disc disease, several studies have reported better outcomes with combined mACDF and CDP than with mACDF or CDP alone. In addition, postoperative evaluation has shown that the complication rate and functional score are excellent or similar, the arthroplasty level is above the fusion level, or there is no significant difference in the pressure applied to the adjacent disc[13].

Although successful clinical outcomes can be achieved with mACDF, postoperative complications such as pseudoarthrosis, instrumentation failure, and adjacent segment degeneration (ASD) have been the biggest concerns[4,14,15,16]. However, pseudoarthrosis is not observed in CDP, new problems such as heterotopic ossification and bone loss occur, and it has proven to be cost-effective compared with long-term follow-up[4,17,18]. In CDP, selecting the appropriate patient group is important to achieve a good prognosis. In addition, the postoperative prognosis of patients with one-or two-segment radiculopathy or myelopathy caused by soft disc herniation is excellent[16].

There are many studies in the literature comparing long-term results after CDP and mACDF. In these studies, no significant difference was found in the results of CDP and mACDF when comparing patients followed for short periods of up to 2 years. However, in the 4-7-year patient follow-up results, CDP results were superior to mACDF in outcomes such as neck disability index, 36-item short health form survey results, and dysphagia, and the incidence of postoperative ASD was found to be lower in the CDP group than in the mACDF group[19,20,21] Hilibrand and Robbins[14] It has been reported that 2.9% of patients undergoing anterior interbody fusion will most likely develop ASD requiring cervical intervention[14]. Again, in studies comparing mACDF and PCF, although there is no difference in clinical outcomes, complication, and reoperation rates, PCF has a lower rate. Cervical alignment, which is costly, is better and does not increase the risk of adjacent segment disease (ASD) [22]. Although ASD was not encountered in our four-group case series, long-term follow-up over 2 years could not be performed because of the distribution of the cases to different centers and the patients' non-compliance with the long-term follow-up protocol.

Table 4. Operation times, outcomes and complications of the cases

			Operation outcome								
			VAS		Odom's				Complication		
Operation	n	Operation time (mean)	Pre	post	E	G	F	P	TDf	CD	
CDP	30	115.50	7.0	0.03	29	1	-	-	1	-	x^2=23.460 p=0.074
CC	10	122.78	6.2	0.7	6	3	1	-	-	1	
CDP+CC	5	141.60	7.4	0.2	5	-	-	-	-	-	
CC +CC	12	132.83	6.9	1.0	7	2	2	1	1	-	

Odom's criteria: excellent (E), good (G), fair (F), poor (P), x^2: Chi-squard test statistic, CDP: Cervical disc prosthesis, CC: Cervical cage, VAS: Visual analogue scale, TDf: Temporary dysphagia, CD: Cage displacement, CDP: Cervical disc prosthesis, n: Number

Long-term prognosis results are important in the fusion of the operated segment after mACDF surgery. The surgeon should also consider the instruments and techniques used in surgery and patient factors. Diabetes, smoking, body mass index, vitamin D deficiency, and cortisone use are factors that negatively affect surgical results[1]. To achieve bone fusion in mACDF surgeries, products such as autologous spongy bone and demineralized bone matrix combined with bone substitute tricalciumphosphate or bone morphogenic protein can be used; however, high fusion cannot be achieved with bone substitutes, and infection may develop[5].

In recent years, different cages have been discussed to achieve osteosynthesis[2,5]. Better fusion was achieved using self-locking cages. Different types of anchors and screws (passing through the cage and settling on adjacent vertebrae) were designed for the cages. In our cases, cages with anchors were mostly used, and in fewer cases, cages with screws were used. Only in 1 case in hybrid surgery in the IV group, a decrease in the height of the vertebral body due to the displacement of the screw cage, pseudoarthrosis and CD, and spinal cord compression findings were detected, and the patient was re-admitted for surgery. In this case, dysphagia, vocal cord paresis, and right upper extremity paresis were detected in the early postoperative period after reoperation, and the vocal cord paresis resolved within 45 days.

CDP is preferred because it facilitates vertebral movement at the operation level and is less likely to cause ASD[4]. With CDP, patients can return to work early and the neck can maintain its natural range of motion. In recent years, disc prostheses made of titanium, chrome cobalt, ceramics, and hard silicone have been introduced[4].

During CDP surgery, which is similar to mACDF surgery, discectomy is performed using an anterior approach. After foraminal decompression, an appropriate disc prosthesis is placed between the intervertebral level. However, some results may be encountered after CDP, such as pseudoarthrosis, ASD, and height loss at the intervertebral level[17,23]. Nevertheless, there have been no long-term consequences related to CDP and cage use in our cases.

Anterior bone loss (ABL) is a potential complication that occurs mid-term at the 5-year follow-up and has been reported in >50% of cases. It can cause disability, increased pain, and loss of the anterior part of the implant, among other issues. The cause of ABL is unknown, but it may be related to infection, debris accumulation, micromotion, and stress protection[23].

In our hybrid case, there was a displacement of the CD and ABL within the first 3 weeks. It is unclear whether the subchondral collapse and ABL in the upper and lower vertebrae of our patient were caused by the surgical technique or the screw cage used. In the relevant retrospective evaluation, it was believed that the bone cancellous structure of the case developed because of the screw cage compression applied at a softer and double distance.

In the last two decades, many randomized controlled trials have been conducted on SDP. The results indicate that CDP helps reduce ASD. It also prevents complications such as pseudoarthrosis and ABL. Moreover, it helps in achieving a more appropriate movement of the spine[2,4].

CONCLUSION

Microdiscectomy with an anterior approach is the preferred surgical method for the treatment of cervical disc disease. Advances in minimally invasive techniques, imaging, microsurgery, and endoscopy techniques have led to the development of current surgical approaches. In the 2-year follow-up of our cases, it was determined that the results were excellent in the CDP patient groups after microdiscectomy. Therefore, in mACDF and CDP surgery, preoperative clinical and radiological evaluation, surgical team skill, instrument characteristics, and early and late postoperative follow-ups are the main factors affecting prognosis.

Ethics

Ethics Committee Approval: This study was approved by the Başkent University Medicine and Health Sciences Research Board (approval number: KA23/267, date: 22.08.2023) and supported by the Başkent University Research Fund.

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: F.A., B.L., G.Ö.S., Y.Ö.P., Concept: F.A., Design: F.A., Data Collection or Processing: F.A., B.L., G.Ö.S., Analysis or Interpretation: F.A., B.L., G.Ö.S., Literature Search: F.A., B.L., G.Ö.S., Y.Ö.P., Writing: F.A., Y.Ö.P.,

Conflict of Interest: The authors have no conflicts of interest to declare.

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CLINICAL OUTCOMES OF EN-BLOC CERVICAL LAMINOPLASTY FOR CERVICAL SPONDYLOTIC MYELOPATHY

Mehmet Meral[1], Rahmi Kemal Koç[2]

[1]*Private Erciyes Hospital, Clinic of Neurosurgery, Kayseri, Turkey*
[2]*Erciyes University Faculty of Medicine, Department of Neurosurgery, Kayseri, Turkey*

ABSTRACT

Objective: To evaluate the clinical outcomes of patients with cervical spondylotic myelopathy (CSM) operated using the en-bloc laminoplasty technique and the effects of surgical timing on clinical outcomes.

Materials and Methods: This study analyzed the preoperative and postoperative outcomes of 32 patients who underwent en-bloc cervical laminoplasty for CSM. The effect of preoperative symptom duration on postoperative clinical outcomes and the clinical outcomes of en-bloc cervical laminoplasty were evaluated. The modified Japanese Orthopedic Association (mJOA) score and Nurick scale were used for preoperative and postoperative functional and neurological evaluation.

Results: The mean age of the patients was 66.3 years. Twenty-one patients were male (65.6%) and 11 were female (34.4%), and the mean follow-up period was 34.7 months. Seven of eight patients with mJOA scores of 15 and above had complete recovery and one had partial benefit. Of the 10 patients with mJOA scores between 12 and 15, 7 improved above 15 points and 3 showed partial improvement. Of the 14 patients with a score below 12, 10 had improved to the 12-15 range, whereas 3 had remained unchanged. Deterioration was observed in one patient.

Conclusion: Low mJOA scores, high Nurick grade, and long preoperative symptom duration negatively affected surgical treatment results.

Keywords: Cervical laminoplasty, cervical spondylotic myelopathy, cervical spinal stenosis, en-bloc cervical laminoplasty, myelopathy

INTRODUCTION

Cervical spondylotic myelopathy (CSM) was described by Stookeyin 1928. It is one of the most serious complications of cervical spondylosis[1]. These presentations may occur because of cervical disc degeneration, nerve root compression, and cervical spinal cord compression (myeloapathy). One, two, or all of these presentations may be observed together in patients[2]. Characteristic symptoms include gait and balance disturbance, ataxia, decreased manual dexterity, dysesthesia, and difficulty in writing. It is the most common cause of spinal cord dysfunction in the adult population[3]. In the cervical region, the canal diameter between C3 and C7 is 17-18 mm and the cervical cord diameter between C1 and C7 is 10 mm. CSM findings develop when the sagittal diameter is 12 mm or less[1]. The disease usually progresses with symptoms and signs related to spinal cord compression. Atrophy and weakness in small muscles of the hands are common in the late stage. In the lower extremities, spastic gait, hyperreflexia, and Babinski symptoms are typical[4,5].

The main factors considered for treating CSM are the time of onset of clinical symptoms, the rate of progression, and the degree of neurologic damage. The aim of surgery is to correct neurological damage and stop the progression of the disease[6-8]. Various surgical methods have been used to date, such as laminectomy and corpectomy. Alternatively, to reduce the complications of laminectomy and corpectomy, Hirabayashi et al.[9] described the open-door laminoplasty method in 1977 to widen the narrowed cervical canal. Later, different laminoplasty techniques were developed. The most commonly used method today is hardware-augmented Hirabayashi's open-door laminoplasty[10]. En-bloc C3-7 laminoplasty was described by Itoh and Tsuji[11]. It was adopted by Hosono et al.[12]. Tumturk et al.[8] popularized C3-6 en-bloc laminoplasty to prevent axial neck pain and loss of lordosis by preserving the posterior ligamentous structure such as interspinous and supraspinous ligaments. They also recommend preservation of the nuchal ligament attached to the C7 spinous process. If C6-7 levels are affected, they recommend C7 arcocristectomy[8]. There is controversy regarding the various techniques that provide the best clinical outcome with the fewest complications[13].

In this study, we evaluated the results of en-bloc C3-6 laminoplasty to prevent axial neck pain and loss of lordosis by preserving the posterior ligamentous structure.

Address for Correspondence: Rahmi Kemal Koç, Erciyes University Faculty of Medicine, Department of Neurosurgery, Kayseri, Turkey
Phone: +90 352 222 41 42 **E-mail:** kocrk@erciyes.edu.tr **Received:** 05.01.2024 **Accepted:** 17.03.2024
ORCID ID: orcid.org/0000-0001-9928-0468

MATERIALS AND METHODS

This study was retrospective. In this study, we analyzed the preoperative and postoperative results of 32 patients who underwent en-bloc cervical laminoplasty for CSM in our clinic between 2008 and 2022. The preoperative symptom duration was divided into three categories. Those who underwent surgery in the first 6 months, 6-18 months and after 18 months. The modified Japanese Orthopedic Association (mJOA) score[14] and Nurick scale[15] were used for functional and neurological evaluation. In the mJOA score, upper extremity, lower extremity, and trunk motor dysfunction, sensory loss, and sphincter dysfunction are evaluated in separate categories, and the full score is 18[16]. Patients were divided into three groups according to their mJOA scores. Fifteen and above, between 12-14, and below 12. The postoperative recovery rate was calculated using the Hirabayashi et al.[9] method. Recovery rate (%)=(postoperative JOA-preoperative JOA)/(18-preoperative JOA)×100[4]. In the Nurick scale, each patient was assigned one of six grades of disability (0-5), based on the degree of difficulty in walking recorded at the time of admission. All patients in our series underwent surgery using the hardware-augmented en-bloc laminoplasty technique[8,17]. One side of the lamina is cut using a high-speed drill. On the other hand, only the outer cortex is cut and the inner cortex of the inner lamina is left untouched. The lamina is then lifted using small angled currents. The ligamentum flavum, interspinous, and supraspinous ligaments are preserved. The lifted lamina was then fixed with mini plates (Figure 1). This study was approved by the institutional ethics committee of Erciyes University Clinical Research Ethics Committee (approval number: 2023/298, date: 26.04.2023).

Statistical Analysis

The data were recorded using SPSS 22 software and analyzed using the same program. Frequency, percentage, mean value, standard deviation, and highest and lowest (min.-max.) values were used for descriptive statistics. For statistical analysis of categorical data, Fisher's exact test was applied because there were fewer than five values. The Shapiro-Wilk test was used to check the suitability of the data for normal distribution. The One-Way Analysis of Variance test was used for statistical analysis of quantitative data in independent groups. Spearman's correlation coefficient was used to show the relationship between the variables. The statistical significance of the difference was set as $p<0.05$.

RESULTS

The mean age of the patients was 66.3±8.5 (min.-max.: 52-88) years. Twenty-one patients were male (65.6%) and 11 patients were female (34.4%), and the mean follow-up period was 34.7±8.8 (min.-max.: 18-52) months. Three patients had single levels, six had two levels, 10 had three levels, and 13 had four levels of spinal stenosis.

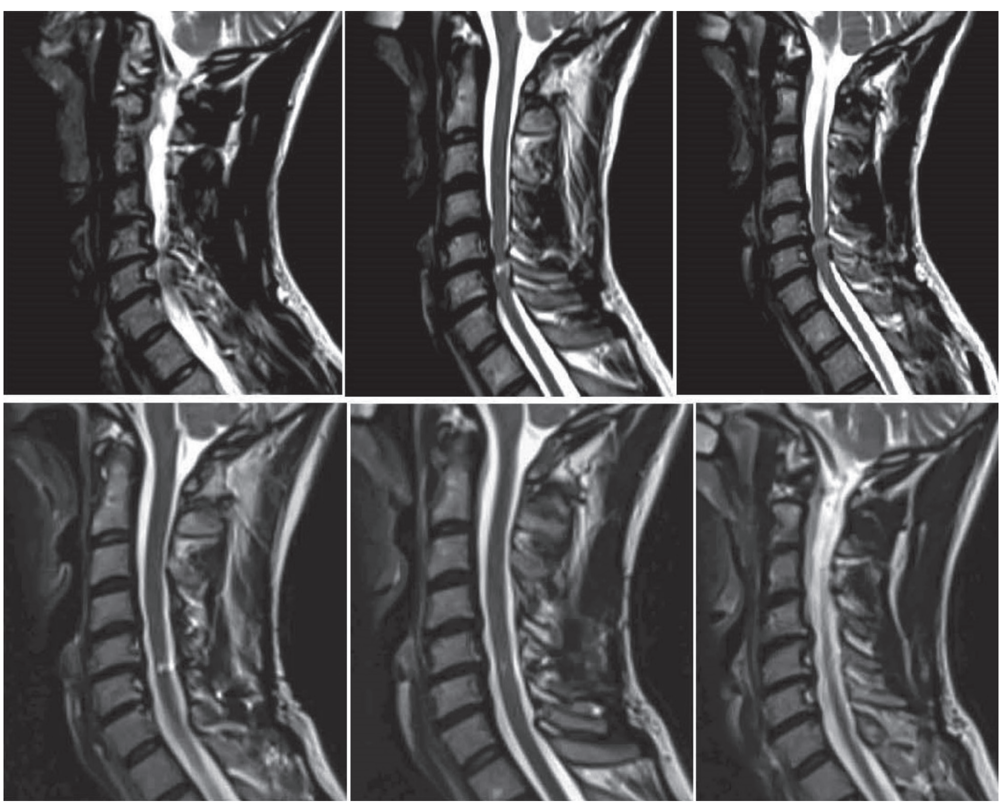

Figure 1. MR images before and after surgery (en-bloc laminoplasty technique) for cervical spondylotic myelopathy
MR: Magnetic resonance

Half of the patients were in the group with symptom duration of 6-18 months. The frequency of symptom durations and recovery rates are presented in Table 1. Although there was no significant correlation between symptom duration and complete recovery (p>0.05), complete recovery rates were higher in patients with symptoms lasting 6 months (Table 1).

The mJOA scores of patients with a symptom duration of 6 months were significantly higher, whereas the mJOA scores of patients with increasing symptom duration also decreased (Table 2).

Seven of 8 patients with mJOA scores of 15 had complete recovery and 1 had partial recovery. Of the 10 patients with mJOA scores between 12 and 15, 7 showed improvement above 15 points and 3 showed partial improvement. Of the 14 patients with a score below 12, 10 improved to the 12-15 range, whereas 3 had no change. Worsening was observed in one patient. Recovery rates according to the mJOA score are given in Table 3. Although there was no significant difference between the groups in terms of recovery rates, recovery rates were higher in the group with an mJOA score of 15 and above. It was observed that the worse the preoperative mJOA value of the patients, the lower the success rate of the operation (Table 3).

The Nurick scores of the patients are given in Table 4. Complete recovery rates were significantly higher in patients with Nurick grades 0, 1, and 2 (p<0.05). Complete recovery was not observed in patients with grades 3 and 4 (Table 4). Nurick grades were also correlated with the mJOA scale at postoperative neurologic follow-up compared with preoperative results.

In our series, axial/radicular pain was relieved in 91% of patients, decreased in 6%, and unchanged in 3%. Sensory deficits were relieved in 35%, decreased in 45%, and unchanged in 20%. Improvement in the complaints of patients with sensory loss started after the 6th month, and sensory loss was permanent in three patients. The motor losses of patients improved good in 18%, fair in 54%, unchanged in 22%, and worsened in 6% after surgery.

The number of operated levels had no effect on functional follow-ups for the mJOA scale and Nurick grade. No complications occurred requiring reoperation, such as cerebrospinal fluid leakage, wound infection, bleeding, or plate-screw malposition, during follow-up.

Table 1. Duration of symptoms and complete recovery rates

Symptom durations	Patients n	Patients %	Full recovery n	Full recovery %	p-value
<6 months	7	21.9	6	85.7	
6-18 months	16	50.0	12	75.0	0.765
>18 months	9	28.1	6	66.7	

Fisher's exact test, n: Patient count

Table 2. Symptom duration and mJOA scores

mJOA scores	Symptom durations <6 months n	%*	6-18 months n	%*	>18 months n	%*	p-value
>15	7	100.0	0	0.0	0	0.0	
12-14	1	6.3	10	62.5	5	31.3	<0.001
<12	0	0.0	0	0.0	9	100.0	

Fisher's exact test, *: Row percentage, mJOA: Modified Japanese Orthopedic Association, n: Patient count

Table 3. mJOA score and recovery rates

mJOA scores	Patients n	Patients %*	Full recovery n	Full recovery %**	p-value
>15	8	25.0	7	87.5	
12-14	10	31.3	7	70.0	0.764
<12	14	43.8	10	71.4	

Fisher's exact test, *: Column percentage, **: Row percentage, mJOA: Modified Japanese Orthopedic Association, n: Patient count

DISCUSSION

When planning treatment for CSM, the severity of neurologic involvement, the rate of disease progression, and the duration of symptoms are essential in deciding the treatment method; however, it is difficult to determine the treatment strategy[7]. Impairment in neurological functions may vary from mild to severe. The mJOA score[15] and Nurick grade[16] are most commonly used in neurologic functional assessment. Patients with an mJOA score above 15 points are considered mildly affected. They have impaired fine motor movements due to loss and dysfunction of intrinsic muscles in the hands and complaints of numbness and clumsiness due to accompanying sensory loss. Patients with mJOA scores of 12-15 are considered moderately affected and have a wide-based gait or loss of balance due to rigidity. Findings such as hyperreflexia, clonus, positive Babinski sign, and positive Romberg test are usually present. Patients who are considered severely disabled (mJOA score below 12) have a severe need for assistance and loss of urinary control in addition to the previously mentioned findings[18]. In the presence of CSM in the narrow canal, the functional neurological picture at presentation may also vary according to the etiology. Again, most patients without pathologic signal change on magnetic resonance imaging are in the mild myelopathic group[18]. Late findings of atrophy and fasciculations in the distal upper extremity and sphincter dysfunction are signs of poor recovery prognosis[19]. It has been observed that 18% of patients with CSM recover spontaneously, 40% are stable, and 40% may worsen without treatment. Intensive conservative treatment has also been reported to give successful results[20]. Cervical traction, cervical immobilization, and other physical therapy agents can be used in conservative treatment, but studies on these agents are insufficient[21]. A short symptom duration increases the success of surgical treatment. It has been reported that surgery performed within the first 18 months from the onset of symptoms gives more successful results[22].

Table 4. Nurick grades and recovery rates of patients

	Patients		Recovery				mJOA scores	
			Full recovery		No complete recovery			
Nurick grades	n	%*	n	%**	n	%**	Mean	SD
Grade 0	11	34.4	9	81.8	2	18.2	14.5	1.9
Grade 1	12	37.5	10	83.3	2	16.7	12.2	1.7
Grade 2	5	15.6	5	100.0	0	0.0	10.4	0.5
Grade 3	3	9.4	0	0.0	3	100.0	9.3	0.6
Grade 4	1	3.1	0	0.0	1	100.0	8	-
p-value			0.009[a]				<0.001[b]	

*: Column percentage, **: Row percentage, [a]: Fisher's exact test, [b]: One-Way Analysis of Variance, SD: Standard deviation, n: Patient count

Surgical treatment should be preferred in patients with a moderate or severe involvement (mJOA) score of 10 or less[16]. Arnasson et al.[23] reported a 69% improvement with posterior surgical intervention in their study and that the results were not related to the patient's age and symptom duration. The main aim of surgical treatment is to stop the progression of deterioration in neurological functions and correct neurological loss[6,8]. The goals of surgical treatment of CSM include decompression of the spinal cord, prevention of cervical instability, and restoration of cervical lordotic alignment[24,25]. Various surgical approaches have been developed to treat CSM. However, there is controversy regarding which surgery provides the best clinical results with the least complications. Factors such as the site of compression, length of the compression level, canal compression ratio, age of the patient, cervical alignment (lordotic, kyphotic, or straight), bone quality, and presence of instability should be considered when choosing the appropriate approach in surgically planned cases[12]. The surgical approach can be performed as an anterior approach, posterior approach, or combined anterior and posterior approach[16].

The use of laminoplasty in cervical myelopathy was first described by Krita in 1968[26]. Cervical laminoplasty was developed in Japan in the 1970s and became popular after the 1980s. There are different laminoplasty techniques. One important consideration is to preserve the structure of the nuchal ligaments attaching to the C7 spinous processes to prevent neck pain. Preservation of the attachment site of the erector spinae muscles to C2 is important for preventing kyphotic deformity[18,27,28]. It has also been reported that the exclusion of C7 in laminoplasty has a positive effect on axial pain in the postoperative period[8]. Tumturk et al.[8] suggested that en-bloc cervical laminoplasty while preserving posterior structures such as interspinous and supraspinous ligaments is useful in preventing postoperative spinal malalignment and axial pain. Arcocristectomy is an effective technique for preventing postoperative axial pain in patients with C6-7 spinal stenosis. Therefore, the en-bloc laminoplasty technique was used in our study.

Arnasson et al.[23] reported a 69% improvement with posterior surgical intervention in these cases and stated that the results were not related to the patient's age or symptom duration. Wang et al.[22] suggested that the patient's age over 50 years was not effective in recovery. The researchers reported that surgery performed within the first 18 months from the onset of symptoms gave more successful results, and the recovery rate was 35% with conservative treatment and 43% with surgical treatment[22]. In our series, as the preoperative symptom duration of the patients was prolonged, the success rate in treatment decreased. The best recovery rate was found in patients operated on within the first 6 months (recovery rate 91%), and the worst recovery rate was found in patients with a symptom duration longer than 18 months (69%). Again in this study, the worse the mJOA score, the lower the postoperative success rate (mJOA 15 and above-91.8%, mJOA 12 to 15-82.5%, mJOA below 12 and lower 73.0%). Evaluation according to Nurick's test was also correlated with mJOA. In our series, a patient with an mJOA score of 8 had worsening neurological status after surgery. We believe that a preoperative symptom duration of approximately 2 years and an mJOA score of 8 were effective in this worsening.

CONCLUSION

In our study, low mJOA scores, high Nurick grades, and long preoperative symptom duration were found to negatively affect the results of en-bloc cervical laminoplasty for CSM. We believe that this situation should be considered when planning the treatment. We believe that further studies in larger series will be useful in this regard.

Ethics

Ethics Committee Approval: This study was approved by the institutional ethics committee of Erciyes University Clinical Research Ethics Committee (approval number: 2023/298, date: 26.04.2023).

Informed Consent: This study was retrospective.

Authorship Contributions

Surgical and Medical Practices: M.M., R.K.K., Concept: M.M., R.K.K., Design: M.M., Data Collection or Processing: M.M., Analysis or Interpretation: M.M., R.K.K., Literature Search: M.M., Writing: M.M.

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RELATIONSHIP OF LUMBAR SPINAL ANATOMICAL STRUCTURES WITH LUMBAR DISC HERNIA AND SPINAL STENOSIS

Halil Can Küçükyıldız[1], Fatih Koç[2], Eren Kıymaz[2], Ünal Özüm[2]

[1]*Atılım University Faculty of Medicine, Medicana International Ankara Hospital, Clinic of Neurosurgery, Ankara, Turkey*
[2]*Sivas Cumhuriyet University Faculty of Medicine, Department of Neurosurgery, Sivas, Turkey*

ABSTRACT

Objective: We aimed to radiologically evaluate the clinical and demographic features accompanying ligamentum flavum hypertrophy and possible accompanying differences in anatomical structures.

Materials and Methods: We evaluated vertebral alignment, integrity of neural structures, diameter of the central canal, posterior longitudinal ligament, ligamentum flavum integrity, and position of the facet joints in patients with lumbar disk herniation and lumbar spinal canal stenosis using magnetic resonance imaging (MRI). Furthermore, we examined the age, body mass index (BMI), and employment status of the patients and the status of the vertebral and paravertebral anatomical structures using MRI. Age, BMI, employment status, ligamentum flavum thickness at the L4–L5 level, interspinous ligament thickness, facet joint diameter, posterior longitudinal ligament integrity, psoas muscle diameter, erector spina muscle diameter, and mean multifidus muscle diameter were also analyzed.

Results: Significant differences were found in age, BMI, employment status, ligamentum flavum thickness, interspinous ligament thickness, mean facet diameter, mean multifidus muscle diameter, mean erector spina muscle diameter, and mean psoas muscle diameter. In addition, separate statistical analyses were conducted between sex, age, employment status, BMI, and lumbar anatomical parameters. Significant correlations were found between lumbar disk herniation and spinal stenosis pathologies based on radiological measurements of lumbar structures, such as the ligamentum flavum, interspinous ligament, and facet diameter, and demographic parameters, such as age, sex, employment status, and BMI.

Conclusion: We examined changes in the anatomical structures accompanying the vertebral column and existing discal or stenotic pathologies. In addition to the demographic characteristics of the patients, changes in the accompanying lumbar spinal anatomical structures, such as degeneration, hypertrophy, and atrophy, may be important. These factors and changes will help plan the treatment process and guide the results.

Keywords: Facet hypertrophy, ligamentum flavum, lumbar disk hernia, lumbar spinal stenosis

INTRODUCTION

Lumbar disk herniation and lumbar canal stenosis are common pathologies in neurosurgery practice. The development of vertebral surgical interventions is important for the treatment of these diseases. Patients with these pathologies often complain of lower back pain, leg pain, paresis, and decreased mobility. In lumbar disk herniation, the clinical symptoms of hernia are caused by the compression of the nucleus pulposus on neural structures, whereas canal stenosis is generally caused by ligamentum flavum or facet hypertrophy[1-5].

Magnetic resonance imaging (MRI) is the most commonly used radiological method in the diagnosis and treatment planning of these diseases[6]. Vertebral alignment, integrity of the neural structures, spinal canal diameter, posterior longitudinal ligament integrity, and position of the facet joints are the major components of MRI evaluation[7]. Along with these assessments, we assumed that additional patient factors such as the patient's age, sex, body mass index (BMI), employment status, and MRI measurements like paravertebral muscle mass, paravertebral ligament thickness could guide the development of diagnostic treatment plans for these patients. Thus, in this study, we aimed to evaluate the effects and accompaniments of factors such as the patient's age, BMI, employment status, and vertebral–paravertebral anatomical conditions on the development of pathologies in patients with lumbar disk herniation and lumbar spinal stenosis.

MATERIALS AND METHODS

We started this study with the assumption of the presence of vertebral-paravertebral pathologies accompanying and causing lumbar disc herniation and lumbar canal stenosis

Address for Correspondence: Halil Can Küçükyıldız, Atılım University Faculty of Medicine, Medicana International Ankara Hospital, Clinic of Neurosurgery, Ankara, Turkey
Phone: +90 533 204 89 40 **E-mail:** drhalilcan@gmail.com **Received:** 23.03.2024 **Accepted:** 22.04.2024
ORCID ID: orcid.org/0000-0003-0922-1750

in retrospective design. This study analyzed data from 215 patients who underwent surgery in our clinic for lumbar disk herniation and spinal stenosis (study group) and 69 patients who applied to our outpatient clinic for lower back pain where no pathology was found on lumbar MRI (control group). The age, sex, BMI, and employment status of the study and control groups were evaluated.

As occupational groups can be divided into various subcategories; in the present study, employment status was divided into three categories: not working in any job (non-worker), working in a job (worker), and working in heavy jobs (heavy worker). People who work in jobs that create a heavy workload or that cause a lot of physical stress were considered heavy workers. As there is a one-to-one correlation between the level being operated on and hypertrophy, only descriptive results were presented. Interspinous ligament thickness, ligamentum flavum thickness, facet joint diameter, erector spinae muscle group volume, psoas muscle group volume, and multifidus muscle group volumes were measured on preoperative lumbar MRI, in sections passing through the pathological segments of the study group and L4-L5 level of the control group (Figure 1). MRI scans were acquired using the Siemens Aera 1.5 Tesla MRI scanner (Siemens, Erlangen, Germany). All measurements were performed using the Sectra IDS7 Workstation (Linköping, Sweden). This study was conducted in accordance with the Declaration of Helsinki and was approved by the Sivas Cumhuriyet University Human Research Ethics Committee (approval number: 2021-01/06).

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, US). To investigate whether variables had a normal distribution and that variance homogeneity assumptions were met, Kolmogorov-Smirnov and Levene tests were used, respectively. Categorical data were expressed as numbers (n) and percentage (%), whereas quantitative data were given as mean ± standard deviation and median (25^{th}-75^{th}) percentiles. The mean differences between groups were compared using Student's t-test, while the Mann-Whitney U test was applied to compare variables without normal distribution. Since there were more than two independent groups, quantitative data were evaluated using a One-Way analysis of variance (ANOVA) or the Kruskal-Wallis test, where appropriate. When the One-Way ANOVA or Kruskal-Wallis test

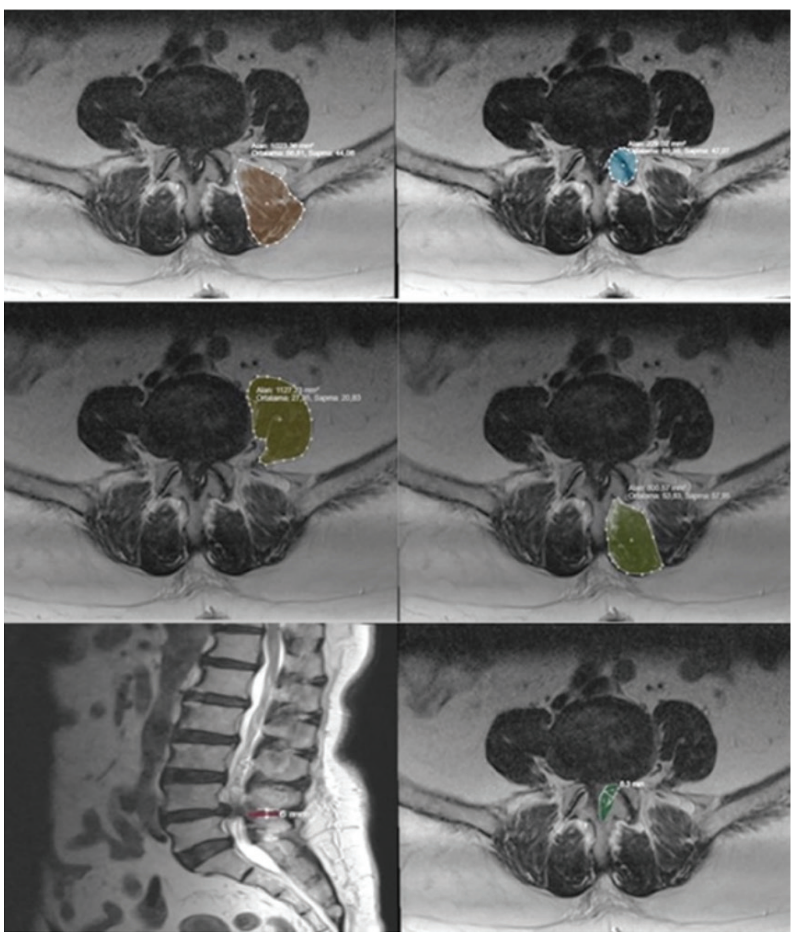

Figure 1. Measurement of interspinous ligament and ligamentum flavum thickness, facet joint, multifidus, erector spinae and psoas muscle areas in sagittal and axial lumbar MRI sections

MRI: Magnetic resonance imaging

indicated significance, post-hoc Tukey honestly significant difference test or Dunn-Bonferroni multiple comparison tests were used to find which group differed from the others. Categorical data were analyzed using Pearson's $\chi 2$ test. The degrees of association between continuous variables were evaluated using Spearman's rank-order correlation analyses. Whether being operable and the presence of hypertrophy had a significant effect on clinical measurements were investigated using quantile regression analyses after adjustment for age, sex, BMI, and employment status. The coefficient of regression, 95% confidence intervals, and t-statistics for each independent variable were also calculated. Quantile regression analyses were performed using STATA 16.1 (Stata Corp., TX, USA). A p-value <0.05 was considered significant.

RESULTS

Descriptive statistics regarding the demographic and clinical characteristics of the patients are shown in Table 1. Comparisons of the demographic and clinical characteristics of the cases according to the operated and non-operated groups are given in Table 2. Both the mean age and BMI were significantly higher in the operated group than in the non-operated group (p<0.001 and p=0.004). No significant difference was found between the groups for male-female distribution and employment status (p=0.223 and p=0.649, respectively). Interspinous ligament thickness, mean facet diameter, mean multifidus muscle diameter, mean erector spinae diameter, and mean psoas muscle diameters were significantly higher in the operated group than in the non-operated group (p<0.05).

Table 1. Demographic and clinical features

	n=284
Age (year)	47.1±14.6
Age range (year)	16-90
Sex	
Male	125 (44.0%)
Female	159 (56.0%)
Employment status	
Non-worker	172 (60.6%)
Worker	68 (23.9%)
Heavy worker	44 (15.5%)
BMI (kg/m^2)	28.9±4.7
Pathology	
Normal	69 (24.3%)
L4-L5 disk herniation	92 (32.4%)
L5-S1 disk herniation	60 (21.1%)
L3-L4 stenosis	19 (6.7%)
L4-L5 stenosis	44 (15.5%)
Interspinous ligament thickness	6.02 (5.01-7.77)
Facet joint diameter	250.4 (193.3-307.3)
Multifidus muscle diameter	816.7 (710.2-983.1)
Erector spinae muscle diameter	1047.7 (920.6-1232.0)
Psoas muscle group diameter	1069.4 (879.0-1481.1)
Ligamentum flavum thickness	5.40 (3.66-6.30)
Operated group	215 (75.7%)
Ligamentum flavum hypertrophy (+)	150 (52.8%)

BMI: Body mass index

Table 3 shows the comparisons of the demographic and clinical characteristics of the cases in the non-operated group with and without lumbar ligamentum flavum hypertrophy. A significant difference was found in the mean age between the groups: control group, non-operated group with ligamentum flavum hypertrophy, and operated group with ligamentum flavum hypertrophy (p<0.001). No significant difference in sex was found between the groups (p=0.026). Moreover, a significant difference was found in the BMI averages of the control group, non-operated group with ligamentum flavum hypertrophy, and operated group with ligamentum flavum hypertrophy (p<0.001). In addition, a significant difference in occupational status was found between the groups, and the unemployment rate in the operated group without hypertrophy was lower than those in the other two groups (p<0.05). The interspinous ligament thickness was higher in the hypertrophy group than in the non-operated group (p=0.021). A significant difference in the mean facet diameters was found between the groups (p<0.001). No significant difference in the mean psoas muscle volumes was noted between the groups (p=0.129).

Table 4 shows the correlation coefficients and significance levels between the age and BMIs of all cases and clinical measurements. Regarding age, a significant inverse correlation was found between the levels of interspinous ligament thickness and psoas muscle diameter, and the same significant correlation was observed between the mean facet diameter and mean multifidus muscle diameter (p<0.05). While a significant inverse correlation was found between BMI and psoas muscle diameters in all cases (r=-0.151 and p=0.011), a significant correlation was found in the mean facet joint diameter, mean multifidus muscle diameter, and mean erector spinae muscle diameter (p<0.001).

Table 5 shows the comparisons of clinical measurements according to sex and employment status. Compared with men, women had significantly lower mean facet diameters, mean multifidus muscle volume, and mean psoas muscle volume (p<0.01). The mean psoas levels were higher in workers and heavy workers than in non-workers (p<0.001).

Table 6 shows the correlation coefficients and significance levels between clinical measurements. Regarding interspinous ligament thickness, a significant and the same directional correlation was observed between the mean facet joint diameter, mean psoas muscle diameter, and mean erector spinae muscle diameter (p<0.05). With the mean facet joint diameters, a significant and the same directional correlation were found between the mean multifidus muscle diameter, mean psoas muscle diameter, and mean erector spinae muscle diameter

Table 2. Demographic and clinical characteristics of the operated and non-operated groups

	Non-operated (n=69)	Operated (n=215)	p-value
Age (year)	37.9±12.1	50.1±14.1	<0.001†
Sex			0.223‡
Male	26 (37.7%)	99 (46.0%)	
Female	43 (62.3%)	116 (54.0%)	
Employment status			0.649‡
Non-worker	41 (59.4%)	131 (60.9%)	
Worker	15 (21.7%)	53 (24.7%)	
Heavy worker	13 (18.8%)	31 (14.4%)	
BMI (kg/m²)	27.5±4.3	29.3±4.7	0.004†
Pathology			N/A
Normal	69 (100.0%)	-	
L4–L5 disk herniation	-	92 (42.8%)	
L5–S1 disk herniation	-	60 (27.9%)	
L3–L4 stenosis	-	19 (8.8%)	
L4–L5 stenosis	-	44 (20.5%)	
Interspinous ligament thickness	5.90 (5.00-6.75)	6.20 (5.05-8.10)	0.012¶
Facet joint diameter	186.1 (155.5-213.1)	273.3 (216.2-327.6)	<0.001¶
Multifidus muscle diameter	715.8 (660.5-823.0)	855.5 (737.9-1025.9)	<0.001¶
Erector spinae muscle diameter	976.5 (829.1-1111.3)	1081.5 (941.4-1262.0)	<0.001¶
Psoas muscle group diameter	1018.0 (816.3-1195.6)	1106.0 (884.2-1515.5)	0.043¶

†: Student's t test, ‡: Pearson's χ^2 test, ¶: Mann-Whitney U test, N/A: Not applicable, BMI: Body mass index

(p<0.001). For the mean multifidus muscle measurements, a significant and the same directional correlation were noted between the mean erector muscle and mean psoas muscle diameters (p<0.001). Finally, a significant and the same directional correlation were found between the mean erector spinae and mean psoas muscle diameters (p<0.001).

DISCUSSION

This study evaluated the clinical and demographic features accompanying ligamentum flavum hypertrophy and possible accompanying differences in anatomical structures radiologically.

The ligamentum flavum is located between the upper and lower vertebrae lamina, posterior of the dural sac, and provides protection and stability to the spinal column. In diseases such as lumbar disk herniation and lumbar spinal stenosis, ligamentum flavum hypertrophy can aggravate the clinical symptoms. Many studies on this subject have shown that age, high BMI, and heavy working conditions can cause ligamentum hypertrophy[8-10]. In the present study, the results obtained support literature data. In addition, changes in the facet joints, paravertebral muscle volume, and other ligamentous structures can be expected following changes in the ligamentum flavum. The results of some studies also support this finding[11,12].

In the present study, no significant difference was found between the groups in terms of male-female distribution. In the literature, no significant sex difference was found in this regard[13]. Moreover, this study focused on the detection of changes in lumbar spinal anatomical structures and accompanying degenerative pathologies. The interspinous ligament thickness, mean facet diameter, and mean multifidus, erector, and psoas volumes were significantly higher in the operated group than in the non-operated group.

Previous studies have reported the relationship between paraspinal muscles and fat volume around the paraspinal muscle and lumbar spinal degeneration[13-15]. These studies have reported that patients with ligamentum flavum hypertrophy also have atrophy of the paravertebral (especially multifidus) muscles and lubrication around the muscle. However, the direct relationship between lumbar spinal degenerative changes and BMI was not investigated in these studies. By contrast, in the present study, a significant correlation was found between high BMI, ligamentum flavum hypertrophy, and surgical indication due to lumbar spinal degenerative diseases.

Other studies have reported facet joint hypertrophy and osteoarthritis in the etiology of ligamentum flavum hypertrophy. The results of these studies agreed with our findings[15]. Factors that influence the development of ligamentum flavum hypertrophy include age, spinal level, mechanical stress, and growth factors. Histologically, increased ligamentum flavum thickness is associated with an increase in fibrosis and a decrease in elastic fibers[15]. Thus, as reported in the present study

Table 3. Demographic and clinical characteristics of the patients with and without lumbar ligamentum flavum hypertrophy

	Non-operated (n=69)	Hypertrophy (-) (n=65)	Hypertrophy (+) (n=150)	p-value
Age (year)	37.9±12.1[a]	42.6±12.2[b]	53.3±13.6[a,b]	<0.001[†]
Sex				0.026[‡]
Male	26 (37.7%)[c]	38 (58.5%)[b,c]	61 (40.7%)[b]	
Female	43 (62.3%)[c]	27 (41.5%)[b,c]	89 (59.3%)[b]	
Employment status				<0.001[‡]
Non-worker	41 (59.4%)[c]	25 (38.5%)[b,c]	106 (70.7%)[b]	
Worker	15 (21.7%)	22 (33.8%)	31 (20.7%)	
Heavy worker	13 (18.8%)	18 (27.7%)[b]	13 (8.7%)[b]	
BMI (kg/m^2)	27.5±4.3[a]	27.5±4.0[b]	30.1±4.8[a,b]	<0.001[†]
Pathology				N/A
Normal	69 (100.0%)	-	-	
L4−L5 disk herniation	-	39 (60.0%)	53 (35.3%)	
L5−S1 disk herniation	-	26 (40.0%)	34 (22.7%)	
L3−L4 stenosis	-	-	19 (12.7%)	
L4−L5 stenosis	-	-	44 (29.3%)	
Interspinous ligament thickness	5.90 (5.00-6.75)[a]	6.00 (5.15-7.35)	6.55 (5.00-8.25)[a]	0.025[¶]
Facet joint diameter	186.1 (155.5-213.1)[a]	204.6 (173.7-253.5)[b]	299.9 (255.0-342.3)[a,b]	<0.001[¶]
Multifidus muscle diameter	715.8 (660.5-823.0)[a]	737.9 (659.1-879.7)[b]	919.7 (794.7-1090.4)[a,b]	<0.001[¶]
Erector spinae muscle diameter	976.5 (829.1-1111.3)[a]	1000.0 (880.8-1122.8)[b]	1121.8 (982.5-1320.4[a,b]	<0.001[¶]
Psoas muscle group diameter	1018.0 (816.3-1195.6)	1186.6 (861.3-1522.5)	1086.3 (884.8-1516.8)	0.129[¶]

[a]: The difference between the non-operated group and the group with hypertrophy is significant (p<0.05), [b]: The difference between the group without hypertrophy and the group with hypertrophy is significant (p<0.05), [c]: The difference between the non-operated group and group without hypertrophy was significant (p<0.05), [†]: One-Way ANOVA, ‡: Pearson's χ^2 test, [¶]: Kruskal-Wallis test, N/A: Not applicablea, BMI: Body mass index

Table 4. Correlation coefficients and significance levels between age and body mass index of all cases and clinical measurements

	Age		BMI	
	Correlation coefficient	p-value[†]	Correlation coefficient	p-value[†]
Interspinous ligament thickness	-0.154	**0.009**	-0.075	0.208
Facet joint diameter	0.476	**<0.001**	0.236	**<0.001**
Multifidus muscle diameter	0.123	**0.038**	0.197	**<0.001**
Erector spinae muscle diameter	0.049	0.410	0.228	**<0.001**
Psoas muscle group diameter	-0.154	**0.009**	-0.151	**0.011**

[†]: Spearman's rank-order correlation analysis, BMI: Body mass index

and previous studies, facet joint hypertrophy accompanied with ligamentum flavum hypertrophy may indicate that mechanical stress is an important factor in the etiology of both.

Study Limitations

One of the limitations of our study; radiological measurements could not be made in 3D. Apart from this, the group examined in this single-centered study could have been larger and th control group could be larger though. We believe that stronger results can be achieved with multicenter studies in the future, with study series in which the study group is larger and technology can be used more powerfully.

CONCLUSION

Lumbar disk herniation and lumbar spinal stenosis are very common diseases in daily neurosurgery practice. In this study, we examined changes in the anatomical structures accompanying the vertebral column and existing discal or stenotic pathologies. In addition to the demographic characteristics of the patient,

Table 5. Comparisons of clinical measurements according to sex and employment groups

	Interspinous ligament thickness	Facet joint diameter	Multifidus muscle diameter	Erector spinae muscle diameter	Psoas muscle group diameter
Sex					
Male	6.30 (5.20-8.10)	262.7 (199.4-337.9)	845.9 (729.5-1068.4)	1101.5 (919.4-1260.7)	1511.6 (1223.6-1798.4)
Female	6.00 (5.00-7.60)	236.2 (187.9-296.9)	794.3 (695.6-945.9)	1032.1 (922.9-1173.4)	916.5 (777.3-1052.0)
p-value†	0.171	**0.007**	**0.009**	0.149	**<0.001**
Employment status					
Non-worker	6.00 (5.00-7.60)	251.7 (193.3-316.4)	806.6 (709.4-958.4)	1038.1 (932.0-1190.4)	955.2 (800.3-1097.9)[a,b]
Worker	6.40 (5.28-8.80)	258.2 (201.6-300.4)	819.9 (697.8-1056.6)	1024.3 (862.8-1247.6)	1491.3 (1223.4-1727.1)[a]
Heavy worker	6.15 (5.33-7.18)	207.5 (173.6-281.6)	879.3 (721.7-1065.9)	1103.3 (989.1-1271.4)	1394.9 (1136.7-1825.8)[b]
p-value‡	0.199	0.083	0.427	0.310	**<0.001**

Descriptive statistics; displayed as median (25^{th}-75^{th}) percentile, †: Mann-Whitney U test, ‡: Kruskal-Wallis test, a: The difference between non-workers and workers is significant (p<0.001), b: The difference between non-workers and heavy workers is significant (p<0.001)

Table 6. Correlation coefficients and significance levels between clinical measurements

	Facet joint diameter	Multifidus muscle diameter	Erector spinae muscle diameter	Psoas muscle group diameter
Interspinous ligament thickness				
Correlation coefficient	0.144	0.065	0.118	0.194
p-value†	**0.015**	0.273	**0.046**	**<0.001**
Facet joint diameter				
Correlation coefficient		0.467	0.275	0.243
p-value†		<0.001	**<0.001**	**<0.001**
Multifidus muscle diameter				
Correlation coefficient			0.528	0.369
p-value†			**<0.001**	**<0.001**
Erector spinae muscle diameter				
Correlation coefficient				0.285
p-value†				**<0.001**

†: Spearman's rank-order correlation analysis

changes in the accompanying spinal anatomical structures such as degeneration, hypertrophy, and atrophy may be important. Considering these factors and changes will help clinicians plan the treatment processes and choose the treatment method and outcomes.

Ethics

Ethics Committee Approval: All measurements were performed using the Sectra IDS7 Workstation (Linköping, Sweden). This study was conducted in accordance with the Declaration of Helsinki and was approved by the Sivas Cumhuriyet University Human Research Ethics Committee (approval number: 2021-01/06).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: H.C.K., F.K., E.K., Ü.Ö., Concept: H.C.K., Ü.Ö., Design: H.C.K., Ü.Ö., Data Collection or Processing: F.K., E.K., Analysis or Interpretation: H.C.K., Literature Search: H.C.K., F.K., E.K., Ü.Ö., Writing: H.C.K., F.K.

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VERTEBROPLASTY COMBINED WITH TRANSPEDICULAR FIXATION FOR THE MANAGEMENT OF NON-TRAUMATIC OSTEOPOROTIC VERTEBRAL FRACTURES ASSOCIATED WITH PEDICLE FRACTURES

Hamisi Mwarindano Mraja[1], Barış Peker[1], Halil Gök[2], Deniz Kara[3], Onur Levent Ulusoy[4], Tunay Şanlı[1], Selhan Karadereler[1], Meriç Enercan[5], Azmi Hamzaoğlu[1]

[1]İstanbul Florence Nightingale Hospital, Scoliosis-Spine Center, İstanbul, Turkey
[2]Ankara Etlik City Hospital, Clinic of Orthopaedics and Traumatology, Ankara, Turkey
[3]Washington University Faculty of Medicine, Department of Orthopaedics and Traumatology, Missouri, USA
[4]Demiroğlu Science University Faculty of Medicine, Department of Radiology, İstanbul, Turkey
[5]Demiroğlu Science University, Scoliosis-Spine Center, İstanbul, Turkey

ABSTRACT

Objective: Non-traumatic osteoporotic vertebra fracture (OVF) in association with bilateral pedicle fracture (PD) is a rare condition. In particular, OVFs demonstrating vacuum cleft sign and superior endplate discontinuity extending to the posterior cortex may be associated with non-traumatic PDs. This coexistence results in an unstable fracture pattern, and when solely treated with vertebroplasty (VP), vertebral collapse develops, leading to dead bone formation. We aimed to evaluate the efficacy of VP combined with transpedicular fixation (TPF) for the management of OVFs associated with PD.

Materials and Methods: Patients treated with VP combined with percutaneous TPF with a fenestrated screw at the same level of OVF were included. Prophylactic VP was performed at one level above and below. All patients underwent magnetic resonance imaging (MRI) and computerized tomography (CT) during preoperative evaluation. Preop and postop CT scans used for vertebral height measurements and comparison.

Results: Thirty-two pts (10M, 22F), mean age 74 (47-92) years of OVF and f/up 30 (24-74) months. Quantative-CT analysis including bone mineral density and t-score mean values was 56.79 mg/cm^3 and -4.38±0.538 respectively. VP combined with TPF was performed at 21 pts (Thoracolumbar), 8 pts (Thoracic), and 3 pts (Lumbar spine). Prophylactic VP was performed at 87 levels. The mean vertebral body angle improvement was 20.9% and the mean local kyphosis angle improvement was 17.2%. The mean anterior vertebral height and posterior vertebral height increased by 13.5% and 3.5%, respectively. None of the pts developed further vertebral collapse and none the pedicle screws pulled out at the final f/up.

Conclusion: According to our study, VP combined with TPF provided stable fixation and prevented further vertebral collapse in patients with OVF associated with pedicle fractures. OVF with a vacuum cleft sign or superior endplate discontinuity extending to the posterior cortex must be evaluated for the coexistence of spontaneous pedicle fracture, which causes instability and vertebral collapse. We recommend routine preoperative CT scan evaluation to determine fracture pattern and check pedicle integrity in addition to MRI scans.

Keywords: Vertebroplasty, transpedicular screw fixation, pedicle fracture, osteoporotic vertebral fractures

INTRODUCTION

Vertebral compression fractures (VCFs) are the most prevalent form of osteoporotic fractures. Although the prevalence of osteoporotic vertebral fractures (OVF) varies according to gender and age, several studies reported a rate between 40-50% among the female population over 50 years of age[1,2]. VCFs lead to pain, kyphosis, reduction in daily activities, and psychological disorders with progressive loss of vertebral height; resulting in a considerable decrease in the life quality of patients[3,4]. On the other hand, the mortality rate of OVFs among elderly patients is higher than that of the normal-age population[5].

Besides the osteoporotic causes, VCFs can be observed in malignancies: such as metastasis of the breast, prostate, thyroid, and lung cancers to the bones, the primary tumors of bone, and the lymphoproliferative diseases (i.e. lymphoma/multiple myeloma)[6]. The discrimination between the osteoporotic VCFs and malignant pathological fractures is

Address for Correspondence: Hamisi Mwarindano Mraja, İstanbul Florence Nightingale Hospital, Scoliosis-Spine Center, İstanbul, Turkey
Phone: +90 553 539 31 02 **E-mail:** hmsmrj752@gmail.com **Received:** 08.04.2024 **Accepted:** 23.04.2024
ORCID ID: orcid.org/0000-0003-1385-5721

critical and can be detected by magnetic resonance imaging (MRI) and computerized tomography (CT)[7,8]. Albeit abnormal bone marrow signals involving the pedicles and/or other posterior elements have been considered as a robust indicator of malignancy in VCFs. Ishiyama et al.[9] reported that the sensitivity and specificity of pedicle involvement on MRI were 84% and 36% for pathological malign fractures, respectively. Moreover, they detected the presence of pedicle edema in 144 MRIs of 225 patients with osteoporotic compression fractures and the presence of the pedicle fractures on CT of 31% of patients with pedicle edema[9].

Non-traumatic OVF patients rarely co-exist with bilateral pedicle fractures. Cases demonstrating vacuum cleft signs and superior endplate discontinuity extending to the posterior cortex may be associated with non-traumatic pedicle fractures. This co-existence eventually results in an unstable fracture pattern.

In the treatment of OVFs, both conservative and surgical methods are used. Treatments aim to reduce back pain and prevent the prognosis of deformity. Conservative treatment includes bed rest, brace, and analgesics. Currently, surgical treatment is preferred for patients with uncontrolled pain despite conservative treatment.

Traditionally, the common surgical treatment in elderly patients with OVFs is vertebroplasty due to their existing numerous comorbidities. However, in the unstable fracture pattern of OVFs co-existing with pedicle fracture, only vertebroplasty can develop further vertebral collapse which eventually leads to dead bone formation.

In the present study, we established a percutaneous transpedicular fixation (TPF) following vertebroplasty to support the vertebral corpus from the posterior column in unstable OVFs associated with pedicle fracture. We evaluated the clinical and radiographic outcomes of vertebroplasty combined with TPF surgery performed in patients with OVF associated with pedicle fractures.

MATERIALS AND METHODS

Patient Preoperative Evaluation

From 2017 through 2022, an analysis of 32 patients with OVF surgically treated with vertebroplasty combined with TPF of pedicle fracture at the same level as the OVF was performed. 10 males and 22 females, with an average age of 74 (47-92) years were included in this study. Radiological and clinical evaluations were analyzed in the preoperatively and both early-postoperatively and final follow-up. Postoperative complications were analyzed. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All patients signed the informed consent for this retrospective study. Ethical approval for this study was obtained from the İstanbul Bilim University Clinical Research Ethics Committee (approval number: 44140529/2016-06, date: 21/01/2016).

Radiological evaluations of the patients including CT scan and MRI were performed. Pedicle fracture was analyzed accordingly using both a CT scan and MRI. Every elderly patient with an OVF associated with pedicle fracture was prepared for vertebroplasty combined with percutaneous TPF with a fenestrated screw at the same level as the OVF. Measurement of vertebral heights and their comparison was performed using preoperative and postoperative CT scans. Also, the bone quality of the patients was analyzed using quantitative computed tomography.

Surgical Technique

All patients were monitored intraoperatively using somatosensory evoked potential (SSEP) and motor evoked potentials (MEP). Following intubation baseline SSEP and MEP values were recorded supine before positioning the patients. To protect the surgical morbidity of pressure sore and peripheral nerve injury, all the patients were well-padded on their bony prominences before positioning. Positioning was done using a Jackson radiolucent, frame with the abdomen freely acquired without any compression and the hips flexed appropriately. SSEP and MEP values were checked immediately after the prone positioning and compared with the initial values of the supine position. Always, the SSEP and MEP values were maintained at the beginning level. Any decrease of more than 20% required re-evaluation and the hip's extension degree was decreased.

According to the preoperative evaluation, first, the level of pedicle fracture was identified using fluoroscopy. A bilateral stab incision was performed at the vertebral level. Bilateral transpedicular placements of an 8 mm cannula into the vertebral body were performed under fluoroscopic guidance. Approval of the locations of the cannula was confirmed. Then from both sides of the vertebral level, each side was inserted with a balloon through the cannulas. The balloons were inflated separately, elevating the endplates and restoring vertebral body height. Afterward, the balloons were deflated and withdrawn, leaving a cavity within the vertebral body.

Then according to the preoperative evaluations, all the adjacent levels planned to be performed prophylactic vertebroplasty were also prepared. Bilateral stab incisions were performed to these adjacent levels and transpedicular placements of an 8 mm cannula into the vertebral bodies were performed under fluoroscopic guidance. Approval of the locations of the cannula was confirmed.

Ultimately, Polymethylmethacrylate (PMMA) bone cement was prepared. Mechanical aspiration of the vertebral bodies before administration of PMMA cement was done. First, the vertebral level with OVF co-existing with pedicle fractures was again inflated with a balloon. Immediately after inflation, the balloons were withdrawn after deflated, and mechanical aspiration was performed to this OVF level and all the prepared adjacent levels for prophylactic vertebroplasty followed by slow injection of a low viscosity cement of approximately 1 cc to each lumbar vertebra level and 0.8 cc to each thoracic vertebra level. The vertebral void was filled with the PMMA cement. Fluoroscopy was used to confirm the restoration of the vertebral body height.

Afterwards, percutaneous pedicle screw insertion started using the standard technique which included opening an initial hole to the medial process of the pedicle and enlargement to the required diameter. Its trajectory was confirmed both anteroposterior and laterally. The marker was then malleted through the trajectory while visualizing via fluoroscopy. Taping was done smaller than the screw size to be used. Always a bigger diameter screw (7.5 mm) was used to acquire more purchases. A probe was used to control any perforation of the dural canal or extravertebral perforation. Afterward, a polyaxial pedicle screw mainly 6.5 mm in diameter was inserted into the thoracic vertebral bodies while a 7.5 mm pedicle screw was inserted into the lumbar vertebral bodies under image guidance. Lastly, the inserted TPF (fenestrated screw) was augmented with a 0.8 cc low viscosity cement injection slowly.

All the procedure was performed under continuous lateral fluoroscopy, alternating both pedicles by using 1 mL syringes simultaneously. Extravasation of the cement from the vertebral body was observed. Termination of the injection was planned whenever there was a presence of perivertebral cement migration.

Postoperative Evaluations

In the postoperative radiologic evaluations; to determine cement leakage, pedicle screw loosening (more than 2 mm halo sign around the screw), pull-out, migration, and fusion; a musculoskeletal radiologist assessed the patients' radiological data. In the early postoperative period, two patients underwent lung X-rays for cement embolism evaluation. These were evaluated by radiologists to investigate the presence of pulmonary cement embolism. Radiopaque images in the lung parenchymal greater than 1 mm were defined as cement embolism.

RESULTS

Thirty-two patients of OVF associated with pedicle fractures underwent vertebroplasty combined with TPF with a mean follow-up of 30 (24-74) months. Vertebroplasty combined with TPF was performed at the thoracolumbar spine in 21 patients, thoracic spine in 8 patients, and lumbar spine in 3 patients. All 32 patients had acute fractures at least at one level with only 8 patients having multilevel acute fractures. OVF cases without pedicle fracture treated with only vertebroplasty were performed at 26 levels. Prophylactic vertebroplasty was performed at 65 levels. In all these patients vertebroplasty combined with percutaneous TPF with fenestrated screw was performed at the acute fracture with only three patients undergoing two-level vertebroplasty combined with two-level percutaneous TPF (Figure 1 and 2). A total of 87 levels were performed vertebroplasty.

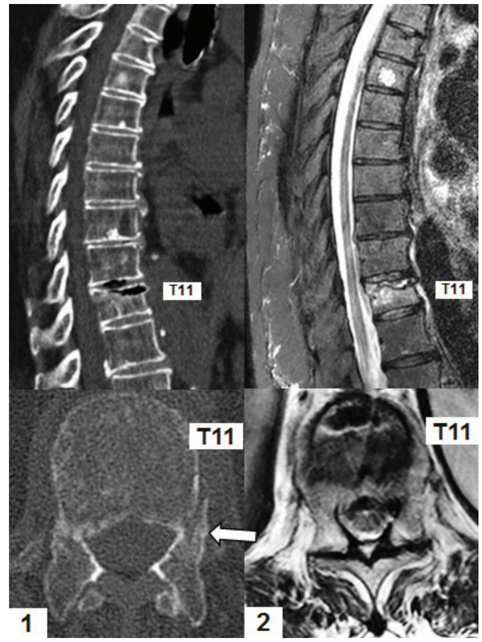

Figure 1. 1) Preoperative CT scan evaluations showing a T11 osteoporotic vertebra fracture demonstrating a vacuum cleft sign and superior endplate discontinuity extending to the posterior cortex may be associated with a pedicle fracture indicated with an arrow. 2) Preoperative MRI scan evaluations showing an acute T11 vertebral fracture

CT: Computerized tomography, MRI: Magnetic resonance imaging

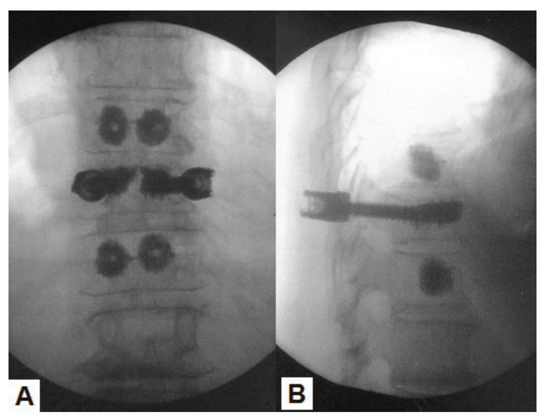

Figure 2. Intra-operative fluoroscopy images showing a single-level transpedicular screw fixation combined with vertebroplasty at the acute T11 vertebral fracture and prophylactic vertebroplasty to the adjacent levels. A) Demonstrating anterior-posterior view. B) Demostrating lateral view

Radiological Evaluations

All the radiological evaluations showed a mean vertebral body angle improvement of 20.9% and a mean local kyphosis angle improvement of 17.2%. The mean anterior vertebral height and posterior vertebral height increased by 13.5% and 3.5%, respectively after vertebroplasty (Figure 3) (Table 1).

Preoperative Quantative-CT analysis including bone mineral density and T-score mean values was 56.79 mg/cm^3 and

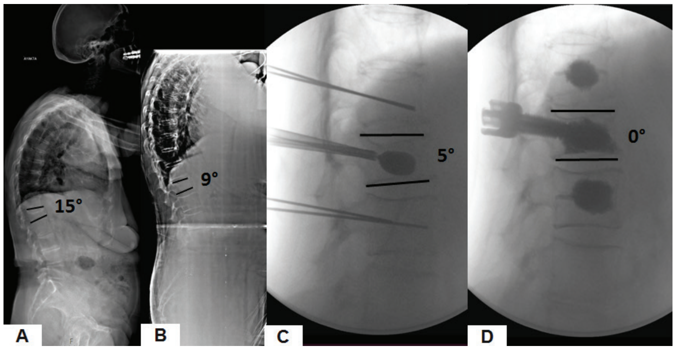

Figure 3. Preoperative standing lateral X-ray evaluation A) and lateral X-ray evaluation, B) taken in a prone position over Jackson table (Mizuho OSI) demonstrating an unstable fracture of L1 osteoporotic vertebra fracture with a vertebral body angle improving from 15° to 9°. C) Intraoperative lateral fluoroscopic evaluation demonstrating kyphosis reduction using balloon inflation at L1 fracture and transpedicular placements of cannulas to the adjacent levels (T12 and L2 vertebrae) for prophylactic vertebroplasty preparation. The balloon inflation improved the vertebral kyphosis from 9° B to 5° C. D) Intraoperative lateral fluoroscopic evaluation demonstrating vertebroplasty combined with bilateral transpedicular fixation of the fracture and prophylactic vertebroplasty at the adjacent levels. Balloon kyphoplasty restored the khyposis to 0°

Table 1. Radiological evaluations of the 32 elderly patients with OVF cases co-existing with PF

	Preoperative	Fup	Correction %
Vertebral body angle	9.4°	7.44°	-20.9
Bisegmental cobb angle	9.5°	7.87°	-17.2
AVH difference	15°	17.03°	13.5
PVH difference	21°	21.74°	3.5

PF: Pedicle fractures, OVF: Osteoporotic vertebral fractures, AVH: Anterior vertebral height, PVH: Posterior vertebral height

-4.38±0.538 respectively. The preoperative mean scores of visual analogue scale and Oswestry disability index were 7.63 and 60 respectively.

In the postoperative follow-up, none of the patients developed cement embolism nor had neurological deficits. Also, no pedicle screw pull-out was developed nor none of the patients developed vertebral collapse.

DISCUSSION

Vertebroplasty is the gold standard for treatment in elderly patients with OVF mainly used to reconstruct the fractured vertebrae. Different methods have been described to reconstruct the vertebra in the occurrence of a split fracture at the anterior column[10-13]. In the literature, treatment of osteoporotic fracture associated with pedicle fracture causing instability between the anterior and posterior column has not been described. Vertebroplasty combined with TPF using fenestrated screws is a new concept we defined to stabilize the two columns (anterior and posterior) in these unstable vertebral fractures by anchoring between them.

In a biomechanical study in which the thoracolumbar fracture models were established, the pedicle was indicated as a significant entity in terms of the mechanic stability, which supports especially the anterior column against the bear tension forces caused by forward bending when there is a bridge between anterior column and posterior ligamentous complex[14]. It was noted that the functional spinal units of the vertebra are subjected to massive compressive loads (preloads). The body weight passing through the anterior vertebra exerts a force on the instant center of rotation in the corpus, and to balance this enforcement in the anterior, the ligaments and muscles in the posterior administer balance out by applying compression force with the assistance of the momentum arm (pedicle), then, these two forces produce a force called the corpus preload, which is in the same direction as gravity. In the flexion state, the force arm of the body mass increases and the posterior structures balance out by generating more forces and leading to more preload. However, this preload in the flexion state is parallel to the gravity but not perpendicular to the corpus vertebrae. There is a separate force perpendicular and parallel to the corpus and this parallel force enforces the corpus forward to the translation; thus, the pedicle balances the force by acting as an anchor by connecting the corpus to the posterior[15].

When pedicle fractures and compression fractures coexist, they are generally considered as malignancy[16,17]. Nevertheless, in a radiological study by Ishiyama et al.[9], an edema in the pedicle was detected in 144 MRIs of 225 osteoporotic fractures (64%), whereby the pedicle fractures were identified in 45 patients on CTs[9]. Furthermore, some studies revealed that the pedicle fractures in compression fractures resulted in resistance to the conservative treatment methods and more collapse during follow-up[18,19].

Traditional vertebroplasty is critical in cases associated with pedicle fracture. Mechanical stability has always been emphasized by analyzing the anterior column whereby treatment techniques described have only involved reconstruction of the anterior column. However, the importance of the middle column is greatly underestimated. Also, the anterior column has been considered as the main load-bearing capacity of the vertebra. In the co-existence of pedicle fracture, only reconstructing the anterior column without any fixation of the pedicle eventually may produce a weak connection between the anterior and posterior columns. Hence, in patients with OVF accompanied by pedicle fracture when only treated with even a satisfactory vertebroplasty fragile vertebra still prevails which may eventually end up with vertebral collapse and splitting.

In 2014, Amoretti and Huwart[16] reported the data obtained after administering a screw system with bone cement under CT and fluoroscopy to 10 patients with split fractures on the vertebral body. In 2018, Cianfoni et al.[17] reported a new minimally invasive internal fixation procedure in which the stenting/cementum complex on the corpus vertebrae with complex VCFs was fixed to the posterior vertebral elements with pedicle screws; the primary aim was to reconstruct the vertebrae by supporting the bone cement and the secondary aim was to provide bone integration with posterior structures using quite biocompatible titanium screws[11]. In 2019, the biomechanical study of the stent-screw-assisted augmentation technique was reported by La Barbera et al.[18] in which three groups were established as the osteoporotic vertebrae, percutaneous vertebroplasty, and stent-assisted augmentation[12]. The collapse and refracture were reported to be reduced in the screw group compared to the other groups since the tension in the anterior and medial column was significantly decreased in the vertebrae treated with stent-assisted augmentation.

In 2021, Yonezawa et al.[19] defined the vertebrae-pediculoplasty method as a new approach in osteoporotic vertebral fractures, in which cannulated screws are utilized with vertebroplasty. The method was recommended especially in the anterior and posterior split fractures that resulted in failures of the vertebroplasty and the advantage of this method was supporting the cement mass with screws from the lamina and pedicle. Additionally, in 2020 cement-screw system was utilized in Kummel's disease to reconstruct the anterior wall in 27 patients and stated their findings as convincing[13]. In our study, vertebroplasty combined with TPF provided stable fixation and prevented further vertebral collapse and splitting in all 32 patients with osteoporotic vertebra fractures associated with pedicle fractures. While using this novel surgical technique, we achieved recoveries in OVFs by ensuring compression to the pedicle fractures. Secondly, as these patients usually have kyphotic deformities, the body weight led to a forward pulling force on the corpus vertebrae, yet we prevented instability in the corpus by utilizing the pedicle screw functioning as an anchor. Thirdly, the pedicle screw in the cement served as a scaffold, allowing the axial loads in the corpus to be shared with the posterior column and protecting the vertebrae from new fractures in the medial column. Ultimately, this novel technique of vertebroplasty combined with TPF provided stable fixation and prevented a further vertebral collapse in all patients with osteoporotic vertebra fractures associated with pedicle fractures.

Study Limitations

Our study has many limitations. First, the patients included were elderly aged hence our mean follow-up was recorded short. Secondly, a relatively small number of patients was included in this novel technique study. Lastly, in this study a control group was not evaluated. Further studies are to be performed to compare patients treated with only vertebroplasty traditionally and those patients treated by combining vertebroplasty and percutaneous transpedicular fixation.

CONCLUSION

According to our study, vertebroplasty combined with TPF provided stable fixation and prevented a further vertebral collapse in all pts with osteoporotic vertebra fractures associated with pedicle fractures. Osteoporotic vertebra fractures having vacuum cleft sign or superior endplate discontinuity extending to the posterior cortex must be evaluated for the co-existence of a spontaneous pedicle fracture which causes instability and vertebral collapse. We recommend routine preoperative CT scan evaluation to determine the fracture pattern and check pedicle integrity in addition to MRI scans.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the İstanbul Bilim University Clinical Research Ethics Committee (approval number: 44140529/2016-06, date: 21/01/2016).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: H.M.M., B.P., H.G., D.K., O.L.U., S.K., M.E., A.H., Concept: H.M.M., B.P., O.L.U., T.Ş., S.K., M.E., A.H., Design: H.M.M., H.G., D.K., T.Ş., S.K., M.E., A.H., Data Collection or Processing: H.M.M., B.P., H.G., O.L.U., T.Ş., M.E., A.H., Analysis or Interpretation: H.M.M., D.K., O.L.U., T.Ş., S.K., M.E., A.H., Literature Search: H.M.M., B.P., H.G., T.Ş., S.K., M.E., A.H., Writing: H.M.M., B.P., H.G., D.K., O.L.U., T.Ş., S.K., M.E., A.H.

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COULD PHARMACOLOGICAL TARGETING MITOPHAGIC OR LYSOPHAGIC SIGNALING PATHWAYS BE A NEW HOPE IN THE TREATMENT OF INTERVERTEBRAL DISC DEGENERATION?

İbrahim Yılmaz[1], Halil Can Küçükyıldız[2], Gazi Akkurt[3], Ali Dalgıç[2]

[1]İstanbul Rumeli University Faculty of Medicine, Vocational School of Health Services, Department of Medical Services and Techniques, İstanbul, Turkey
[2]Ankara Medicana International Hospital, Clinic of Neurosurgery, Ankara, Turkey
[3]Ankara Medicana International Hospital, Clinic of Anesthesiology, Ankara, Turkey

ABSTRACT

The relationship between mitophagy, a selective form of macroautophagy/autophagy that targets dysfunctional or excessive amounts of irregular mitochondria for degradation, and mycophagy, a selective autophagy mechanism for the removal of dysfunctional/unwanted lysosomes, in the context of intervertebral disc degeneration (IVDD) has not been sufficiently elucidated. This study was conducted to investigate the question, "Can IVDD be delayed or halted through pharmacological targeting of mitophagic or dysphagic signaling pathways?". For this purpose, systematic searches were conducted in the PubMed electronic database without country or language restrictions until March 21, 2024, using sequential searches with keywords related to the topic using "and/or" combinations to select high-evidence studies. Findings from studies meeting the research criteria and undergoing full-text assessment were compiled into an Excel spreadsheet using Microsoft Office. Results are presented in counts and/or frequencies (%). Following a comprehensive literature search, 12.720 studies were encountered, with 11.49% being reviewed. Although no clinical research related to the topic was found, no studies fully encompassed the inclusion criteria or the keywords "mitophagy"/"lysophagy" with "IVDD". Based on the existing literature, it is impossible to determine the level of evidence regarding the effect of mitophagic and/or dysphagic signaling pathways on IVDD or to discuss the effectiveness and reliability of targeting these pathways in treating degeneration. To establish evidence-based conclusions on this research topic, findings from multicenter, double-blind, randomized, and clinical trials involving a larger number of cases in different populations need to be evaluated.

Keywords: E3 ubiquitin, G3BP1, mitochondrial dynamics, Parkin, PINK1, sequestrotomy

INTRODUCTION

Mitophagy is a process whereby cells selectively degrade and remove damaged or dysfunctional mitochondria(1). Mitochondria, the organelles responsible for energy production within cells, can generate harmful byproducts when damaged. Mitophagy is believed to play a central role in mitochondrial quality control, including processes such as mitochondrial biogenesis and dynamics. It is considered the most effective way to eliminate damaged or unwanted mitochondria. By eliminating damaged or dysfunctional mitochondria, mitophagy helps maintain cellular health, preventing the accumulation of harmful substances. It has been proposed as a crucial mechanism to maintain cellular homeostasis and prevent diseases related to mitochondrial dysfunction(2).

Recent research suggests that dysregulation of mitophagy may contribute to intervertebral disc (IVD) degeneration (IVDD) by disrupting cellular homeostasis, increasing oxidative stress, and promoting inflammation and cell death in IVD cells(3,4).

Additionally, it is suggested that dysfunctional or impaired mitophagy may promote disc degeneration by leading to the accumulation of damaged mitochondria, increased oxidative stress, and inflammation in nucleus pulposus (NP) cells(5). Fundamental mechanisms proposed in the literature for mitophagy include the involvement of mitochondrial quality control mechanisms, such as phosphatase and tensin homolog-induced putative kinase 1 (PINK1) and Parkin, which play significant roles in tagging damaged mitochondria for removal when triggered by various cellular stressors such as oxidative damage, depolarization of mitochondrial membrane potential, or accumulation of damaged mitochondrial proteins(6).

Address for Correspondence: İbrahim Yılmaz, Tekirdağ Dr. İsmail Fehmi Cumalıoğlu City Hospital, Tekirdağ, Turkey
Phone: +90 632 701 28 58 **E-mail:** dryilmazi@yahoo.com **Received:** 02.04.2024 **Accepted:** 22.04.2024
ORCID ID: orcid.org/0000-0003-2003-6337

Another mechanism involves the effects on autophagosome formation, where autophagy receptors such as p62/Sequestosome-1 (SQSTM1) and nuclear domain 10 protein 52 (NDP52) are proposed to bind to damaged mitochondria, leading to the formation of autophagosomes around them, facilitating their recognition by autophagy receptors for degradation[7].

NDP52 plays important roles in ubiquitin-mediated protein degradation. It is well known that the ubiquitin-proteasome system is another important degradation system in host cells. Following ubiquitylation, invading pathogens can be cleared by host cells via autophagy. Autophagy receptors such as NDP52 and SQSTM1 play intermediate roles in autophagy and ubiquitylation[8].

Furthermore, a mechanism involving fusion with lysosomes is reported, where autophagosomes containing damaged mitochondria fuse with lysosomes to form autolysosomes, leading to the degradation of engulfed mitochondria by acidic environments and lysosomal enzymes.

In the recycling of degraded components, the breakdown products such as amino acids and fatty acids that emerge after degradation are recycled for cellular processes or excreted from the cell[9].

The breakdown products are then recycled or expelled from the cell for cellular processes. Lysophagy, conversely, is a selective form of autophagy that targets unhealthy and unwanted lysosomes for removal in normal mammalian cells[10].

In lysophagy, several basic steps target damaged or dysfunctional lysosomes for removal. Damaged or dysfunctional lysosomes are typically identified through oxidative stress, nutrient deficiency, or other insults. Once identified, damaged lysosomes are captured by double-membrane vesicles called autophagosomes, which aim to degrade cellular components targeted for degradation[11]. Like mitophagy, in lysophagy, autophagosomes containing damaged lysosomes merge with functional lysosomes, forming autolysosomes. As a result, the acidic environment and lysosomal enzymes within autolysosomes facilitate the degradation of damaged lysosomal contents, including proteins, lipids, and other macromolecules. The breakdown products are recycled for cellular processes or expelled from the cell after degradation. Overall, lysophagy helps maintain cellular homeostasis by removing damaged lysosomes and preventing the accumulation of toxic cellular remnants, contributing to cellular function and health[12]. Dysregulation of lysophagy can lead to cellular dysfunction and contribute to various pathological conditions.

In this systematic review, based on the hypothesis that maintaining appropriate mitophagy/lysophagy to prevent degenerative changes associated with IVDD could be crucial for preserving IVDD health and function, a systematic review is planned to be conducted.

MATERIALS AND METHODS

The study adhered to the Preferred Reported Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines[13,14].

Search Strategy

Systematic searches were conducted on the PubMed electronic database up to March 21, 2024, to evaluate published studies examining mitophagic/lysophagic signaling pathways associated with IVDD. Searches were conducted sequentially using the keywords "mitophagy", "lysophagy", in combination with "annulus fibrosus", "NP", and "IVDD" without country or language restrictions. Additionally, manual literature searches were performed by examining the reference lists of significant articles to identify other relevant studies.

Selection Criteria

The inclusion criteria for studies were as follows:

Studies conducted on humans and preclinical studies conducted on live mammalian subjects *in vivo* or *in vitro* cell cultures were included.

Clinical trials, if available, were considered, excluding non-randomized and non-blinded trials.

Exclusion criteria encompassed comments, editorials, letters to the editor, protocols, guidelines, meta-analyses, systematic reviews, and reviews.

The studies were selected based on their evidence level, which was determined according to the criteria set by Lijmer et al.[15-17].

After evaluating studies meeting the inclusion criteria following the keyword searches, information such as publication year range, examined signaling pathways, and characteristics related to tested pharmaceutical or pharmacological agents were recorded.

If the authors disagreed, the issue was discussed, and the senior author's (A.D.) opinion prevailed.

Figure 1 (PRISMA 2009 flow diagram) depicts the screening process for studies that did not meet the inclusion criteria and were thus excluded from our systematic review[18].

Statistical Analysis

After systematic literature searches, data were compiled in an Excel spreadsheet using Microsoft Office Program (version 10). While initially planned to assess heterogeneity using the

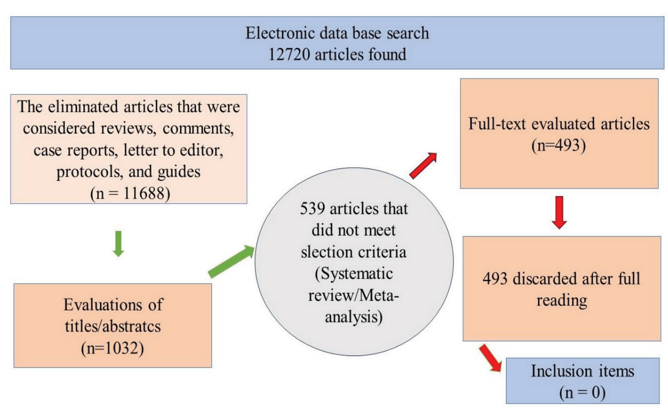

Figure 1. Flowchart of selection of studies for inclusion in umbrella review

Cochrane Q test, statistical evaluation could not be performed due to the absence of high-level clinical trials meeting the inclusion criteria. Descriptive statistics were used to analyze the obtained data, and the results were presented in counts and/or percentages (frequency, %).

RESULTS

Using the keyword "IVD", 41.698 results from 1890-2024 were found, of which 12.614 were identified as studies associated with disc degeneration between 1942 and 2024 (Table 1).

After a comprehensive literature search, no clinical trials or studies fully covering the topic of interest, "mitophagy"/"lysophagy" and "IVDD", were found.

DISCUSSION

All members of the Ras protein family belong to a class of proteins called small guanosine triphosphate (GTP) ases and play a role in transmitting signals within cells (signal transduction). Ras, the prototype member of the Ras protein family, is activated "ON" by incoming signals, subsequently activating other proteins and genes related to cell growth, proliferation, differentiation, and survival. Mutations in Ras genes can produce persistently active Ras proteins, resulting in unwanted and overly active signaling within cells, even without incoming signals. Therefore, Ras inhibitors are being intensively researched to treat various diseases with Ras overexpression, primarily cancer types and many other neurological conditions[19,20].

A study investigating the relationship between autophagy, ferroptosis, and potentially related molecules reported that compression pressure induces excessive iron accumulation and ferroptosis in human NP cells by inactivating autophagy and inducing lysosomal damage. Specifically, Ras GTPase-activating protein-binding protein 1 (G3BP1), primarily located in lysosomes, coordinates lysophagy activity through the G3BP1 and tuberous sclerosis complex (TSC)2 signaling pathways[10]. Functional impairment of G3BP1/TSC2 accelerates lysosomal damage and ferroptosis in NP cells. Additionally, inhibition of the mammalian target of rapamycin (mTOR) signaling by rapamycin improves lysosomal damage and protects cell ferroptosis[10]. *In vivo* experiments also demonstrate the role of G3BP1/mTOR signaling in the progression of IVDD. G3BP1 coordinates lysophagic activity to protect against cell ferroptosis associated with compression during IVDD. These findings demonstrate the relationship between lysophagy and compression-induced cell ferroptosis, while also indicating the positive role of G3BP1, which may provide potential targets for IVDD treatment[10].

In a study reporting that hypoxia-inducible factor-1-alpha (HIF-1α) alleviates compression-induced apoptosis of NP-derived stem cells by regulating autophagy, the dependence of BNIP3-like protein (BNIP3L) on HIF-1α-dependent expression, known as B-cell lymphoma-2 and adenovirus E1B 19 kDa-interacting protein-3 (BNIP3), and Nix, a proapoptotic gene regulated by histotoxic hypoxia, has been widely accepted as the fundamental mechanism of hypoxia-induced autophagy. Depletion of both components completely abolishes mitophagy and significantly increases cell death[21].

The mitochondrion is the center for bioenergetic processes, where substrates from the cytoplasm are utilized for fatty acid oxidation, the tricarboxylic acid (TCA) cycle, the electron transport chain, and respiration. Additionally, the mitochondrion serves as a platform for the biosynthesis of amino acids, lipids, nucleotides, heme, and iron-sulfur clusters and functions as its antioxidant defense through nikotinamid adenin dinükleotid fosfat.

Table 1. Searches performed before a detailed examination of the full texts of the articles

Keywords (year range of publication)	Case reports (amount)	Clinical trial (amount)	Review (amount)	Systematic review (amount)	Meta analysis (amount)	Total (amount)
IVDD (1942-2024)	434	493	1454	285	254	12619
IVDD + Mitophagy (2013-2024)	0	0	6	0	0	49
Lysophagy (2011-2024)	0	0	1	0	0	11
Mitophagy + AF (2019-2024)	0	0	0	0	0	3
Mitophagy + NP (2018-2024)	0	0	0	3	0	37
Lysophagy + AF (2013)	0	0	0	0	0	1
Lysophagy + NP (2011-2024)	0	0	0	0	0	9
IVDD + Mitophagy + Lysophagy	0	0	0	0	0	0

IVDD: Intervertebral disc degeneration, NP: Nucleus pulposus, AF: Annulus fibrosus

A study emphasizing that BNIP3 translocation to mitochondria mediates hypoxia-induced mitophagy in NP cells, but whether BNIP3 also regulates mitochondrial function and metabolism in hypoxic NP cells remains unknown, reported that BNIP3 degradation enhances mitochondrial morphology[22]. In a study reporting that BNIP3 deficiency in NP cells reduces glycolytic capacity, reflecting lower lactate/H+ production and lower adenozin trifosfat production rates, the authors have reported that loss of BNIP3 redirects glycolytic flux into pentose phosphate and hexosamine biosynthesis, as well as into pyruvate, leading to increased TCA flux using 1-2-13C-glucose. They observed increased autophagic flux, decreased disc height index, and abnormal expression of collagen type-X (an early sign of disc degeneration) in young adult BNIP3 knockout mice. These findings indicate that in addition to regulating mitophagy, BNIP3 also plays a role in preserving mitochondrial function and metabolism, and disruption of mitochondrial homeostasis may support disc degeneration[22].

CsA-induced mitophagy inhibition partially abolished the protective effects of melatonin against NP cell apoptosis, highlighting mitophagy's role in mediating melatonin's protective effect on IVDD[17]. Additionally, melatonin has been shown to inhibit the expression of extracellular matrix (ECM) degradation enzymes such as matrix metalloproteinase-13 and a disintegrin and metalloproteinase with thrombospondin motifs 5, while preserving the ECM content of collagen type-II, aggrecan, and Sox9. *In vivo*, melatonin treatment has been reported to improve degeneration in a puncture-induced experimental rat IVDD model[23]. These results suggest that melatonin protects NP cells against apoptosis through the induction of mitophagy and improved disc degeneration, potentially providing a therapeutic strategy for IVDD[23].

In previous studies, it was reported that mitochondrial dysfunction contributes to apoptosis and urolithin A (UA) specifically triggers mitophagy[24]. The protective effect of UA-induced mitophagy against tert-butyl hydroperoxide (TBHP)-induced apoptosis in NP cells was demonstrated in vitro. and was investigated in the *in vivo* experimental IVDD rat model. They have been reported that UA can activate mitophagy in primary NP cells, and UA treatment inhibits TBHP-induced mitochondrial dysfunction and the intrinsic apoptosis pathway. Mechanistically, UA has also been mentioned to promote mitophagy by activating 5' adenosine monophosphate (AMP)-activated protein kinase (AMPK) signaling in TBHP-induced NP cells. It has been shown *in vivo* that UA effectively alleviates the progression of puncture-induced experimental IVDD in rats, and they argue that UA may be a new and effective therapeutic strategy for IVDD[24].

In a study where the interaction between circular RNAs CircERCC2 and the miR-182-5p/Sirtuin (SIRT)-1 axis was investigated, it was reported that downregulation of circERCC2 increased miR-182-5p levels and decreased SIRT1 levels in degenerative NP and TBHP-stimulated NP *in vitro*[25]. They provided the first evidence that circERCC2 activates mitophagy and inhibits apoptosis through the miR-182-5p/SIRT1 axis, suggesting that circERCC2 could be a potential therapeutic target for IVDD[25].

In 2021, it was reported that zinc finger protein/tumor necrosis factor α-induced protein-3 (A20) can inhibit the activation of the nuclear factor kappa-B (NF-κB) signaling pathway and promote autophagy[26]. Therefore, it has been reported that A20 can improve IVDD by regulating inflammation through autophagic pathways mediated by NF-κB in human NP cells[26]. Subsequently, in 2023, it was reported that A20 promotes mitophagy, weakens pyroptosis, and inhibits ECM degradation, thus significantly improving IVDD. Mechanistically, it was reported in a study that A20 reduces pyroptosis and further suppresses cellular mTOR activity. In a study reporting that A20-induced mTOR inhibition promotes mitophagy through the AMPK signaling pathway activated by AMP, it was further reported that A20 suppresses mTOR pathway activation induced by lipopolisakkarit (LPS), supporting BNIP3-mediated mitophagy, thereby inhibiting LPS-induced pyroptosis. These findings suggest that A20 may regulate IVDD through mitophagy and ECM degradation inhibition[27].

Additionally, in the literature, using live mammalian subjects and *in vitro* tissue and cell models, it is mentioned that nucleotide-binding oligomerization domain (NOD)-like receptor family member X1 (NLRX1) can facilitate mitochondrial quality by combining mitophagy activity and mitochondrial dynamic factors such as dynamin 1-like protein, which is involved in the division of mitochondria and peroxisomes. It is reported that in NP cells with NLRX1 damage, mitochondrial collapse occurs and the compensatory PINK1-Parkin RBR E3 Ubiquitin Protein Ligaz (PRKN) signaling pathway is activated, leading to excessive mitophagy and aggressive NP cell senescence[28]. NLRX1 has been shown to initially interact with the zinc transporter SLC39A7 and modulate mitochondrial Zn^{2+} through the formation of an NLRX1-SLC39A7 complex on the mitochondrial membrane of NP cells, subsequently regulating mitochondrial dynamics and mitophagy and improving IVD[28].

Sestrin2 (Sesn2), a highly conserved, stress-responsive protein, can be triggered by a variety of noxious stimuli such as hypoxia, DNA damage, oxidative stress, endoplasmic reticulum stress, and inflammation. Many transcription factors, including Hif-1α, p53, nuclear factor E2-related factor 2 (Nrf2), activating transcription factor (ATF)-4, ATF-6, regulate Sesn2 expression. Upon induction, Sesn2 generally leads to activation of AMPK and inhibition of the mechanistic target of mTOR1C. To maintain cellular homeostasis, Sesn2 and its downstream molecules directly scavenge reactive oxygen species (ROS) or indirectly influence the expression patterns of key genes associated with redox, macroautophagy, mitophagy, endoplasmic reticulum stress, apoptosis, protein synthesis and inflammation[29].

In a study reported that Sesn2 functions as a regulator between the mitochondrial unfolded protein response (UPRmt) and mitophagy in IVDD[30], it has been mentioned that the mitochondrial UPRmt can induce mitophagy to protect the cell from unfolded protein. In the study reported that Sesn2 is considered to be a key molecule that transmits UPRmt and mitophagy in the IVD, it is mentioned that silencing Sesn2 can reverse the protective effects of nicotinamide riboside (NR) on NP cells and inhibit mitophagy induced by UPRmt[30]. Sesn2 has also been mentioned to promote the translocation of cytosolic Parkin and SQSTM1 to damaged mitochondria, respectively, thus increasing mitophagy. They have been reported that NR, Sesn2-/- mice do not completely attenuate IVDD, but UPRmt may attenuate IVDD through regulation of Sesn2-induced mitophagy[30].

Additionally, the literature mentions that NOD-like receptor family member X1 (NLRX1) can facilitate mitochondrial quality by combining mitochondrial dynamic factors and mitophagy activities, thereby regulating mitochondrial division in vascular tissues. It is reported that in NP cells with NLRX1 damage, the compensatory PINK1-PRKN signaling pathway is activated, resulting in mitochondrial collapse and aggressive NP cell aging. NLRX1 is shown to interact with the zinc transporter SLC39A7 and modulate mitochondrial Zn2+, subsequently regulating mitochondrial dynamics and mitophagy, thus alleviating IVDD[31].

In a study using a hydrogen peroxide (H_2O_2)-induced NP cell aging model and a rat acupuncture IVDD model to investigate the role of cannabinoid type 2 receptor (CB2R) in IVDD, p16INK4a expression was shown to increase with a decrease in CB2R expression[32]. They reported that CB2R activation significantly reduced the number of SA-β-gal positive cells and suppressed the expression of p16INK4a and senescence-associated secretory phenotypes and the high mobility group[32]. Additionally, activation of CB2R has been reported to promote the expression of collagen type-II and Sox9, inhibit collagen type-X, and restore the balance of the ECM. It has also been shown that CB2R plays a role in the aging or regulation of the AMPK/GSK3β signaling pathway and NP cells in the rat experimental IVDD model. It has been stated that activation of CB2R may attenuate IVDD[32].

Selenophosphate synthetase-1 (SEPHS1) has been reported to play an important role in reducing oxidative stress in an osteoarthritis model by reducing ROS production, thereby delaying the occurrence and development of osteoarthritis. Overexpression of SEPHS1 and inhibition of Hippo-Yap/Taz have been reported to alleviate IVDD in rats[33].

In a study reporting that SIRT3 expression decreased in degenerated NP cells but increased in H2O2-derived NP, it was emphasized that upregulation of SIRT3 reduced oxidative stress, delayed cellular aging, and reduced IVDD via the AMPK/PGC-1α signaling pathway[34]. There is also a claim in the literature that hyaluronic acid improves IVDD by promoting mitophagy activation[35]. A study reported that MitoQ, through the PINK1/Parkin signaling pathway, restores mitochondrial dynamic balance, alleviates the disruption of mitophagosome-lysosome fusion and lysosomal function, and increases Nrf2 activity, thus eliminating damaged mitochondria, improving redox balance, and increasing cell survival. It has been reported to represent a promising therapeutic strategy for IVDD[36].

In a study in which optineurin (OPTN), a selective mitophagy receptor, was tested in a rat disc degeneration model[37], it was emphasized that H_2O_2-induced cellular senescence was significantly inhibited and ECM-related protein expression increased in NP cells. They demonstrated that OPTN attenuates oxidative stress-induced NP cellular senescence and ECM degeneration by promoting mitophagy to clear damaged mitochondria and excess ROS, thereby slowing the progression of IVDD[37].

Following lentivirus (LV)-shLRRK2 transfection in human degenerative NP and rat NP cells, the therapeutic effects of LV-shLRRK2 on IVDD were evaluated. In the study reporting that LRRK2 expression increased in degenerative NP cells[38], it was reported that LRRK2 deficiency significantly suppressed oxidative stress-induced mitochondria-dependent apoptosis in NP cells and promoted mitophagy. The study revealed that LRRK2 plays a role in the pathogenesis of IVDD and that knockdown of LRRK2 inhibits oxidative stress-induced apoptosis through mitophagy, emphasizing that inhibition of LRRK2 may be a promising therapeutic strategy for IVDD[38].

Vitamin D receptor (VDR) is a steroid hormone receptor that can regulate autophagy. In a study that sought to answer the question of whether VDR alleviates IVDD by promoting autophagy, a negative correlation was reported between VDR expression and IVDD. It was also reported in the study that overexpression of VDR promoted mitophagy and prevented apoptosis and mitochondrial damage under oxidative stress, and that mitophagy inhibition by 3-methyladenine, an autophagy inhibitor, eliminated the protective effect of VDR activation. The study revealed that VDR activation ameliorates oxidative damage and reduces NP cell apoptosis by promoting PINK1/Parkin-dependent mitophagy, indicating that VDR may serve as a promising therapeutic target in the management of IVDD[39].

It has been hypothesized that downregulation of vascular endothelial growth factor A creates a new effect in non-vascular tissues through mitophagy regulation, and it has also been reported in the literature that it accelerates NP degeneration mediated by advanced glycation end products by inhibiting protective mitophagy in high glucose environments[40].

In summary, research into the molecular mechanisms underlying IVDD has identified multiple pathways and molecules involved in regulating cellular processes, such as autophagy, mitophagy, apoptosis, ferroptosis, and ECM degradation. These findings provide valuable insights into potential therapeutic targets for the treatment of IVDD, although further research is needed to elucidate the complex interactions and signaling pathways involved fully.

CONCLUSION

In the context of IVDD, lysophagy may play a role in maintaining cellular homeostasis by clearing damaged components within disk cells such as NP and annulus fibrosus dysregulation of lysophagy may contribute to the progression of IVDD by impairing the ability of IVDD cells to remove cellular debris and maintain tissue integrity. Mitophagy, particularly within disk cells in the avascular and nutrient-deprived IVD environment, is believed to play a crucial role in preserving mitochondrial quality control and cellular homeostasis in IVDD. Dysregulation of mitophagy has been implicated in the pathogenesis of IVDD, as impaired mitophagy can contribute to the degenerative process by accumulating dysfunctional mitochondria, increased oxidative stress, and, ultimately, cell death. Therefore, promoting healthy mitophagy may hold therapeutic potential for mitigating the progression of IVDD. However, further research is needed to fully understand the relationship between lysophagic or mitophagic signaling pathways and IVDD.

Ethics

Authorship Contributions

Surgical and Medical Practices: İ.Y., H.C.K., G.A., A.D., Concept: İ.Y., A.D., Design: İ.Y., A.D., Data Collection or Processing: İ.Y., H.C.K., G.A., Analysis or Interpretation: İ.Y., A.D., Literature Search: İ.Y., G.A., Writing: İ.Y., H.C.K.

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