

## Artículo original

# Ligamentum flavum in lumbar spinal stenosis, disc herniation and degenerative spondylolisthesis. An histopathological description

*Ligamento amarillo en estenosis lumbar espinal, hernia de disco y espondilolistesis degenerativa. Una descripción histopatológica*

Reyes-Sánchez A,\* García-Ramos CL,† Deras-Barrientos CM,§  
Alpizar-Aguirre A,|| Rosales-Olivarez LM,¶ Pichardo-Bahena R\*\*

Instituto Nacional de Rehabilitación «Luis Guillermo Ibarra Ibarra».

**ABSTRACT. Introduction:** Changes in ligamentum flavum (LF) related to degeneration are secondary to either the aging process or mechanical instability. Previous studies have indicated that LF with aging shows elastic fiber loss and increased collagen content, loss of elasticity may cause LF to fold into the spinal canal, which may further narrow of the canal. **Material and methods:** A total of 67 patients operated with the surgical indications of lumbar spinal stenosis (LSS), lumbar disc herniation (LDH) and lumbar degenerative spondylolisthesis (LDS) were included. LF samples were obtained from patients who had LSS (39), LDH (22) and LDS (6). Specimens were examined with regard to chondroid metaplasia, calcification, fragmentation of collagen fibers, cystic degeneration, fibrillar appearance, and hypercellularity. **Results:** The most frequent histopathological changes were hyalinization and fragmentation of collagen fibers occur in 34%, neovascularization in 40.3% and irregular arrangement of elastic fibers is the most prevalent change with 56.7% of the total samples. There is a difference in the presence of certain changes in the LF according

**RESUMEN. Introducción:** Los cambios en el ligamento flavum (LF) relacionados con la degeneración son secundarios al proceso de envejecimiento o a la inestabilidad mecánica. Estudios anteriores han indicado que LF con envejecimiento muestra pérdida de fibras elásticas y aumento del contenido de colágeno, la pérdida de elasticidad puede hacer que el LF se pliegue en el canal espinal, disminuyendo su espacio. **Material y métodos:** Se incluyeron 67 pacientes operados de estenosis lumbar espinal (LSS), hernia de disco lumbar (LDH) y espondilolistesis degenerativa (LDS). Se obtuvieron muestras de LF de pacientes que tenían LSS (39), LDH (22) y LDS (6). Se examinaron especímenes con respecto a metaplasia condroide, calcificación, fragmentación de fibras de colágeno, degeneración quística, apariencia fibrilar e hiper celularidad. **Resultados:** Los cambios histopatológicos más frecuentes fueron la hialinización y la fragmentación de las fibras de colágeno (34%), neovascularización en 40.3%, y la disposición irregular de las fibras elásticas es el cambio más frecuente con 56.7% del total de muestras. Existe una diferencia en la presencia de cambios en el

## Level of evidence: III. Comparative retrospective study.

\* Chief of Division of Spine Surgery, National Institute of Rehabilitation, Mexico.

† Research in Spine Surgery, National Institute of Rehabilitation «Luis Guillermo Ibarra Ibarra», Mexico.

§ Spine Surgery, San Juan de Dios, National Hospital, San Miguel, El Salvador.

|| Spine Surgeon, National Institute of Rehabilitation «Luis Guillermo Ibarra Ibarra», Mexico.

¶ Chief of Service of Spine Surgery, National Institute of Rehabilitation «Luis Guillermo Ibarra Ibarra», Mexico.

\*\* Pathologist, National Institute of Rehabilitation «Luis Guillermo Ibarra Ibarra», Mexico.

### Corresponding author:

Carla Lisette García Ramos

Department of Spine Surgery, National Rehabilitation Institute of Mexico, Av. Mexico-Xochimilco Núm. 289, Col. Arenal de Guadalupe, CP. 14389, Mexico City, Mexico. Tel: 59-99-1000, ext. 12204.

E-mail: carla0608@hotmail.com

Este artículo puede ser consultado en versión completa en: [www.medigraphic.com/actaortopedica](http://www.medigraphic.com/actaortopedica)

to the diagnosis, being statistically significant for fragmentation of collagen fibers ( $p = 0.045$ ), cystic degeneration ( $p = 0.001$ ), fibrillar appearance ( $p = 0.007$ ) and hypercellularity ( $p = 0.005$ ) all of these, being more prevalent in LDS group. LHD group presented fragmentation of collagen fibers in 45.5% ( $p = 0.045$ ) and fibrillar appearance in 4.5% ( $p = 0.009$ ). **Conclusions:** There is not evidence of cellular hypertrophy in the histopathological analyses, thickening of the LF can be seen by bulking of LF followed by collapse of motion segment.

**Keywords:** Ligamentum flavum, hypertrophy, thickness, lumbar pathology, spinal stenosis.

LF, de acuerdo con el diagnóstico, siendo estadísticamente significativo para la fragmentación de las fibras de colágeno ( $p = 0.045$ ), la degeneración quística ( $p = 0.001$ ), la apariencia fibrilar ( $p = 0.007$ ) y la hiper celularidad ( $p = 0.005$ ) todos ellos, siendo más frecuentes en el grupo LDS. El grupo LHD presentó fragmentación de las fibras de colágeno en 45.5% ( $p = 0.045$ ) y la apariencia fibrilar en 4.5% ( $p = 0.009$ ). **Conclusiones:** No hay evidencia de hipertrofia celular en los análisis histopatológicos, el engrosamiento del LF se puede ver por abultamiento del mismo, seguido de colapso del segmento de movimiento.

**Palabras clave:** Ligamentum flavum, hipertrofia, espesor, patología lumbar, estenosis espinal.

## Introduction

The normal ligamentum flavum (LF) is a well defined elastic structure containing 80% elastic fibers and 20% collagen fibers.<sup>1,2</sup> LF covers the posterior and lateral walls of the spinal canal.<sup>3</sup>

LF contains the purest form of elastic tissue among ligaments; these elastic fibers decrease with age and are replaced by fibrous tissue.<sup>1,3,4</sup>

Also decreased in degenerative pathologies in lumbar spine and presented misalignment of the elastic fibers, collagen replacement, alterations in the structure and array of elastic fibers and collagen/elastin ratio and development of calcification over time;<sup>1,5</sup> however, none of these studies evaluated all of these parameters in combination.<sup>6,7,2</sup>

These results were not seen in lumbar disc herniation (LDH) patients. An increase in collagen fibers were observed, but no statistically significant differences were detected between the groups when comparing with lumbar spinal stenosis (LSS); there has been a significant difference in elastic fiber misalignment between the groups.<sup>5</sup>

All these changes cause reductions in LF elasticity, increased of fibrosis,<sup>1,2</sup> and make the LF thickened and to fold into the spinal canal, which may further narrow of the canal,<sup>3</sup> and is considered a prodrome of its ossification.<sup>8,7</sup>

LF thickening is considered a major contributor to the development of LSS and a prodrome of its ossification<sup>8,7,9</sup> it compresses the nerve roots of the cauda equina<sup>3</sup> and surgical removal of the thickened LF can help treat LSS.<sup>3</sup>

The purpose of this article is to describe the histopathological changes that occur in some of the degenerative diseases of the lumbar spine, including lumbar degenerative spondylolisthesis (LDS), lumbar spinal stenosis and lumbar disc herniation, and also show the changes presented histopathologically with respect to the age.

## Material and methods

All procedures and protocols were conducted in accordance with the principles of Helsinki Declaration, written informed consent was obtained from all participants in accordance with standard operative procedures.

This study included sixty seven patients who were admitted to the Departament of Spine Surgery in our center between 2014 and 2015 and were operated with surgical indications of lumbar spinal stenosis (LSS), lumbar disc herniation (LDH) and lumbar degenerative spondylolisthesis (LDS). In this study all patients fulfilled the following criteria: 1. Age > 18 years, 2. No previous surgery on spine, 3. Diagnosis verified by magnetic resonance scan. Patients with history of osteoporosis, immunosuppression, chronic corticosteroid use, intravenous drug use, fever of unknown origin, history of cancer, unexplained weight loss, or progressive/disabling symptoms were excluded from the study.

LF samples were obtained from the 39 patients who underwent decompressive surgery for LSS, 22 patients who underwent lumbar discectomy for LDH and 6 patients who underwent decompressive surgery and fusion for LDS.

All patients were diagnosed if there were significant MRI findings indicative of these conditions and if clinical manifestations were thought to be compatible with the MRI results. There was no calcification of LF according to preoperative computed tomography scans and X rays.

## Outcome parameters

LF materials obtained from patients during surgery were subjected to histopathological analyses. The tissue samples were immediately fixed for 24 hours. Subsequent to preparation with ethanol and xylene, tissue was placed in paraffin and sections were cut to 5  $\mu$ m thickness using a microtome. Tissue preparations were

stained with hematoxylin and eosin, and were evaluated by two pathologists who were blinded to the nature of the groups. Specimens were examined with regard to chondroid metaplasia, calcification, fragmentation of collagen fibers, cystic degeneration, fibrillar appearance, hypercellularity, and the presence of others degenerative changes.

### Statistical analysis

Data were analyzed using the IBM Statistical Package for Social Sciences ver. 20 (SPSS Inc., Chicago, IL, USA). Parametric tests were applied to data of normal distribution and nonparametric tests were applied to data of questionably normal distribution. Continuous data were presented as mean  $\pm$  standard deviation or median (minimum-maximum), as appropriate. We used ANOVA to analyze variances between groups. All differences associated with a chance probability of  $\leq 0.05$  were considered statistically significant.

### Results

Sixty-seven patients (33 males, 34 females) met the eligibility criteria for the study. Of these patients whose charts were reviewed, the mean age was 54.37 years (range, 19-87 years).

In the analysis by age group, we found that the highest percentage of sample is within the group between 44 and 65

years; in the group of LDH are the youngest patients with a  $p = 0.0001$  (Table 1).

Groups did not differ from each other regarding age ( $p = 0.980$ ), but differ in gender ( $p = 0.0001$ ).

The most frequent histopathological changes were hyalinization and fragmentation of collagen fibers occur in 34% of the total samples, neovascularization in 40.3% and irregular arrangement of elastic fibers is the most prevalent change with 56.7%.

A multiple linear regression was performed to evaluate the effect of age and gender with the presence of the most important changes in the analysis (hyalinization, fragmentation, irregular fiber arrangement and neovascularization) and those were not predictors in the mentioned changes (Figures 1 to 7).

There is a difference in the presence of certain changes in the flavum ligament according to the diagnosis, being statistically significant for fragmentation of collagen fibers ( $p = 0.045$ ), cystic degeneration ( $p = 0.001$ ), fibrillar appearance ( $p = 0.007$ ) and hypercellularity ( $p = 0.005$ ).

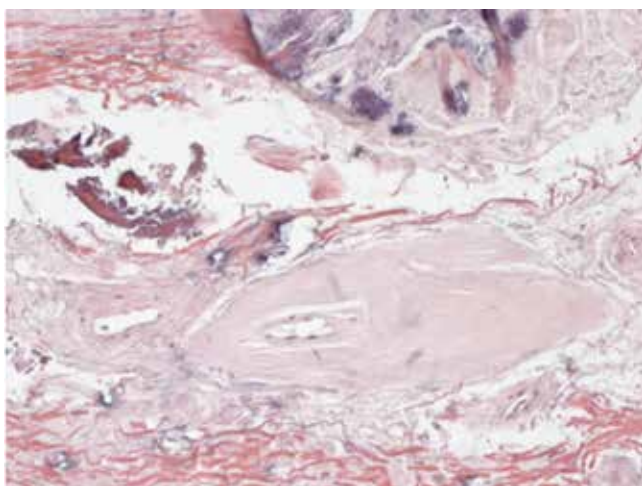
The group of LDS presented separation of collagen fibers, cystic degeneration, fibrillar appearance and hypercellularity with  $p$  value  $< 0.05$  (Table 1). There is an association between degenerative spondylolisthesis and the separation of collagen fibers. We found the LDH group had fragmentation of collagen fibers, fibrillar appearance, despite belonging to a younger age. The LSS group showed fragmentation of collagen fibers, cystic

Table 1: Description of the sample.

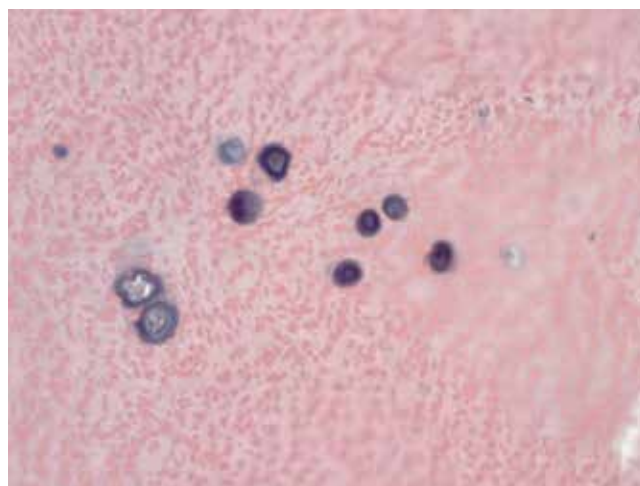
Parameter	Diagnosis			Total	p
	Lumbar spinal stenosis	Lumbar disc herniation	Lumbar degenerative spondylolisthesis		
n (%)	39 (58.2)	22 (32.8)	6 (9)	67 (100)	
Age in years M (SD)	61.49 (12.60)	39.91 (11.15)	61.17 (9.45)	41.61 (8.95)	0.980
	%	(%)	(%)	(%)	
Group 1 (19-43 years)	0.0	4.5	0	4.5	
Group 2 (44-65 years)	47.8	28.4	7.5	83.6	
Group 3 (66-87 years)	10.4	0.0	1.5	11.9	
Gender					0.0001
Men	43.6	63.6	33.3	49.3	
Women	56.4	36.4	66.7	50.7	
Histopathological changes					
Chondroid metaplasia	25.6	22.7	16.7	65.0	0.881
Calcification	23.1	36.4	0.0	59.5	0.169
Fragmentation of collagen fibers	23.1	45.5	66.7	89.8	0.045
Cystic degeneration	2.6	0.0	33.3	35.9	0.001
Fibrillar appearance	10.3	4.5	50.0	64.8	0.009
Hypercellularity	0.0	0.0	16.7	16.7	0.006

On the top we observed distribution by group according to the age, we observed that 83.6% of the sample corresponds to the group between 44 and 65 years of age, the highest percentage in LDH group is in the youngest group ( $p = 0.0001$ ) and analysis by gender. In the bottom we described histopathological changes presented in the different groups; the LSS group has more prevalence of chondroid metaplasia; the LDH group has more prevalence of calcification; and the LDS group has more fragmentation of collagen fibers, cystic degeneration, fibrillar appearance and hypercellularity.

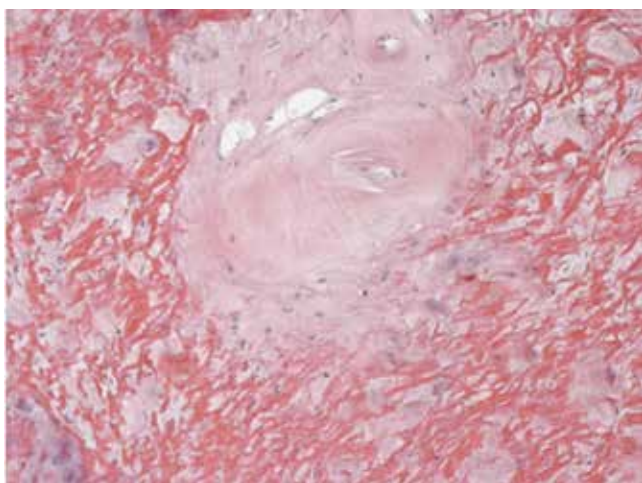




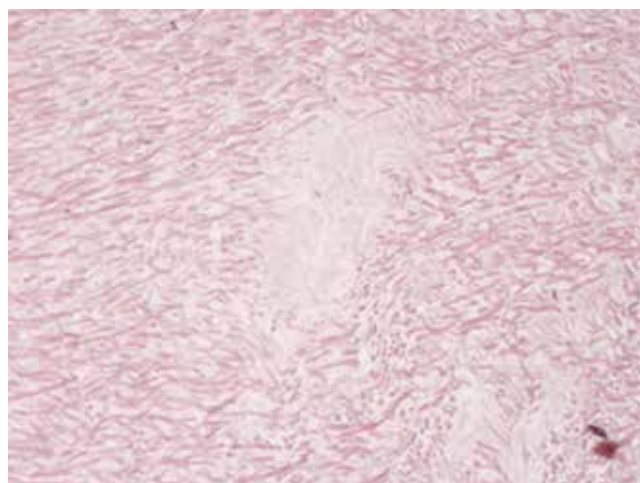
**Figure 1:** Immersed in the yellow ligament there is accentuation of the vascular pattern with. In this case with hyalinization of the vascular walls.



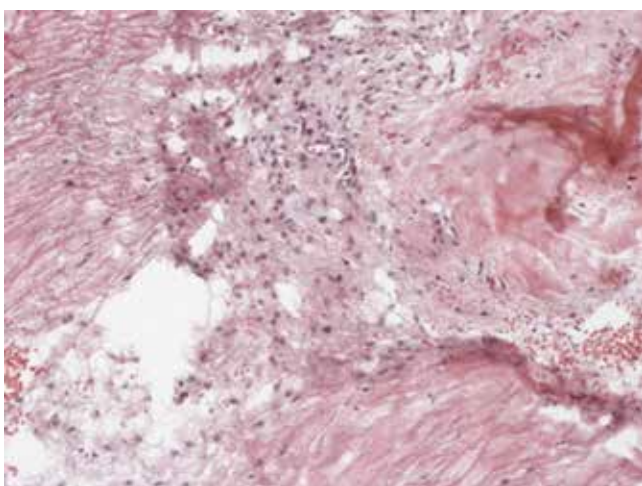
**Figure 4:** There are areas of calcification immersed in the elastic fibers, which are seen round, basophilic and concentric, which resemble bodies of psammoma.



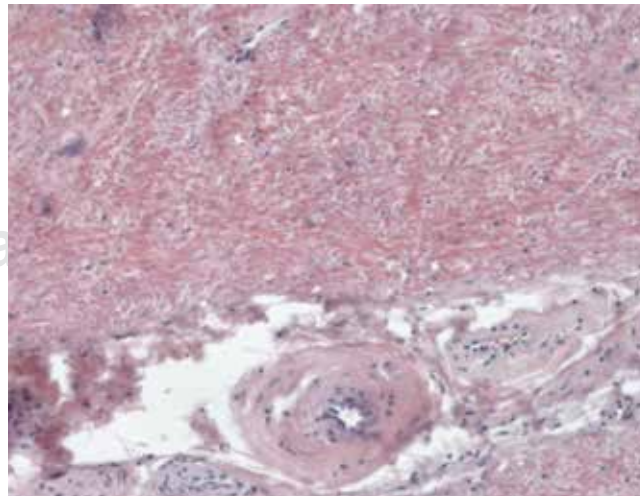
**Figure 2:** There are nodular areas of fibrosis with accentuation of the vascular pattern.



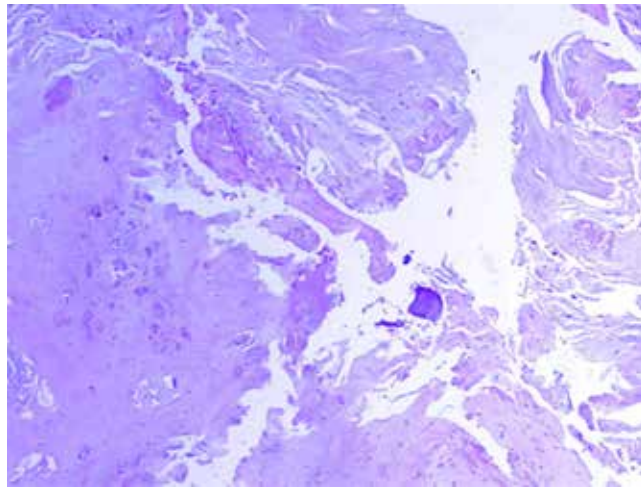
**Figure 5:** In the ligament flavum there are acellular basophilic amorphous nodular zones, which give them a hyalinized appearance.



**Figure 3:** Areas of mononuclear inflammatory infiltrate associated with fragmentation of elastic fibers are observed.



**Figure 6:** Areas with increased cellularity.



**Figure 7:**

On the surface there are areas of frayed appearance, which correspond to the areas of fibrillar degeneration.

degeneration, fibrillar appearance and hypercellularity (Table 1).

## Discussion

We sought to compare the histopathological changes found in patients with LSS, LDH, LDS. Altun Idiris found that calcification was not detected ( $0.00 \pm 0.00$ ) in the discectomy group,<sup>5</sup> in our analysis calcification was detected in 36.4% of the samples of LDH group. In our study the groups did not differ with regard to mean calcification, chondroid metaplasia, ( $p=0.881$  and  $p=0.169$ , respectively). But differ in fragmentation of collagen fibers, cystic degeneration, fibrillar appearance and hypercellularity, most of this changes were seen in LDS, these results could be cause by instability rather than age o degenerative disease in the spine.

The mean age of patients in the stenotic group did not differ from that of the discectomy group.<sup>5</sup> However we found the highest percentage in LDH (72.7%) group is in the youngest group (19-43 years old). And also we observed some degenerative changes in the LDH group like fragmentation of collagen fibers in 45.5% and fibrillar appearance in 4.5%. we concluded the same that Postacchini no peculiar changes occur in patients with disc herniation, and showed similar features to those of ligaments from control subjects of similar ages.<sup>10</sup>

In spinal stenosis, fibrotic changes, chondroid metaplasia, and calcification reduce the elasticity of the ligaments, wich may thus bulge into the spinal canal in the standing position even if they are normal in thickness, which could explain why we found statistically significant differences between the groups in age and histopathological changes.<sup>10,11</sup>

Debility of the study is the sample, is small and we don't have the same number of patients in each group and we don't have a control group. Because of these limitations, our results should be interpreted with caution. In addition, it is important to note our analysis

did not focus on the mechanism of the development of spinal stenosis.

Degeneratives changes in LF may occur as a result of elastic fiber misalignment, the instability in DS cause the degenerative changes observed in LF. Further studies determining the pathogenesis of LSS are needed.

## Conclusions

LDS present more degeneratives changes like fragmentation of collagen fibers, cyst degeneration and fibrillar appearance, than the other groups and these is caused by instability.

The group of LDH present degenerative changes despite belonging to a younger age.

There is not evidence of cellular hypertrophy in the histopatological analyses, thickening of the LF can be seen by bulking of LF followed by collapse of motion segment.

## References

1. Zhong ZM, Zha DS, Xiao WD, et al. Hypertrophy of ligamentum flavum in lumbar spine stenosis associated with the increased expression of connective tissue growth factor. *J Orthop Res.* 2011; 29: 1592-7.
2. Altinkaya N, Yildirim T, Demir S, Alkan O, Sarica FB. Factors associated with the thickness of the ligamentum flavum: is ligamentum flavum thickening due to hypertrophy or buckling? *Spine (Phila Pa 1976).* 2011; 36(16): E1093-7.
3. Sairyo K, Biyani A, Goel VK, et al. Lumbar ligamentum flavum hypertrophy is due to accumulation of inflammation related scar tissue. *Spine (Phila Pa 1976).* 2007; 32: E340-7.
4. Kosaka H, Sairyo K, Biyani A, et al. Pathomechanism of loss of elasticity and hypertrophy of lumbar ligamentum flavum in elderly patients with lumbar spinal canal stenosis. *Spine (Phila Pa 1976).* 2007; 32: 2805-11.
5. Altun Idiris ZYK. Hitopathological analysis of ligamentum flavum in lumbar spinal stenosis and disc herniation. *Asian Spine J.* 2017; 1(11): 71-4.
6. Yoshida M, Shima K, Taniguchi Y, Tamaki T, Tanaka T. Hypertrophied ligamentum flavum in lumbar spinal canal stenosis: pathogenesis and morphologic and immunohistochemical observation. *Spine (Phila Pa 1976).* 1992; 17: 1353-60.

7. Yoshiiwa T, Miyazaki M, Notani N, Ishihara T, Kawano M, Tsumura H. Analysis of the relationship between ligamentum flavum thickening and lumbar segmental instability, disc degeneration, and facet joint osteoarthritis in lumbar spinal stenosis. *Asian Spine J*. 2016; 10(6): 1132-40.
8. Fukuyama S, Nakamura T, Ikeda T, Takagi K. The effect of mechanical stress on hypertrophy of the lumbar ligamentum flavum. *J Spinal Disord*. 1995; 8(2): 126-30.
9. Trigg SD, Devilbiss Z. Spine conditions: lumbar spinal stenosis. *FP Essent*. 2017; 461: 21-5.
10. Postacchini F, Gumina S, Perugia D, DeMartino C. Ligamenta flava in lumbar disc herniation and spinal stenosis. Light and electron microscopic morphology. *Spine (Phila Pa 1976)*. 1994; 19(8): 917-22.
11. Kumar V, Abbas A, Aster J. *Robbins basic pathology*. 10th ed. Philadelphia: Elsevier, 2018. p. 48.