STRUCTURE, FUNCTIONS AND ROLE OF ENDPLATES IN THE DEVELOPMENT OF DEGENERATIVE DISEASES OF THE SPINE: A LITERATURE REVIEW

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The endplate is crucial for maintaining normal functioning of a healthy intervertebral disc. It provides structural support of the spine and regulates the flow of nutrients and the metabolic processes in the disc. With age and in the pathogenesis of diseases, the cartilage undergoes degeneration and calcification thus disrupting the access of nutrients to the cells and altering the biochemical and morphological structure of the endplate and metabolic processes throughout the disc. A number of evidences points to the existence of the endplate innervation, so its damage can be a source of chronic low back pain. The presented literature review highlights the questions of anatomy and physiology of vertebral endplates and describes relationships between changes in their morphological and molecular structures and degenerative lesion of intervertebral discs and chronic back pain syndrome. The material of the study included abstracts of articles from the PubMed database, articles published in The Journal of Bone and Joint Surgery, Spine, European Spine Journal and in other journals over the past 15 years. If necessary, books and articles of previous years were used.

Key Words: intervertebral disc, endplate, structure, functions, degeneration, chronic low back pain.

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The spine, as a link in the biomechanical chain of the musculoskeletal system, experiences significant stress. The main dynamic element of the spine is the intervertebral disc (IVD). The main mechanism leading to the development of IVD pathology is low regenerative potential of cells, which is associated with a decrease in the blood supply in people older 20–25 years of age. The main structure responsible for IVD metabolism is endplates. They are anatomically located in the caudal and cranial regions of the vertebral body and represent a bilayer consisting of cartilaginous and bone tissues. The bone part of the endplates is located on the side of the vertebral body, while the cartilaginous (hyaline cartilage) part is localized on the IVD side. These structures are mechanically robust and at the same time permeable, which provides the exchange of metabolites between cells, the intercellular substance of the IVD and the vascular network of the vertebral body. In a healthy disc, endplates protect the hydrated nucleus pulposus from prolapse into the cancellous bone of the vertebral body and simultaneously absorb the hydrostatic pressure that results from mechanical loading on the spine [46]. Endplate damage can lead to the development of a local pathological response in the form of inflammation, which can further result in the subsequent degenerative processes in the IVD [3]. Taking into account the fact that the bone part of the endplates contains nerve endings, impairment of its structure of various etiologies can lead to the development of pain in the spine [17, 36].

The aim of the study is to analyze currently available literature data on the structure and functions of the endplates as well as their role in the development of degenerative diseases of the spine and the genesis of vertebrogenic pain syndrome.

Endplate structure

The endplate is a bilayer formation, which consists of cartilaginous layer and subjacent subchondral bone. However, in most discussions, it is broadly considered as a thin layer of hyaline cartilage located between the vertebral body bone and IVD tissues. The thickness of the cartilaginous layer of the endplate varies from 0.1 to 2.0 mm [29, 41, 55] and is known to depend on the vertebra position and level: it is thinner in the center and upper levels of the spine and thicker in the periphery and in the vertebrae of the lower regions [56]. Cartilage of the endplate is not connected to the vertebral bodies, and the direct connection with the IVD is carried out through the lamellae of the medial sections of the fibrous ring [31, 44, 65].

As in case of the articular cartilage, extracellular matrix of the endplate cartilage contains the gel of hydrated molecules of proteoglycans stabilized by a network of type I and II collagen fibrils [60]. After maturation of the skeleton, the cell population consists mainly of chondrocytes. Taking into account the characteristics of the cells and the biochemical composition of the extracellular matrix, the structure of the endplate cartilage is similar to the hyaline cartilage of the joints but without a distinct zonal structure. In addition, endplate cartilage is distinguished by the organization of collagen fibers: collagen fibers are oriented in different directions in different zonal regions of healthy articular cartilage, while they are located horizontally, i.e., parallel to the vertebral bodies, in the cartilage [74].

The biochemical composition of the endplate cartilage is crucial for the normal functioning and structural integrity of the IVD. Unlike the articular cartilage, the large proteoglycan of the endplate, aggrecan, is shorter, with its molecular dimensions varying greatly [5, 12, 60]. Proteoglycans determine water content and regulate the transport of nutrients and metabolites to the IVD. In addition, a decrease in the content of proteoglycans in the endplate cartilage and a decrease in its permeability lead to a decrease in the content of these molecules in the adjacent nucleus pulposus, which causes changes in the IVD structure [6, 58, 65].

Biomechanical function of the endplate

In axial compression on the spine, the pressure inside the IVD affects not only the overall shape of the disc, but also deforms the endplate. Young healthy cartilage of the endplate can restore its shape after a moderate loading [17, 44, 47].

Biochemical composition determines the biomechanical properties of cartilage, i. e., its ability to withstand load or deformation. Excessive mechanical load, especially the one that has been applied repeatedly, can lead to a change in the tissue architecture, conditions of cell functioning and, consequently, changes in the biochemical composition of the endplate. It is also associated with a disorder of viscoelastic characteristics of the tissue. As it has been shown by Fields et al. [17], the biochemical composition of the endplate tissue significantly influences its stretching properties. The elastic modulus of the endplate cartilage significantly correlates with the collagen content in the tissue and the collagen to glycosaminoglycan ratio. Damage to the endplate structure reduces the elastic modulus and collagen to glycosaminoglycan ratio, i.e., the relationship between the molecular structure and tissue function is disrupted [17]. Thus, the structure of the endplate strongly depends on the biomechanical load exerted on it, and the ability of the endplate and IVD tissue to withstand mechanical stress: structural integrity of the matrix and physiological balance of collagen, proteoglycans and water content in it.

Thickness, porosity and curvature are important structural determinants of the biomechanical function of the endplate: thick, dense endplates with a high degree of curvature are stronger than thin, porous and flat endplates [35, 40, 50, 75]. Compression load affects the overall shape of the IVD and also deforms the endplate cartilage and the subjacent cancellous bone of the vertebral bodies [44, 47]. Moreover, the mechanical damage to the spinal motion segment always begins with increased mobility of the endplate (detachment from the adjacent bone), which is confirmed by histological studies [30, 31, 47].

Role of the endplate in the IVD nutrition

IVDs of an adult human are devoid of blood vessels. In addition to poor blood supply in external layers of the fibrous ring, the nutrient supply of mature IVD almost completely depends on the diffusion of dissolved substances through the endplate cartilage due to the concentration gradient between the blood plasma and the tissue matrix [25, 45, 61, 64, 72]. Transport of metabolites through the endplate is the main route of nutrient supply to the cells of the nucleus pulposus [25, 58, 59]. Blood vessels and lacunae of the bone marrow are adjacent to the cartilage layer of the plate [44, 63] and form channels for glucose and oxygen supply to the IVD and removal of metabolic products from it. The intensity of metabolic flows through the endplate cartilage depends on direct contact with the channels of the red bone marrow of the vertebrae or the vessel rudiments. Furthermore, the central region of the endplate is vitally important for metabolic processes in the IVD matrix, since this is the region where the endplate cartilage is the thinnest, while the adjacent microscopic blood vessels are the most numerous [71, 72, 75].

Substances of small molecular sizes (glucose, lactate and oxygen) pass through the IVD matrix mainly by diffusion, while larger molecules can be transported with a convective flow of the fluid created by mechanical compression of the IVD and restoration of its volume after load reduction. Therefore, the endplate structure must balance the opposite biophysical requirements: it must be rigid in order to withstand mechanical destruction and at the same time sufficiently permeable in order to improve nutrient transport efficiency. Thin, porous parts of the endplate can contribute to the normal functioning of the IVD, while thick and impermeable plates contribute to vertebral integrity [7, 44, 54, 75].

There are other factors affecting the transport of substances in the IVD matrix. Theoretically, the dissolved substances can diffuse freely into the IVD through the fibrous ring or the endplate. However, the actual transport of metabolites directly depends on the molecule size and its ionic charge [47, 64]. High concentration of proteoglycans endows the tissue of normal IVD with a general negative charge, which means that small uncharged solutes (glucose and oxygen) diffuse relatively freely. Negatively charged molecules (ions of sulfate and chloride) cross the endplate matrix relatively easily but hardly diffuse into the tissue of the nucleus pulposus. Positively charged cations (sodium and calcium) freely penetrate into the tissue. Larger

uncharged solutes (immunoglobulins and macromolecules, including enzymes), as a rule, are difficult to penetrate into a healthy IVD due to their size. Apparently, there are two more important factors affecting the diffusion of solutes in the IVD: proximity of the vessels to the endplate region and the structural properties of the dissolved substances. The cartilage significantly mineralizes with age [21, 59], i. e., the tissue structure in the endplate and subchondral bone region undergoes reconstruction, and this can cause a change in the flux of dissolved substances between the IVD and the red bone marrow of the vertebral body [47]. This will inevitably lead to a change in the cell functioning conditions and, as a consequence, remodeling of the IVD tissue.

The mechanical stress also affects the transport of nutrients into the IVD. Most of the scientific facts on the transport of nutrients to the IVD have been formed using the method of mathematical modeling. Theoretical modeling, alongside with a few in vivo experiments, often yields contradictory results. Malandrino et al. [45] reported that mechanical loading enhances the transfer of nutrients to the IVD by reducing its height. Jackson et al. [38] state that the compressive mechanical stress reduces nutrient transfer due to a decrease in the diffusion coefficient in the extracellular matrix as a result of a decrease in tissue porosity. In addition, Gullbrand et al. [27] studied the transport of substances to the IVD in rabbits and reported the possibility of increasing or decreasing the rate of nutrient transfer by varying the load amount. Giers et al. [18] confirmed the role of the endplate as the main transport point for substances in the IVD in experiments in vitro with pig discs. Compressive loads, especially static ones, practically do not change the intensity of dye flows to the IVD, while stretching reduces the short-term transport of substances, i.e., the mechanical load can cause changes in the substance transport under certain conditions.

Age-related changes in the endplate structure

The typical changes in the structure of the endplate cartilage during aging are similar to the general characteristics of the age-related rearrangements in all IVD tissues: decrease in the content of water, proteoglycans and type II collagen, accumulation of types X and I collagen. As a result, the endplate cartilage is gradually thinned and calcified [5, 21, 32, 48]. Low water content in the endplate cartilage at the age of 5–15 years can be due to a decrease in the concentration of proteoglycans [5]. The ability of these compounds to retain water creates high hydrostatic pressure in the cartilage, the decrease in which plays a certain role in the endplate structure damage [62, 63], since it is a potent regulator of the functional activity of chondrocytes [43, 44, 67, 70]. Histological and radiological studies have revealed changes in the structure of the endplate matrix in healthy adults compared to children [44]. Phases of maturation and aging (at the age of 15–40 years) are characterized by a general decrease in the synthetic and proliferative activity of cells. Aging cells can provoke the development of degeneration by reducing the intensity of anabolism or increasing catabolism activity [29]. For this reason, age-related changes in the endplate tissue take place in parallel with IVD degeneration. Such morphological, histological and molecular changes are launched by the second decade of life [5, 29, 44, 58].

Although the specific mechanisms determining changes in the endplate structure remain unclear, age-related changes coincide with degenerative processes in the IVD. As a rule, a marker of chondrocyte hypertrophy (for instance, type X collagen) is actively expressed during this period [5]. Rodriguez et al. [58] studied endplate mobility in the human spine, its permeability, the number of cells, and the content of glycosaminoglycans in the nucleus pulposus and concluded that instability of the endplate in the IVD system, a decrease in the synthetic activity of cells and the content of extracellular matrix molecules with age are the conditions for development of degenerative changes.

Cartilage calcification is detected on X-ray images in the form of a sclerosing surface [74]. Permeability of the endplate, as well as the diffusion of nutrients in the IVD, decrease under such conditions and accelerate its degeneration. Calcification is probably due to an increase in the free calcium content in the microenvironment of the endplate, which can originate from the subjacent cancellous bone of the vertebral body [21]. For instance, Grant et al. [21] noted that an increase in the concentration of free calcium significantly changes the metabolic processes in the tissue: it suppresses the synthesis of collagen and proteoglycans, promotes degradation of proteoglycans through activation of catabolic enzymes, positively regulates the activity of alkaline phosphatase, and increases the expression of osteogenic markers in the endplate cartilage.

The origin of age-related changes in the endplate structure may be the appearance and accumulation of lesions that arise as a result of mechanical loading, morphological features of the local cartilage structure as well as the state of the IVD. Endplates in the cranial part of the vertebral bodies are known to be thinner and supported by a less dense cancellous bone [75]. Damage often occurs in the central part of the endplate, which is the thinnest and weakest part [16, 19, 20, 59, 75]. Accumulation of lesions can lead to the appearance of local vulnerable spots (locus minoris resistentiae), in which microfractures subsequently appear. As a result, the endplate becomes thinner and porous, which is accompanied by a decrease in its rigidity and strength [49, 59]. Endplate degeneration leads to changes in the IVD tissue structure typical for degeneration processes, since abnormal pressure can inhibit the IVD cell metabolism and accelerate the breakdown of the matrix architecture [2, 28, 37, 43, 67]. Defects of the endplate structure may impede nutrient transfer to the cells of the nucleus pulposus [72] or provoke inflammatory reactions in IVD or in the whole spine [54].

Endplate degeneration

The nutrient medium inside IVD significantly affects cell viability, the rate of their proliferation and their energy metabolism [8, 9, 26, 32, 34, 64]. One of the factors that can trigger the development of IVD tissue degeneration is the disruption of nutrient intake resulting in a decrease in oxygen tension, glucose concentration or pH (due to the increase in lactate concentration). As a result, the number of viable or functionally active cells decreases, as well as their ability to synthesize matrix proteins (e.g., collagen and proteoglycans) and maintain homeostasis of the extracellular matrix. Thus, the conditions for triggering IVD degeneration process arise [25, 32, 33, 37, 42, 64, 71]. The origin of the development of these events can be impaired permeability of the vertebral endplates. Most researchers consider such impairment as the main cause of IVD degeneration, since the endplates can block rapid exchange of liquids, metabolites and convection of solutions [22, 25, 72]. Impaired permeability of the endplate can develop as a result of cartilage calcification [17, 30, 52, 58, 61], subchondral bone sclerosing [58], weakening of the IVD as a result of its mobility developed due to the separation of the cartilaginous element from the vertebral body that occurs in people at the third decade of life [31, 58, 59] as well as due to the closure of endplate pores [7]. Excessive compression forces also provoke degeneration, since severe loads reduce the volume of the vascular bed in the bone part of the endplate [7, 30].

Degenerative processes change the structure of the endplate extracellular matrix: the cartilage is thinned; the activity of the synthetic processes in the cells, as well as the content of proteoglycans, collagen and water, decreases; calcification develops [5, 44, 57, 59]. Change in the biochemical composition of the endplate directly affects metabolite fluxes in IVD [4, 5, 68]. It is worth mentioning that a number of researchers [10, 15, 41, 51, 54] indicate activation of the angiogenesis processes in the subchondral bone and diffusion in IVD tissues in pronounced degeneration. The mechanisms underlying the degeneration/calcification of the endplate are not clear, but many details of this process are known: enhanced expression of aggrecanase (ADAMTS), matrix metalloproteases (MMP), type X collagen, alkaline phosphatase, and inflammatory cytokines such as interleukin-1 (IL-1) [11, 13, 14, 23, 24, 55, 73]. However, the causes of such biochemical changes have not been specified yet.

The search for an answer to this question led the group of researchers to the assumption that increase in the content of free ionized calcium (Ca^{2+}) in tissue affects homeostasis of the endplate, since the ion participates in the regulation of the synthesis of matrix proteins: types I and II collagens, proteoglycans, as well as aggrecanase activity [21, 45]. Moreover, Ca^{2+} positively regulates the activity of alkaline phosphatase and increases the expression of osteogenic markers [21]. The content of Ca^{2+} is consistently higher in the human endplate cartilage with manifestations of IVD degeneration. An increase in the Ca^{2+} level reduces secretion and accumulation of types I and II collagen and proteoglycans in cultured human endplate cells. Ionized calcium affects the synthesis of matrix protein by activating the calcium-sensitive receptor. In addition, the level of aggrecan (the largest proteoglycan of the endplate cartilage) is affected by aggrecanase activity because an increase in Ca^{2+} directly enhances its activity. Furthermore, experiments on IVD tissue cultures demonstrated that introduction of Ca^{2+} into the culture is enough to provoke the onset of degenerative processes: to increase endplate cartilage mineralization and decrease glucose diffusion in the IVD. The source of the intake of free calcium in IVD, as suggested by Grant et al. [21], can be the vertebral body that directly contacts with the endplate. Vertebral bodies contain a significant amount of the cancellous bone, which undergoes permanent reconstruction. Osteoporosis can serve as a probable cause of an increase in the Ca^{2+} yield in the immediate vicinity of an endplate, since the loss of bone mass is most pronounced in the spine. Ions of Ca^{2+} can penetrate into the endplate cartilage, which leads to its accelerated calcification and IVD degeneration. The authors believe that the preventive treatment of osteoporosis under IVD degeneration conditions may have a therapeutic potential.

Influence of endplate degeneration on the development of chronic lumbar pain

There are numerous possible sources of chronic vertebrogenic pain, but one of the most important is considered to be pathologically altered innervated endplates [1, 3, 17, 53, 68]. Nerve endings of degenerated endplates are additionally sensitized by chemical or mechanical stimuli. In addition, the concentration of receptors per unit area of an endplate is much higher than in adjacent IVDs [3, 17]. The theoretical basis for provoking discogenic pain is the mechanical stimulation of nociceptors by sensitized chemical derivatives. Sensitization of nociceptors within the external region of the fibrous ring can be achieved by increasing the pressure inside IVD. It is generally believed that nociceptors of the endplate can be activated in a similar way in case if their structure is weakened by damage [53]. Proliferation of blood vessels and nerve fibers was histologically detected in the subchondral bone of the endplates resected in patients with chronic lumbar pain, especially in the area of microdamage [5, 44]. The growth of nerve endings and vessels in the IVD is promoted by neurotrophic factors produced by cells under the influence of mediators of inflammation in the IVD [1, 3, 23]. In addition, IVD cells are able to produce pro-inflammatory cytokines and can themselves serve as nociceptive triggers [36]. Other signaling molecules that are small in size, such as leukotrienes, prostaglandins, and nitric oxide, are potent direct stimulators of nociceptors. By-products of the IVD cell metabolism, such as lactic acid, can also stimulate nerve endings. Dissolved substances are capable of freely diffusing within the IVD from the source of their formation to nociceptive receptors in the external region of the fibrous ring and the endplate [36].

At the present time, the question of the role of endplates in the development of chronic lumbar pain remains to be open. For instance, Spanish researchers studied the relationship between endplate degeneration and manifestations of lumbar pain in Southern Europeans on a sample of 300 patients with lumbar pain and without it by comparing the MRI data of the lumbar spine and clinical data as well [39]. A multifactorial regression logistic model has been developed with correction for gender, age, body mass index, life expectancy, the effect of smoking, physical activity, IVD degeneration, and the relationship between IVD degeneration and changes in the endplate structure in order to assess the relationship between changes in the endplate and manifestations of chronic lumbar pain. The results have shown that IVD degeneration was the only variable in the selected analysis model that affects lumbar pain manifestations and, as a consequence, changes in the endplate are not associated with chronic pain in Southern Europeans.

Williams et al. [69] established that Schmorl's hernias, as the most common types of endplate lesions, do not have a reliable association with back pain, as evidenced by epidemiological studies on a large population. However, traumatic and destructive types of damage to the endplate have a significant association with pain, as indicated by clinical observations [66].

Unlike IVD lesions, endplate damage is not considered as a cause of back pain in broad research studies. An explanation for this may be the impossibility to identify the type of endplate lesion by radiological methods in the absence of a unitary, systematized and generally accepted classification of these lesions. This makes the objective identification of the relation between pain and changes in the endplate difficult, which requires further research.

Conclusion

Endplates have a complex anatomical and physiological structure and a whole spectrum of different functions. The features of their molecular architecture and biochemical composition provide optimal viscoelastic properties. Endplates have an important role in maintaining the normal structure and physiology of IVD. The type and extent of endplate lesions, although to a different extent, directly affect the development of degenerative processes in the adjacent IVD. Identification of the role of endplate lesions as one of the causes of vertebrogenic pain is an important task. This knowledge can be used in practical medicine for understanding the pathogenesis of degenerative changes and possible targeted therapeutic effects.

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