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Pathophysiology of Temporomandibular Joint Arthritis: Review

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As for temporomandibular joint arthritis (TMJ OA), managing the contributing factors at an early stage through accurate diagnosis is necessary to prevent irreversible bone changes. TMJ OA, which is a multi-organ disease caused by various pathophysiological mechanisms, is developed mainly due to mechanical overload. It is a disease characterized by degeneration of articular cartilage and subchondral bone as a low-level inflammatory arthritis condition developed by dysregulation of catabolic and anabolic activity of chondrocytes. Age, mechanical overload sensing of cartilage, chondrocyte apoptosis, catabolic enzymes, inflammatory factors, abnormal remodeling of subchondral bone, and estrogens may be involved in the pathogenesis of arthritis. Therefore, a comprehensive evaluation is needed to diagnose and manage progressive cartilage degeneration, subchondral bone remodeling, and associated symptoms of TMJ OA.

Key Words: Pathophysiology; Temporomandibular joint; Temporomandibular joint arthritis; Temporomandibular joint disorder

INTRODUCTION

Temporomandibular joint arthritis (TMJ OA) affects 8%-16% of the population, is more common in women, and increases with age [1]. TMJ OA is described as a degenerative joint disease in the Diagnostic Criteria for Temporomandibular disorders (DC/TMD). The TMJ OA shows osseous changes and degeneration of surrounding tissues in one or both of the temporomandibular joints. In addition, the patients complain of crepitation on history taking. However, osteoarthritis is a disease with low sensitivity and specificity compared to other diseases defined by DC/TMD. Computer tomography scans of TMJ OA show erosion, sclerosis, pseudocyst, and flattening of articular eminence and/or condyle [2].

TMJ OA is a multifactorial disease that is caused by various pathophysiological mechanisms [3]. The temporomandibular joint is a complex organ composed of several tissues such as the masticatory muscle ligament, articular disc, bone, and cartilage. These constituent tissues interact with heredity, environment, nerves and hormones, which in turn causes TMJ OA [3]. Therefore, a comprehensive evaluation is needed to diagnose and manage progressive cartilage degeneration, subchondral bone remodeling, and associated symptoms of TMJ OA [4]. To this end, the mechanism and associated factors of TMJ OA are reviewed to establish the background data necessary for the early and accurate diagnosis of TMJ OA.

THE STRUCTURE AND BIOMECHANICAL PROPERTIES OF THE TEMPOROMANDIBULAR JOINT

The mandibular condylar cartilage is a multiple layered tissue that plays an important role in the function of the temporomandibular joint. Mandibular condylar cartilage reduces the load on the subchondral bone with the joint disc, and is composed of fibrocartilage unlike most of other joints. The fibrous layer of mandibular condylar cartilage is on its surface and consists of fibroblast-like cells. The proliferative layer, which is placed under the fibrous layer, serves to separate the fibrocartilaginous fibrous zone from the hypertrophic zones, and has a role as a cell reservoir. Under the proliferative layer, there is a hypertrophic zone, a calcified zone, and a subchondral bone zone. These tissues get nourishment from intra-articular synovial fluid and subchondral bone marrow [5,6]. The histological structure of articular eminence is similar to that of condyle. From the outermost layer, there is fibrous articular tissue, proliferative layer, chondrocyte in fibrous matrix, and bone of articular eminence layer [7].

In the structure analysis of biological molecules, chondrocytes are surrounded by a large amount of matrix macromolecules. The macromolecules are composed of proteoglycans, glycosaminoglycans (GAGs), and collagens of type I, II, IX, X, and XI. Hyaluronic acid (HA), a principal GAG, mainly maintains viscosity and causes a decrease in bio rheological properties. Proteoglycans are proteins which constitute the superficial zone of the articular catilage. These proteoglycans include lubricin and chondroitin sulfate substitution. Lubricin is a mucinous glycoprotein with a molecular weight of 345 kilodaltons (kDa) and contains a small amount of keratan. Chondroitin sulfate substitution is present in the superficial layer of articular cartilage and has a role of a boundary lubrication. The collagen fibers of fibrocartilage have tensile and shear strength. Type I collagen mainly presents on the surface of mandibular condyle, and type II and X collagen mainly present in hypertrophic zones which have characteristics of hyaline cartilage [8].

In cartilage which has the configuration explained above, anabolism occurs during dynamic loading, and catabolism occurs during excessive static loading. The resistance to compression depends on the density of proteoglycans. Besides, since most fibers of condylar cartilage travel forward and backward, the cartilage has good resistance to shearing stress, but poor resistance to viscous properties. In addition, when excessive shear stress occurs, the molecular weight of HA decreases and joint lubrication is destroyed [8,9].

PATHOPHYSIOLOGIC MECHANISM OF TEMPOROMANDIBULAR JOINT ARTHRITIS

1. Various Factors and Associated Mechanisms of Temporomandibular Joint Arthritis

TMJ OA was believed to be a cartilage disease, but is now considered as a multi-factorial disease of cartilage, bone (bone marrow), joint disc, ligament, muscle, and nerve [10].

1) Age

Calcium content of the articular disc increases with age. As the concentration of 6-sulfate disaccharide in chondroitin sulfate increases, the concentration of keratan sulfate, one of GAG, in human cartilage also increases with age. In addition, as the content of GAGs increases, the osmotic swelling pressure of cartilage increases, resulting in cartilaginous stiffness [11,12].

2) Mechanical overload

Mechanical overload is the main causative factor in the destruction of the mandibular condylar cartilage as in other synovial cartilages. Chondrocytes, especially hypertrophic chondrocytes, have evolved mechanoresponsive mechanisms, which, when activated, increase metabolism, initiate pathological mechanisms, and result in irreversible cartilage destruction [8,13].

At the molecular level, several degeneration processes of articular cartilage due to the recognition of mechanical overload occur. One of them is proteolysis of extracellular matrix components by the plasminogen activator system, and another one is chondrocyte apoptosis by endoplasmic reticulum stress-induced cell death. These processes result in thinning of the condylar cartilage [14]. The initial degenerative changes of osteoarthritis are known to be caused by the downregulation of Indian hedgehog signaling [15].

When mechanoresponsive mechanisms are activated, chondrocytes reproduce and proliferate to form various cells. In this reaction, type II collagen, a principal matrix molecule, is synthesized. The splice-variant form of type II collagen is normally expressed during the development of chondroprogenitor cells, however it is also observed in both early and late osteoarthritis. This indicates a potential reversion of chondrocytes to an early developmental phenotype, which may be developed during the degeneration of caltilage [16]. In the case catabolic process is highly activated, many aggrecan fragments degraded by matrix metalloproteinase (MMP) are secreted in synovial fluid. The secreted aggrecan fragments can be used as a marker for increased turnover [17,18].

3) Apoptosis and autophagy of chondrocytes

Apoptosis of chondrocytes is prominent in the early stages of cartilage degeneration [19]. Oxidative stress formed by an increase in intracellular reactive oxygen species causes chondrocyte apoptosis. Cytokines, developed in the process of chondrocytes apoptosis, cause destruction of subchondral bone. Furthermore, autophagy, normal adaptation process under nutrient stressing conditions, is observed in early articular cartilage degeneration of TMJ OA. The Excess of autophagy can also cause autophagic cell death in chondrocytes. More precisely, rapamycin (a potent autophagy inducer) could protect young chondrocytes, whereas excessive activation of rapamycin results in autophagic cell death in osteoarthritis chondrocytes [19,20].

4) Catabolic enzymes

Activation of various catabolic enzymes such as MMP, aggrecanases, disintegrin, and metalloproteinase with thrombospondin motifs is involved in the TMJ OA. Nuclear factor (NF)-κB signaling pathway induces upregulation of Wnt-5A, and as a result of this process, development of interleukin (IL)-1β–induced catabolism, and elevated expression of high-temperature requirement serine protease A1 (HtrA1) is observed in the early stages of TMJ OA, and elevated expression of HtrA1 initiates the degradation of the chondrocyte pericellular matrix, especially type II collagen. The major mediators of cartilage degeneration are MMP-1, -3, -9, and -13 that metabolize aggrecan, and collagen type II, and aggrecanases (aggrecanase-1 and -2) that metabolize aggrecan [21,22].

5) Inflammation

In synovial tissues and synovial fluid with TMJ OA, inflammatory mediators such as IL-12, IL-1β, IL-6, IL-17, IL-23, tumor necrosis factor-α, and monocyte chemoattractant protein (MCP)-1 are observed, among which MCP-1 plays an important role in recruiting the mononuclear cells in synovial fluid. These changes cause a decrease of the lubrication in the synovial fluid and a degeneration of the subchondral bone [23,24].

6) Abnormal remodeling of subchondral bone

Chondrocytes contribute to the destruction of subchondral bone by regulating the receptor activator of NF-κB ligand and the osteoprotegerin (OPG). Stromal cells-derived factor 1, MMP-9, and IL-6, affected by chondrocytes, contribute to subchondral bone remodeling [25,26].

Transforming growth factor beta 1 acts as an initiator of subchondral bone turnover increase and bone density decrease in TMJ OA, and causes an increase in apoptosis by upregulation of MMP-9, MMP-13, and vascular endothelial growth factor in mandibular condyle chondrocytes [27].

7) Estrogen

17b-estradiol induces the secretion of OPG and protects bones from systemic and local inflammatory factors. When it is deficient, inflammation is caused by various factors, subsequently bone resorption is developed, and new bone formations are inhibited [28].

Mandibular condyle proliferation is inhibited by an estrogen receptor (ER)-β–dependent mechanism. Subchondral bone and cartilage degeneration driven by upregulation of Fas and caspase 3-related proapoptotic genes is inhibited by ER antagonists. In contrast, estrogen has a protective effect on TMJ chondrocytes by inhibiting the expression of nitric oxide [29]. Therefore, the function of estrogen in the pathogenesis of TMJ OA has not been clearly identified. In addition, the effects of other female hormones, including relaxins and progestins, on the progression of cartilage degradation in TMJ OA should be further evaluated [14].

2. Association of Various Tissues and Organs for Osteoarthritis

1) Muscle

Traditionally, pathologic conditions of muscle have been considered to occur secondary to joint pain, but recently, it is believed that abnormal muscle movements and sensory dysfunctions of muscle may contribute to the cause of arthritis. In addition, changes in the muscles were observed before the onset of joint pain. However, the exact mechanism has not yet been elucidated [30,31].

2) Obesity and adipose tissue

Adipose tissue is an active endocrine organ and secretes adipokines, leptin, adiponectin, and resistin. Leptin affects osteoblasts and chondrocytes, and adiponectin plays a proinflammatory action. Bone marrow contains arachidonic acid, which contributes to the production of prostaglandins. The association of osteoarthritis histological severity and lipid accumulation in cartilage was reported [32-34]. In a TMJ OA study, the degeneration of the joint was associated with mechanical overload and high-fat diet [35].

3) Nervous system

The nervous system, the endocrine system, and the musculoskeletal system influence one another. Leptin affects bone through the hypothalamic pathway, and severe sensory neuropathy causes rapid joint destruction [36]. Various neuropeptides and enzymes, such as substance P, alpha-calcitonin gene-related peptide, vasointestinal peptide P, pituitary adenylate cyclase-activating peptide, neuropeptide Y, serotonin, glutamate, tyrosine hydroxylase and norepinephrine have related receptors in bone cell lineages [37]. Cocaine and amphetamine-regulated transcript, melanocortin 4 receptor and the cannabinoid receptor CB1 regulate bone remodeling and energy homeostasis, all of which show high levels of expression in the hypothalamus [38].

4) Vascular changes

Vascular infiltration from the subchondral bone to the calcified cartilage is observed in early arthritis [39]. These microvascular changes may change the subchondral bone blood flow, which consequentially changes the nutrition of the cartilage, or cause bone ischemia to accelerate the progression of arthritis [40,41].

CONCLUSION

TMJ OA is a low-level inflammatory disease characterized by degeneration of articular cartilage and subchondral bone. The TMJ OA is induced by dysregulation of the catabolic and anabolic activity of chondrocytes. The main cause of the dysregulation is mechanical overload, and other associated factors are age and estrogen. Muscle dysfuction, adipose tissue, nervous system, and vascular changes may be involved.

TMJ OA should be diagnosed under consideration of its multifactorial disease characteristics. Many studies are trying to make an accurate diagnosis based on various factors reflecting the pathophysiological mechanism, radiographic and clinical findings of TMJ OA [42-44], and further efforts should be made for early and accurate diagnosis and management of TMJ OA through the development of diagnostic markers which reflect various mechanisms.

CONFLICT OF INTEREST

No potential conflicts of interest relevant to this article are reported.

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