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Mini Review

Biochemical Changes of Synovial Fluid in Temporomandibular Joint Disorders

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Abstract

Temporomandibular joint disorders, which are in the study area of dental clinicians, are painful disease affecting quality of life. For making treatment plan, it is necessary to know biochemical changes take place in this disease. In this article, two main factors changed in this disease were reviewed. While inflammatory markers in synovial fluid such as arachidonic acid metabolites, cytokines, matrix degradation products, matrix degrading enzymes form the first group, changing of free radicals such as superoxide and hydroxyl radicals, hydrogen peroxide, lipid peroxides and nitric oxide are the other observed parameters in this disorder. These information also contributes to the development of tissue engineering strategies.

Keywords: *Biochemistry; Synovial Fluid; Temporomandibular Joint Disorders*

Introduction

Temporomandibular joint disorders (TMDs) reduce life quality by causing pain and dysfunction, functional limitations of the mandible, or clicking in the temporomandibular joint (TMJ) during motion and one third of adults are affected of the western population according to the epidemiological reports [1-3].

Biochemical reactions in healthy and pathological conditions of TMJ have to be known to understand related disorders and for effective treatment planning.

The main biochemical change in the TMDs and development articular pathology is the degradation of components of extracellular matrix such as collagen, hyaluronic acid (HA) and other glycosaminoglycans (GAGs) [4]. These changes play an important role aetiology and pathology of TMDs.

In the inflammatory conditions, biochemical alterations occur in the synovial fluid (SF) filling the synovial membrane covering the joint space. This fluid consist of blood plasma, hyaluronic acid and other GAGs. Lubrication, shock absorption, cartilage protection and nutrition of the articular cartilage are the main functions of SF [5]. In the patients with TMD, biochemical changes in SF occur depend on mainly two factors.

Arachidonic acid metabolites, inflammatory cytokines, matrix degradation products, matrix degrading enzymes such as matrix metalloproteinase are the first group factors and have been detected in SF in patients with TMDs. Cyclooxygenase (COX-2) and other enzymes that produce prostaglandins and leukotriene B4 effect on matrix degradation.

There are some studies that indicate free radicals are the causative factors of inflammation of normal TMJ [6]. These factors can be accepted second group agent that cause biochemical changes in SF.

In painful joint, some specific changes can occur in the content of SF. Takashasi., *et al.* [7] have reported that protein concentration in SF was higher in painful joint than that of pain-free joint. Alstergren., *et al.* [8] have found that a significant correlation between the concentration of PGE2 in SF and painful mandibular movement. COX-2 enzyme is inhibited by the non-steroidal anti-inflammatory agents (NSAIDs) such as ibuprofen aspirin, indomethacin and prostaglandin synthesis is blocked. Anti-inflammatory glucocorticoids also block the production of prostaglandin by inhibiting phospholipase A2 enzyme.

There are some neuropeptides account for the local inflammatory process and tissue destruction [9]. Substance P (SP), calcitonin gene-related peptide (CGRP), neurokinin A (NKA), neuropeptide Y (NPY) were found in SF with TMDs [10,11]. These neuropeptides have vasodilatory effect on arterial and venous vessel and coexist in the patients with inflammatory disease that of microcirculatory disturbances and tissue destruction.

The cytokines especially interleukin- I (IL-1), interleukin- 6 (IL-6) and tumor necrosis factor α (TNF-α) were found in SF of patients with TMDs as mediators of destructive process [6,12-14]. Therefore, detection of these inflammatory cytokines in SF, may be a useful indicator to diagnose the destruction of articular cartilage and inhibition of proteoglycan synthesis.

Recently, significantly elevated levels of elastin-derived peptides (EDPs) and IL-6 in the synovial fluid of the TMJ were found to be potential indicators of the pathological conditions of the joint [15].

MMPs are the enzymes that degrade of proteins in cartilage matrix such as collagen, gelatin, laminin and fibronectin. In normal condition these enzymes are in equilibrium with tissue inhibitor of metalloproteinases for maintaining enzymatic synovial homeostasis. In the inflammatory condition of cartilage, this balance is distorted and degradation of cartilage initiate. If the synovial inflammation is prolonged, destruction of articular surface can occur [16].

Main GAGs of proteoglycan part of cartilage besides hyaluronic acid are chondroitin-4-sulphate (C-4S), chondroitin-6-sulphate (C-6S) and keratan sulphate. It was reported that [17,18], the level of CS and the ratio to HA may correlate with the degree of degenerative change in TMJ.

Since C-4S and C-6S are related with synovial and cartilaginous tissues respectively, the concentration of them may be a valuable marker of PG degradation in TMDs.

The effects of free radicals on TMJ

In TMDs, the other biochemical changes in SF is the production of oxidants also called free radicals such as superoxide and hydroxyl radicals, hydrogen peroxide, lipid peroxides and nitric oxide [5].

Free radicals have a non-paired electron at the outermost orbital. Their structure is very unstable. They try to get electrons interacting with molecules around them to reach a stable structure. Free radicals, by virtue of their reactive structure, interfere with and damage cellular components such as lipids, proteins and nucleic acids. This oxidative damage contributes to the aetiology of many chronic health problems such as inflammatory diseases.

Reactive oxidative radical species are released nonenzymatically by hypoxia, which occurs due to overloading of the joint. Superoxide anion radical is one of these free radicals and produced in the intra-articular space by the excessive overloading that may lead prolonged ischaemia and hypoxia [19].

Mechanically-damaged of membrane lipid peroxidation can also cause production of superoxide anion radical. This harmful reactive oxygen species increase the activity of Phospholipase A2 by degradation of HA that protect surface phospholipids from being effected by Phospholipase A2. PG and collagen are also effected from free radicals and degradation of these proteins can occur [20].

The other free radical is NO produced in a kind of cells stimulated with proinflammatory cytokines including IL-1β,TNF-α, interferon-γ [21,22]. There are some studies that synovitis and TMJ pain may occur depend on NO produced in the extravascular space [23,24].

There is an antioxidant system against the free radicals including vitamins such as vit E, vit C, β carotene, several metalloenzymes including glutathione peroxidase (Se), catalase (Fe) and superoxide dismutase (Cu, Zn, Mn) and the other molecules such as glutathione, uric acid, ceruloplasmin, bilirubin and albumin. It was reported that albumin has an effect of biological antioxidant in inflammation [25].

The effect of free radicals in the pathogenesis of degenerative TMDs have not well clarified. Direct measure of free radicals in SF is very difficult, evaluation of antioxidants level in TMJ would be an alternative way [5].

Conclusion

In order to get successful outcomes in treatment of TMDs, multidisciplinary collaboration such as medical-dental management model, biomimetic approach for repairment of the living tissue, biocompatibility of implant materials are recommended [26].

Dental clinicians should have information and investigate molecular mechanism of TMDs, for early diagnosis, treatment and possible prevention of TMDs. Particularly, research on oxidative stress in SF in relation to clinical findings, may give an idea of the onset and development of TMDs.

Characterization of the biochemical and biomechanical properties of TMJ and peripheral structures, both in healthy and diseased cases, also contributes to the development of tissue engineering strategies [27].

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