American Journal of Medicine and Medical Sciences 2020, 10(4): 229-232
DOI: 10.5923/j.ajmms.20201004.13

Etiology and Pathogenesis of Intervertebral Disc Degeneration

Isroilov Rajabboy[1,*], Makhkamov Nosirzhon[2], Ermatov Nizom[3]

[1]Republican Pathological Anatomical Centre, Uzbekistan
[2]Tashkent Medical Academy, Tashkent, Uzbekistan
[3]Andijan State Medical Institute, Uzbekistan

Abstract This paper presents data on the etiology and pathogenesis of degenerative changes in the intervertebral disk. At present, it is established that the chronic inflammatory process is formed in the places of local decrease of oxygen supply. Taken together, these conditions contribute to the reduction of cells in the disc controlling the matrix and degenerative processes become irreversible. Polymorphism was also detected in genes encoding MP-3 and a correlation with an increased risk of degenerative changes in elderly patients was found. In the pathogenesis of degenerative changes there are mechanical effects, changes in the composition of extracellular matrix, reaction of proinflammatory cytokines, neurotrophin expression in degenerating disc, and activation of matrix metalloproteinases.

Keywords Spine, Intervertebral disk, Hernia, Protrusion, Degeneration

Insufficient nutrient supply in the disk cells is one of the most important factors contributing to the emergence of degenerative changes. N.A. Horner and J.P.G. Urban [16], studying the survival of disk cells in various conditions, have proved that if an adequate amount of glucose and oxygen is not supplied or the optimal pH level is not maintained, the disk cells die and stop producing proteoglycan molecules, the disk loses water and dehydrates. Insufficient supply of nutrients begins with an idiopathic loss of vessels in the end plate, which is the only source of nutrients in the gelatinous nucleus, and calcification of the end plate [17,32,56]. Not only is the movement of nutrients strenuous, but the outflow of metabolism products, in particular lactate, whose concentration is becoming critical, also slows down [38]. Oxygen concentration decreases to the center of the disc, and lactic acid content increases, which causes "acidification" of the medium in the disc center [19,25,39,42,54]. At present, it is established that the chronic inflammatory process is formed in places of local decrease of oxygen supply [20,33,44,58]. Together these conditions contribute to the reduction of the number of cells in the disc controlling the matrix. Degenerative processes become irreversible mechanical effects.

For a long time, excessive strain, smoking and obesity were considered to be the causes of intervertebral disc degeneration. Currently, experimental and epidemiological studies have shown that these factors alone do not often lead to disc degeneration [21,36,57]. A direct correlation between the appearance of degenerative processes, intensity and frequency of intervertebral disk loading has not been established. On the contrary, the synthesis of proteoglycans increases with increasing rational physical activity [22].

Genetic factors of intervertebral disc degeneration. In studies involving twins, it was noted that along with physical activity, an important role in the emergence of degenerative processes in intervertebral discs is inherited predisposition [23], which is manifested in 52-74% of observations and increases with age [21,24]. Genetic predisposition is manifested by polymorphism of genes encoding extracellular matrix proteins. The polymorphism affecting collagen was mainly found in genes encoding collagen type I, II and IX [25-29].

The polymorphism affecting the gene encoding aggregan contributes to the risk of early disc degeneration at many levels [30,31]. Mutations in collagen type IX have recently been associated with mutations in the non-collagen protein of the matrix (the intermediate protein of cartilage layers - OYR). It is assumed that OYR participates in the regulation of the signaling pathway of tumor growth factor B (FRB) and that this regulation is of leading importance in the etiology and pathogenesis of disc degeneration [32]. However, it is not only polymorphism in genes encoding matrix proteins that are associated with disc degeneration. Recently, a connection between degenerative changes and mutation in pro-inflammatory cytokine IL-1 [33,34] and IL-6 has been found.

* Corresponding author:
NizomErmatov@tma.uz (Isroilov Rajabboy)
Published online at http://journal.sapub.org/ajmms

Polymorphism in genes encoding MP-3 has also been detected and a correlation with an increased risk of degenerative changes in elderly patients has been established [36]. The polymorphism was also detected in the gene encoding the vitamin D receptor [37]. The results of the scientific research testify to the importance in the formation of degenerative changes in intervertebral disks of genetic disorders. Genetic disorders result in the disturbance of matrix proteins balance, their synthesis, as well as the regulation of the inflammatory process, which in the presence of inadequate external factors promotes the progression of degenerative changes in the intervertebral disk. In the presence of genetic predisposition, the tissue is weakened and trauma may occur even when average exposure is applied [38].

Change of composition of the extracellular matrix. The thickness of the disk decreases due to reduced synthesis of proteoglycan in the gelatinous nucleus reduced hydration. Non-enzymatic collagen glycosylation, which occurs during normal protein functioning and contact with glucose or other reducing monosaccharide, is also essential in the progressive reduction of disk thickness. Chemical condensation is a reaction of the amine-group compound) and aldehyde (SNO-group). Aldehyde is usually added to the free NH2 group of the end amino acid or one of the available E-amino groups of extra lysine (in most proteins). The glycosylated derivatives are oxidized to form a more stable carboxymethyllysine (KML) molecule. This process, like the loss of aggrecane molecules, reduces disc thickness and promotes cracking. The more active the process is, the less blood supply and oxygen concentration are [1,32].

Proinflammatory cytokine reaction in degenerating disc. In the study of disc tissue, it was found that its cells synthesize a large number of signal molecules involved in the pro-inflammatory and associated metabolic reactions. Among them are pro-inflammatory signal molecules of interleukins, including IL-1a, IL-1R, IL-6, tumor necrosis factor (TNF-a), granulocytic/macrophagal colony stimulating factor (GMCSF), IL-8, RANTES (regulated by activation, synthesized and secreted by T-lymphocytes) and IL-10. In addition to inflammatory signal molecules, inflammatory mediators are synthesized in the disc tissue: leukotrienes B4, thromboxane B2, prostaglandin E2 and, accordingly, the enzymes involved in these signal reactions (phospholipase A2 and COX-2). The expression of cytokine receptors on disk cells indicates that these cells not only initiate the signal, but also have mechanisms for an adequate response to pro-inflammatory mediators. Some researchers provide strong evidence that chondrocyte-like cells of the jelly-like nucleus are the source of pro-inflammatory mediators in the degenerating disc. A relationship has been established between the level of pro-inflammatory cytokines, IL-6 and IL-8 and the severity of pain syndrome [5,14,36], which indicates the likely involvement of pro-inflammatory cytokines not only in degenerative processes in the disc but also in the formation of pain syndrome.

Activation of matrix metalloproteinases. Disorganization of the disk matrix is one of the main signs of its degeneration. Accordingly, collagen, proteoglycans and fibronectin components of the pattern in the disk cells produce enzymes that specifically destroy these components. The most studied are metalloproteinases (MPs) - pro-theases that destroy different types of collagen [19]. In degenerating disk the expression of all classes of proteinases -1, -2, -3, -9 is activated. Using disk cells isolated in different animals as well as humans, it has been shown that cells synthesize MF in vitro spontaneously, under hydrostatic pressure [1] or when stimulated by IL-1 [2]. In addition to regulating expression, MF activity is also regulated at the posttranslational stage; in particular, they bind to the MF tissue inhibitor (TIMP), which regulates the amount of free proteinase [3]. The research results confirm that MF expression is accompanied by an increase in the level of TIMP [4]. Degeneration of discs increases the expression of TIMP-1 and TIMP-2, and the expression of TIMP-3 practically does not change [5]. In some studies of degenerative processes, an imbalance of TIMP-1 and MP-3 has been found [6].

In addition to collagen, the main proteoglycan, aggregican, also degrades in degeneration. At present, the proteins destroying aggrecan are insufficiently studied; it is known that aggrecanase 1 is involved in this process [7]. Besides MF, another important group of proteinases - cathepsins - is also capable of splitting collagen and proteoglycans. It has been shown that the activity of D, L, K, and G cathepsins in the degenerating disk increases. This is due to separation of the end plastics and disorganization of the fibrous ring [8]. Inflammatory cytokines and growth factors play a certain role in regulation of cathepsin activity [9]. Although MF and catheapsin substrates intersect to a great extent, it is noted that MF are active at neutral pH, while catheapsins are maximally active in an acidic medium [10].

The property of the cathepsins to be activated in an acidic medium may be necessary for the late stages of degeneration when the accumulation of lactate in disk tissue causes "acidification" of the medium.

Activation of neurotrophin expression in degenerating disc. Normally, the intervertebral disk is devoid of innervation. Nerve fibers are detected only in the uppermost layers of the fibrous ring and the end plate above the gelatinous nucleus [11]. When the intervertebral disk degenerates, vessels and nerves grow into the fibrous ring and jelly nucleus. The expression on ingrowing nerve fibers Trk A and B - receptors of nerve growth factor (NGF) and BDNF has been shown, which indicates the sensitivity of these nerve endings to NGF [12]. Neurotrophins NGF and BDNF - survival and activation factors of anabolic processes in nerve cells - are excreted not only by nerve cells but also by intact cells of various tissues, including cartilage. In degenerating intervertebral disk, NGF is synthesized by chondrocyte-like cells of fibrous ring and cells of jelly nucleus [13]. The correlation between the degree of degenerative processes severity and expression of NGF and BDNF has been established [14]. It is supposed that in

degenerating disc, the activation of neurotrophin synthesis is connected with an inflammatory reaction. Thus, Y. Abe and co-authors [15] proved the activation of gene expression and NGF protein secretion after treatment of IL-1P and BDNF cells. These results, as well as data on the increase in the synthesis of pro-inflammatory cytokines in a degenerating intervertebral disk, suggest a connection between these processes and the formation of pain syndrome. Since new nerve fibrils are only found in the disc in pain syndrome, it can be argued that their formation is a characteristic feature of the degenerating disc. Available evidence on the presence of growth factors in the degenerating disc in pain syndrome confirms that a striking effect can be achieved by inhibiting the NGF action from blocking the pain syndrome.

REFERENCE

[1] Vitko, N.K. Clinical and radiation diagnostics of degenerative-dystrophic changes of the lumbar spine: Autoref. dis. cand. med. Science / N.K. Vitko. Obninsk, 1997 – p.23.

[2] Voronina, T.A. Mechanism of Action and Justification of Mexidol Application in Neurology / T.A. Voronina, L.D. Smirnov, I.I. Goreinova // Scientific and Practical Conference on Neurology. M.-2000. - pp. 2-4.

[3] Gerasimova, M.M. Cytomedina in complex therapy of the lumbar-sacral radiculopathies (in Russian) / M.M. Gerasimova // Cortexin. Five years' experience of domestic neurology; under edition of A.A. Skoromtsa, M.M. Diakonov. - Spb: Science. 2005. - pp. 156-167.

[4] Glanz, S. Biomedical Statistics: Per. of English. 1999. – p.459.

[5] Gusev, E.I. Plasticity of the nervous system / E.I. Gusev, P.R. Kamchatnov // Journal of Neurology and Psychiatry. S.S. Korsakov Journal of Neurology and Psychiatry (in Russian). -2004. №3. pp. 73-79.

[6] Dutton, C.S. Basics of osteopathy / C.S. Dutton. Almaty. -1998. -p.59.

[7] Jones, D.M. Strain-Contrastrain: Osteopathic system of diagnosis and treatment (in Russian) / D.M. Jones // Osteopathy-medicine of the XXI century (info bulletin of Russian Osteopathic Association). -1998. -pp.22-23.

[8] Drivotinov, B.V. Autoimmune reactions role in pathogenesis of relapses and remissions of the root pain syndrome in lumbar osteochondrosis (in Russian) // Peripheral nervous system. Minsk (in Russian) // Peripheral nervous system. - 1978. - Exhibit 1. - pp.62-67.

[9] Drivotinov, B.V. Manual therapy for neurological manifestations of lumbar osteochondrosis (literary review) / B.V. Drivotinov, D.S. Ban // Meditsinskii zhurnal. 2006. -№1. - pp. 19-22.

[10] Jarkov, P.L. Osteochondrosis and other dystrophic changes of the spine in adults and children / P.L. Zharkov. Moscow: Medicine, 1964.-p.191.

[11] Jarkov, P.L. Shape of the cervical spine in different age periods / P.L. Zharkov, V.M. Fedosov // Archive of anatomy. №5. - 1989. - pp. 35-37.

[12] Jarkov, P.L. Osteochondrosis and other dystrophic changes of the spine in adults and children / P.L. Zharkov. Moscow: Medicine, 1994. -p.240.

[13] Zhulev, N.M. Osteochondrosis of the spine: Manual / N.M. Zhulev, Yu.D. Badzgaradze, S.N. Zhulev. St. Petersburg: Lan, 1999. – p.592.

[14] Zaslavsky, E.S. Pain muscular-dystrophic syndromes (etiology, pathogenesis, clinic, treatment): Author's thesis of Dr. med. M., 1980. – p. 34.

[15] Zinyakov N.T., Zinyakov H.H. To the question of classification and terminology of hernia of intervertebral discs / N.T. Zinyakov, H.H. Zinyakov (in Russian) // Manual therapy. 2007. - №3 (27). - pp. 22-28.

[16] Ignatov, Yu.D. Neurophysiological mechanisms of pain (in Russian) / Yu.D. Ignatov, A.A. Zaitsev // Pain syndrome. JL, Medicine, 1990. -pp. 7-65.

[17] Klimenko, A.B. Atlas of manual therapy techniques for spinal osteochondrosis / A.B. Klimenko, A.A. Skoromec, M.O. Screamer. A.B. Klimenko, A.A. Skoromez, M.O. Vykrykach. - 1995. – p.189.

[18] Klushnik, T.P. Autoantibodies to the factor of nerve growth at nervous psychic diseases and disorders of nervous system development / Autoref. d.d., MD. Moscow, 1997.-p.47.

[19] Kogan, O.G. Immunopathological aspects of spine osteochondrosis and its neurological syndromes. Problems of autoal lergy / O.G. Kogan. Tallinn, 1975. - pp. 224-225.

[20] Colo T., Vereien M. Practical manual on osteopathic manipulations / T. Colo, M. Vereien. 2003. P.199.

[21] Korshunova, E.Yu. Cytokine Profile in Patients with Scar-Safe Epiduritus / E.Yu. Korshunova, L.A. Dmitrieva, Sorokovikov, Z.V. Koshkareva, O.V. Sklarenko (in Russian) // Neurological bulletin. 2009. - T. XLI. - V.A. Dmitrieva, L.A. Dmitrieva, Sorokovikov, Z.V. Koshkareva, O.V. Sklyarenko // Neurological Gazette. 2009. 2. - pp. 29-33.

[22] Kryzhanovsky, G.N. General pathophysiology of nervous system: Manual / G.N. Kryzhanovsky. M: Medicine 1997.

[23] Kuznetsov, V.F. Stenosis of the lumbar spinal canal (a new concept in vertebrology) / V.F. Kuznetsov. - Minsk: Nauka I tekhka, 1992. P.52.

[24] Kukushkin, M.JL Neurogenic pain syndromes. Based on materials published in the "European Journal of Pain" (2002) / M.JI. Cuckoo // Pain. 2003 в. - №1 (1). pp. 69-71.

[25] Levit, K. Manual Medicine / K. Levit, J. Zahse, V. Yanda. Moscow: Medicine, 1993. – p.511.

[26] Treatment of lumbar spondylogic neurological syndromes/ Edited by A.A. Skoromtsa // SPb.: Hippocrates, 2001. p.160.

[27] Lindenbraten, L.D. Basic Clinical Syndromes and Tactics of Radiation Screening / L.D. Lindenbraten, A.B. Zubarev, V.V. Kitaev, A.I.Shehter. Moscow: "Vidar" Publishing House, 1997. – p. 321.

[28] Lobzin, B.C. Pain syndrome in diseases of nervous system / V.S., Lobzin // Pain syndrome; edited by V.A. Mikhailovich, Yu. - pp. 233-255.

[29] Lobzin, B.C. Dynamic Compression Radiculo-Neuropathy / B.C. Lobzin, N.M. Zhulev // Spondylogennye i myogennye daze nervnoi sistem. Syndromology of osteochondrosis. -Kazan, 1990. Pp. 9-13.

[30] Luvsan, G. Traditional and Modern Aspects of Eastern Reflexology / G. Luvsan. M., Nauka, 1986. – p.576.

[31] Lucik, A.A. Compression syndromes of osteochondrosis of the cervical spine.

[32] Lucik, A.A. Compression syndromes of osteochondrosis of the cervical spine / A.A., Lucik. Novosibirsk: "Publisher", 1997.-400 p.

[33] Radiation anatomy of the person / Under edition of T.N. Trofimova - SPb: "Publishing house of SPbMPP", 2005. 496 p.

[34] Malkov, S.S. Diagnostic tests and techniques of hip joint mobilization / S.S. Malkov, D.E. Mokhov, S.V. Novoseltsev // Manual therapy. 2009. - № 3 (35). -pp. 92 -102.

[35] Malkov, S.S. Lower extremity. Osteopathic diagnostics and treatment. S.S. Malkov, C.B. Novoseltsev, D.E. Mokhov, A.E. Prikhodko. St. Petersburg: S.S. Publishing House, St. Petersburg Un-ta, 2010. - 113 p.

[36] Mangal, R. Magnetic resonance tomography in traumatic and dystrophic lesions of the spine: Autoref. diss. cand. med. Science / R. Mangal. M., 1999. - 16 p.

[37] 36. Mokhov, D.E. Posturology in diagnostics of somatic dysfunctions / D.E. Mokhov, C.B. Novosel'tsev. St. Petersburg: "SPbMPMAPO Publishing House", 2011. - 56 p.

[38] Mokhov, D.E. Peculiarities of osteopathic diagnostics and treatment of lower limb kinetic dysfunctions / D.E. Mokhov,

[39] C.B. Novoseltsev, C.C. Malkov, A.E. Prikhodko // St. Petersburg: "Publishing House of SPbMPP", 2011. 102 p.

[40] Mokhov,... D.E. Osteopathic diagnostics and treatment of lumboishialgia caused by disturbed proprioreception of feet / D.E. Mokhov, C.B. Novosel'tsev (in Russian) // Traditional medicine. 2011. - № 2 (25).-pp. 34-40.

[41] Maitland G. Manipulations on the spine / G. Maitland. M.: Polygran Institute, 1992. - 176 p.

[42] V.N. Naboichenko, Manual therapy of internal organs. Book 1 / V.N. Nabochenko, V.N. Bindyukevich, I.V. Shinkarev. K.: "Attica" Publishing House, 2005. - 408 p.

[43] Nazarenko, G.I. Vertebrogenous lower back pain. Technology of diagnostics and treatment; under edition of G.I. Nazarenko / G.I. Nazarenko, I.B. Heroeva, A.M. Cherkashov, A.A. Rukhmanov. Moscow: OJSC "Publishing house "Medicine", 2008. - 456 p.

[44] Netter, F. Atlas of human anatomy, 4th ed. / F. Netter. Moscow: GOTAR-Media, 2007. - 624 p.

[45] Novosel'tsev, C.B. Osteopathy as a method of the lumboishialgium treatment (in Russian) / S.V., Novosel'tsev. Kazan: KSMU, 2001. - pp 96-97.

[46] Novoseltsev C.B. Osteopathy. Main methods of treatment and self-help. - St. Petersburg, Nevsky Prospekt, 2003. – 160p.

[47] Novoseltsev, C.B. Position rolliz / C.B. Novosel'tsev // Proceedings of the International Congress "Reflexotherapy and Manual Therapy in the XXI century". (19-21 May 2006). Moscow, Russia. 2006. - pp. 273-275.

[48] Novoseltsev, C.B. Introduction to osteopathy. Craniodiagnostics and correction techniques (in Russian) / C.B. Novoseltsev. St. Petersburg, OOO "Publishing house Foliant", 2007. – 344p.

[49] Novoseltsev, C.B. Osteopathic approach to the neurological manifestations treatment in patients with degenerative-dystrophic changes in the lumbosacral spine (in Russian) / C.B. Novosel'tsev // Manual therapy. 2008. - № 2 (30). - pp. 25-28.

[50] Novoseltsev, C.B. Crucifixion. Anatomical-functional relations and roles in the biomechanics of a human body (in Russian) / C.B. Novosel'tsev, D.B. Simkin (in Russian) // Manual therapy. 2008. - № 3 (31). - pp. 89-99.

[51] Novoseltsev, C.B. Diagnostic tests and methods of the sacroiliac joint mobilization (in Russian) / C.B. Novosel'tsev (in Russian) // Manual therapy. 2008. - № 4 (32). - pp. 78-84.

[52] Novoseltsev, C.B. Introduction to osteopathy. Soft tissue and joint techniques (2nd ed.) / C.B. Novoseltsev. St. Petersburg: "Publishing House Foliant" LLC, 2009. - 320 p.

[53] Novoseltsev, C.B. Biomechanical disorders in patients with lumbar disc hernia and their osteopathic correction / C.B. Novosel'tsev, D.B. Yesterday // Manual therapy. - — 2009. -№3 (35). pp. 64-72.

[54] Novoseltsev, C.B. Pathogenetic mechanisms of lumbar spondylogic neurological syndromes formation in patients with lumbar disc herniations (in Russian) / C.B. Novosel'tsev (in Russian) // Manual therapy. 2010. - № 3 (39). - pp. 77-82.

[55] Novoseltsev, C.B. Basics of conservative treatment of patients with lumbar intervertebral disc hernia (in Russian) / C.B. Novosel'tsev, E. JI. Malinovsky. St. Petersburg: "Publishing House Foliant", 2011. - 272p.

[56] Novoseltsev, C.B. Manual therapy of spondylogenous pain syndromes in hernia and protrusion of intervertebral disks / C.B. Novosel'tsev, E.L. Malinovsky, V.V. Smirnov, M.V. Savvova, V.V. Lebedeva (in Russian) // Manual therapy. 2011. - № 3 (42). - pp. 24-31.

[57] Novoseltsev, C.B. Peculiarities of the biomechanical disorders in the spine at protrusions and herniations of the intervertebral disks (in Russian) / C.B. Novosel'tsev, E.L. Malinovsky, V.V. Smirnov, M.V.