Matrix Metalloproteinases and Temporomandibular Joint Disorder

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Temporomandibular disorders (TMD) are progressive degenerative disorders that affect the components of the temporomandibular joint (TMJ), characterized by pain and limitations in function. Matrix metalloproteinases (MMP) are enzymes involved in physiological breakdown of tissue that can have a pathological effect from an increase in activity during inflammation.

Keywords: matrix metalloproteinases ; temporomandibular joint disorder ; temporomandibular joint

1. Introduction

The temporomandibular joint (TMJ) is classified as a ginglymoarthrodial joint, allowing for rotational and translational movements in normal function. Its primary components include the glenoid fossa of the temporal bone, the articular disc, the head of the mandibular condyle, and masticatory muscles. This joint is capable of remodeling even after growth has stopped, allowing it to make structural changes and adapt to different physiological demands [1].

Temporomandibular disorders (TMD) are a group of degenerative disorders involving the components of the TMJ, which can lead to displacement of the disc, joint remodeling, and eventually osteoarthritis [2]. Disc displacement can occur anteriorly, posteriorly, medially, or laterally; however, it is most commonly displaced anteriorly [3]. TMD affects around 25% of the population, and it is characterized by orofacial pain, restricted range of motion, joint dysfunction, and ultimately, a decreased quality of life [2][4]. The etiology of TMD is still a topic of discussion; however, some known risk factors include trauma and microtrauma, malocclusion, and psychological factors, such as stress and anxiety [5].

The progression of TMD is classified primarily based on the location of the disc and its mobility during mandibular movement. In a normal functioning joint, the disc remains between the head of the mandibular condyle and the glenoid fossa through the full range of movement. In early stage TMD, the disc is displaced anteriorly when the mandible is closed and reduces to a normal location upon opening, classified as anterior disc displacement with reduction (ADDwR). In late stages of TMD, the disc is anteriorly displaced in both closed and open positions, classified as anterior disc displacement without reduction (ADDwoR). These later stages tend to be associated with more pain and limitation in mandibular mobility [2].

A more advanced staging guide to the internal derangements of TMD was created by Wilkes in 1989, placing patients into five categories based on clinical, radiographic (tomographic, arthrographic, and magnetic resonance imaging) and findings during surgery, including gross surface and anatomic changes to the disc and other components of the TMJ [6]. In the first stage, the early stage, patients present with clicking of the joint, but no pain, limited range of motion, or other symptoms. Radiographically and surgically, the disc is displaced slightly anteriorly, but all other aspects of the joint are normal. In Wilke's early/intermediate stage, the patient presents with additional symptoms, including episodes of pain, tenderness, and mechanical problems associated with the joint. Radiographically and surgically, the disc is displaced anteriorly, with slight deformation of its posterior aspect. In the intermediate stage there are more occurrences of pain, mechanical problems, including locking and decreased range of motion. In Wilke's intermediate/late stage of TMD, the patient has a chronic pain and decreased range of motion. Radiographically and surgically, an increased severity in comparison to the intermediate stage is noted, along with remodeling of the hard tissue surfaces of the joint. The disc, however, has yet to be perforated up to this stage. In the final stage, the late stage, patients present with crepitus and grinding in the joint with mandibular movement, chronic pain, restricted range of motion, and an overall decrease in function. Radiographically and surgically, the disc and hard tissues of the joint have undergone significant deformation, remodeling, and arthritic changes have occurred, including perforations of the attachments and erosion of articulating surfaces [6].

Matrix metalloproteinases (MMPs) are the major enzymes involved in extracellular matrix (ECM) and basement membrane remodeling and degradation, along with other enzymes, such as a disintegrin and metalloproteinases (with or without thrombospondin), and plasminogen activators, among others [7][8][9]. These enzymes are seen in both physiological and pathological processes, including embryogenesis, apoptosis, bone remodeling, inflammation, arthritis, and cancer [7][8]. However, the role of MMPs is not limited to the ECM, as they have also been shown to play a role in regulating inflammatory response, namely by processing chemokines, growth factors, receptors, proteases, and other molecules and proteins [9]. They are a family of 26 endopeptidases that degrade collagen, gelatin, proteoglycans, and other ECM components, and they are regulated at the level of their gene expression (cytokines, growth factors, hormones, and others), posttranslational activation, and endogenous inhibition (tissue inhibitors of metalloproteinases [TIMP]) [8][10]. As inflammation occurs, however, processes involving these enzymes shift from physiological to pathological, and MMP activity results in excess tissue breakdown and damage [11].

2. General Outcomes

Initial searches using the MeSH terms indicated above resulted in 34 studies, nine of which were duplicates and three of which were unable to be accessed. After removing duplicates and inaccessible studies, 22 studies remained. One study was not included due to samples being cadaveric, one focused on interleukins (IL) and used unspecified MMPs as markers for IL, two were animal studies, and two others were literature reviews. All other studies satisfied both the English language and the living human subject inclusion criteria, leaving 16 total studies. After including only studies published within the past 10 years, 6 studies remained, all of which were accepted based on all other indicated inclusion and exclusion criteria[12][13][14][15][16][17][18][19][20][21].

3. Description of Included Studies

In 2018, Perotto et al. used 39 disc samples from 27 patients to look at MMP-13 expression in TMD. Exclusion criteria for subjects Perotto's study included use of orthodontic appliances, chronic anti-inflammatory use, history of diseases causing impaired immune function, such as HIV, diabetes, or any use of immunosuppressive therapy. The patients, with a mean age of 33.59, then filled out a pain questionnaire, had a clinical examination, and radiographs or CT imaging was performed for diagnostic purposes, placing patients into groupings of either ADDwR or ADDwoR. Surgery was performed on patients and samples were obtained and underwent immunohistological staining to analyze for MMP-13 activity. The researchers did not find a significant difference in expression of MMP-13 in samples from patients with TMD, in either the ADDwR or the ADDwoR groupings, when compared to the control group.

Almeida et al. (2014) analyzed activity of two matrix metalloproteinases and their protein levels in TMD, both MMP-2 and MMP-9. Study, 45 disc samples from 33 patients (mean age of 32.36 years) were analyzed using immunohistological staining. Diagnosis was made using a pain questionnaire and clinical examination, grouping patients into ADDwR and ADDwoR, and selected patients were treated surgically following unsuccessful non-surgical treatment. Following immunohistochemical staining of samples obtained during surgery, MMP-2 was found to be significantly increased in samples from subjects with TMD when compared to the control. It was also found that there was an increase in MMP-2 in samples from patients with ADDwoR when compared to ADDwR, suggesting a correlation between progression of TMD and MMP-2 levels. Levels of MMP-9 showed no significant difference between the TMD disc samples when compared with control disc samples.

Loreto et al. (2013) used immunohistochemical staining to look at MMP-7 and MMP-9 in disc samples from subjects with TMD. They used 25 disc samples from 25 patients (mean age of 34), which were obtained surgically following unsuccessful non-surgical intervention after diagnosis using a history of present illness, clinical examination, and MRI. They assessed the severity of the disease by looking at unassisted maximum mouth opening and using a visual analog scale to assess pain. Following staining, both MMP-7 and MMP-9 were found to be expressed at levels significantly higher in samples from patients with TMD when compared to control samples.

Planello et al. (2011) analyzed the frequency of polymorphisms in genes coding for MMP-1, MMP-3, and MMP-9 proteinases in patients with TMJ degeneration. The study was conducted on 232 individuals, 115 of which had TMJ degeneration and a mean age of 42.82. To diagnose the study group, the researchers used MRI and/or CT scans to image one or both mandibular condyles. Genomic DNA was gathered from epithelial buccal cells and a PCR reaction was performed for MMP-1, MMP-3, and MMP-9 coding genes. A genotype analysis using restriction fragment length polymorphisms was performed, and the frequency of each allele was determined in both groups. Compared to the control group, there was a statistically significant association between the MMP-1 genotype and the TMJ degeneration group. No association was found between the MMP-3 and MMP-9 genotypes and TMJ degeneration.

Milosevic et al. (2015) studied polymorphisms of multiple genes in order to investigate their role in TMD. The study included 182 healthy individuals and 100 patients with TMD, with a mean age of 37.12. The TMD in the study group was assessed using clinical signs and symptoms. Genomic DNA was gathered from buccal swabs and genotyping was conducted in order to evaluate MMP-9 polymorphisms. The researchers found a significant difference in genotype and allele frequency in the MMP-9 gene of TMD patients when compared to the control group.

Luo et al. (2015) studied polymorphisms of MMP-1 genes in healthy individuals and patients with articular disc derangement and TMJ osteoarthritis. The researchers split patients into three groups, as follows: Group A included 185 healthy individuals; Group B included 141 patients with unilateral ADDwR; and Group C included 321 patients with ADDwoR, 115 of which did not present TMJ osteoarthritis (C1) and 206 of which presented TMJ osteoarthritis (C2). These patients were diagnosed through clinical and radiographic examinations. Genomic DNA was extracted from buccal swabs and a PCR analysis was conducted in order to assess variations in the MMP-1 gene. Comparisons between the groups showed a variety of allele distributions. Groups A and B did not show a significant statistical difference. Groups A and C showed a noticeable statistical difference with an odds ratio of 2.455 after adjusting for age. When observing the subgroups in Group C, Group C1 had no difference with group B, while Group C2 had a significant statistical difference and an odds ratio of 1.912. Groups C1 and C2 showed no significant statistical difference. Overall, their findings suggest the MMP-1 gene is upregulated in patients with ADDwoR, and the presence of TMJ osteoarthritis had no influence.

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