Review

Matrix Metalloproteinases and Temporomandibular Joint Disorder: A Review of the Literature

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Abstract: 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. A PubMed search of the current literature (within the past 10 years) was conducted to identify human studies involving matrix metalloproteinases activity in TMJ components of patients with TMD. Two separate searches results in 34 studies, six of which met inclusion criteria. Immunohistochemistry and gene analysis were used to evaluate MMP expression in the study groups. This review showed the strongest evidence for involvement of MMP-1, MMP-2, and MMP-9 in TMD; however, limitations included low sample sizes and a lack of recent clinical studies. Future research with more definitive conclusions could allow for additional pharmaceutical targets in MMP when treating patients with temporomandibular disorders.

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 [7–9]. 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].

Some MMPs have been suggested as being involved in angiogenesis, apoptosis, and osteoarthritis, processes which are seen in temporomandibular joint disorders [7]. Angiogenesis, found mostly in the synovial membrane in TMD, allows for new vessel formation to combat the hypoxia associated with an increase in the intra-articular pressure seen in TMD [12]. Chondrocytes undergo apoptosis in the early stages of TMD as the disc begins to remodel, and eventual cartilage degradation occurs, leading to osteoarthritic changes [4]. With evidence of the involvement of MMPs in these processes, and with the processes playing a crucial role in the progression of TMD, it would seem that MMP activity would be increased in joints of patients with the disorder. This paper aims to review the current scientific literature in order to investigate potential links between various MMPs and TMD.

2. Methodology

2.1. Search Protocol

Two independent electronic searches were conducted by two reviewers using PubMed to find relevant literature using Medical Subjective Headings (MeSH) Terms. The MeSH terms included in each search were:

1. "Temporomandibular Joint Disorders/enzymology" (Mesh) **OR** "Temporomandibular Joint Disorders/metabolism" (Mesh) **OR** "Temporomandibular Joint Disorders/pathology" (Mesh)) **AND** "Humans" (Mesh)) **AND** "Immunohistochemistry" (Mesh)) **AND** "Matrix Metalloproteinases" (Mesh)
2. "Temporomandibular Joint Disorders" (MeSH Major Topic) **AND** "Matrix Metalloproteinases" [MeSH Major Topic]) **AND** "Humans" (MeSH Terms)

2.2. Selection Protocol

Inclusion and exclusion criteria were determined before the search results were evaluated. Inclusion criteria used in selection included the following:

1. English language;
2. Living human subjects;
3. Publication within the past 10 years (since 2009);
4. Studies that evaluated samples of TMD and the level of MMP in the disease.

Exclusion criteria used in selection included the following:

1. Case studies;
2. Pilot studies;
3. Literature reviews.

2.3. Data Analysis

The data collected from each selected study, summarized in Table 1, included MMP type assessed in the study, sample size and groups, mean age involved in study, TMJ assessment, and the results of the study. Since the studies differed significantly in their methodology, a direct data analysis was unable to be conducted, and further evaluation of the quality of the included studies, such as statistical power, was not done beyond looking at the sample size.

Table 1. Studies that fit the inclusion criteria and published within the past 10 years [11,13–17]. Anterior disc displacement with reduction (ADDwR); anterior disc displacement without reduction (ADDwoR); matrix metalloproteinases (MMP); temporomandibular joint (TMJ).

Included Researcher's Characteristics and Main Results					
Authors	Experimental Sample	Age of Experimental Sample (Mean)	MMP Assessed and Method	TMJ Assessment	Result
Perotto et al., 2018	Group 1: Healthy 8 Samples Group 2: ADDwR 21 Samples Group 3: ADDwoR 10 Samples	33.59	MMP-13 Immuno-Histochemical Staining (IHC)	Clinical Examination, Symptoms, Panorex	No significant different in MMP-13 expression
Almeida et al., 2014	45 Samples from 33 Subjects	32.26	MMP-2, MMP-9 IHC	Clinical Examination, Symptoms, Panorex	Upregulation of MMP-2. No significant difference in MMP-9 expression.
Loreto et al., 2013	25 Samples from 25 Subjects	34.2	MMP-7, MMP-9 IHC	Clinical Examination, Symptoms, MRI	Upregulation of both MMP-7 and MMP-9.
Planello et al., 2011	115 Samples from 115 Subjects	42.82	MMP-1, MMP-3, MMP-9 DNA Purification, PCR, Genotype Analysis	CT Imaging, MRI, History of Symptoms	Upregulation of MMP-1. No association with MMP-3 and MMP-9.
Milosevic et al., 2015	100 Samples from 100 Subjects	37.12	MMP-9 DNA Extraction, Genotype Analysis, PCR	Clinical Evaluation, History of Symptoms	Upregulation of MMP-9.

Table 1. *Cont.*

Included Researcher's Characteristics and Main Results					
Authors	Experimental Sample	Age of Experimental Sample (Mean)	MMP Assessed and Method	TMJ Assessment	Result
Luo et al., 2015	Group A: 185 Healthy Group B: 141 ADDwR Group C1: 115 ADDwoR w/o OA Group C2: 206 ADDwoR w/ OA	Group A: 33.49 Group B: 36.64 Group C: 37.22	MMP-1 DNA Sampling, Genotype Analysis	Clinical and Radiographic Examinations, Symptoms	Upregulation of MMP-1 in ADDwoR with or without TMJ osteoarthritis.

3. Results

3.1. 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. Studies with researcher's characteristics and main results excluded from this review due to date of publication are included in Table 2 for additional comparison.

Table 2. Studies that fit all inclusion criteria, but were published more than 10 years ago [18–27].

Excluded Researcher's Characteristics and Main Results					
Authors	Experimental Samples	Age of Experimental Samples (Mean)	MMP Assessed and Method	TMJ Assessment	Result
Tiilikainen et al., 2005	54 Samples from 54 Subjects	36.3	MMP-3, MMP-8 IHC	Clinical Examination, CT, MRI, Symptoms	No significant difference between severity of TMD in expression of MMP-3 or MMP-8.
Ishimaru et al., 2000	94 Samples	31.33	MMP-1, MMP-3 IHC	Clinical Examination, Panorex, Arthrograms, Visual Analog Score Calculations	Upregulation of both MMP-1 and MMP-3.
Kanyama et al., 2000	10 Samples from 10 Subjects	29.7	MMP-1, MMP-2, MMP-3, MMP-9 IHC	Clinical Examination, MRI, Symptoms	Upregulation of MMP-1, MMP-2, MMP-3 and MMP-9.
Marchetti et al., 1999	11 Subjects	No Mean Range: 26–43	MMP-2 IHC	MRI and Macroscopic Examination	Upregulation of MMP-2.
Yoshida et al., 1999	16 Subjects	41.12	MMP-3 IHC	-	Upregulation of MMP-3.
Fujita et al., 2008	54 Samples from 50 Patients	36.2	MMP-3 Enzymography, Western Blot Analysis, Immuno-precipitation	Clinical and Radiographic Examinations,	Upregulation of MMP-3.
Srinivas et al., 2000	44 Subjects	36	MMP-2, MMP-8, MMP-9 Enzyme Activity, Western Immunoblotting	Symptoms, Clinical and Radiographic Examination, Surgical Observation	Upregulation of MMP-2, MMP-8, and MMP-9
Yoshida et al., 2006	44 Samples from 35 Subjects	36.6	MMP-2, MMP-9 Sample Collection, MRI, Western Immunoblotting	Clinical Examination, MRI, Symptoms	Upregulation of MMP-2 and MMP-9.

Table 2. *Cont.*

Excluded Researcher's Characteristics and Main Results					
Authors	Experimental Samples	Age of Experimental Samples (Mean)	MMP Assessed and Method	TMJ Assessment	Result
Mizui et al., 2001	86 Subjects	Range: 19–84	MMP-2 Proteolytic Activity, Enzymogram	Radiographic Analysis	Upregulation of MMP-2.
Tanaka et al., 2001	41 Samples from 38 Subjects	34.8	MMP-2, MMP-9 Enzyme Activity, Immuno-blotting, Gelatinolytic Activity	Symptoms, Clinical and Radiographic Exam	MMP-2 and MMP-9 were upregulated more in ADDwoR than in ADDwR.

3.2. 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. In this 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, as well as other enzyme polymorphisms outside the scope of this review. 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.

4. Discussion

Differences in study design, groupings of samples, and MMPs analyzed prevented direct analysis of data in the present studies. Three studies, those of Perotto, Almeida, and Luo, not only grouped samples on the presence and absence of TMD, but also in the degree to which the disease had progressed, either ADDwR or ADDwoR. Many of the studies analyzed different MMPs, and there were different techniques used to test for expression of the MMP, including immunohistochemical staining and PCR. Four of the included studies, those of Almeida, Loreto, Planello, and Milosevic, analyzed the same MMP, MMP-9, and while Almeida and Planello found that there was no significant different in samples from subjects with TMD, Loreto and Milosevic found an increase in expression. The Kanyama study in 2000, the Srinivas study in 2000, the Yoshida study in 2006, and the Tanaka study in 2001, which were excluded due to date of publication, found that MMP-9 was upregulated in disc samples from subjects with TMD. The inconclusiveness as to whether or not there is a correlation between the levels of MMP-9 expression and TMD of some of the studies can likely be contributed to the small sample size in each.

Aside from MMP-9, the only other overlap of MMP in the included studies was MMP-1, which was found to be upregulated in TMD samples in both the study conducted by Planello, as well as the study conducted by Luo. Aside from these two MMPs, there is no additional overlap between MMPs analyzed in the included studies; however, there is some ability to compare with the studies excluded due to date of publication. MMP-2, which was found by Almeida to be upregulated in disc samples from subjects with TMD, was also found to have higher expression in TMD samples by Kanyama, Marchetti, Srinivas, Mizui, and Tanaka.

Based on the information present in the included studies, it is difficult to draw a definitive conclusion with respect to the involvement of most MMPs in TMD, even when the studies that were excluded due to date of publication are considered. The strongest evidence for MMP involvement in TMD lies with MMP-1, MMP-2, and MMP-9; however, there were limitations in all of the studies, the biggest being sample size, which ranged from only 25 to 141 samples in the included studies.

5. Conclusions

Despite the high prevalence of TMD in the population, current treatment modalities tend to have a poor long-term success and few patients seek treatment [2]. The available modalities are

diverse, ranging from non-invasive techniques, such as physical therapy, ultrasound, low-level laser therapy, and splints, to minimally invasive techniques, such as corticosteroid injections, arthrocentesis of the joint, with or without platelet-rich plasma or hyaluronic acid injections, and arthroscopic surgery, to invasive procedures for the more advanced stage of TMD, which include discectomy, disc replacement, and the most invasive, total joint replacement [2,28,29]. It is recommended that attempts at treatment begin with non-invasive techniques and progress to invasive techniques, as risks with the invasive techniques involving open joint surgery can include facial nerve and optic lesions, transarticular and intracranial perforations, and pre-auricular hematoma, among others [3]. Further limitations and complications of arthroscopy, arthrocentesis, and orthognathic surgery used for treatment of TMD include arteriovenous fistula, pseudoaneurysm, infection, broken instruments in the joint, and condylar resorption [30,31]. Additionally, bruxism and dysfunctional oral habits have been shown to be risk factors for recurrent TMD symptoms after orthognathic surgery [32]. Due to limitations and complications of surgery, it is necessary to develop more efficacious techniques in non-invasive and pharmaceutical therapies for treating TMD.

Some of the pharmaceutical therapies for TMD include botox and cyclobenzaprine, which induce muscle relaxation, NSAIDs, and corticosteroids, which reduce pain and inflammation, and tricyclic antidepressants, which work to reduce pain [33]. However, these agents work to target the effects that TMD has on the patient rather than an underlying cause. To the researchers' knowledge, there are currently no pharmaceutical agents that are used to target an element of the underlying pathogenesis of TMD, such as MMPs, to stop the progression of this debilitating disorder.

There is ongoing pharmaceutical research to uncover potential MMP inhibitors for therapeutic use in different disease processes, such as cancer [34]. Thus far, however, limitations have prevented identification of a suitable therapeutic agent. The poorly understood specificity of their biological substrates makes it difficult to target specific MMPs, which causes detrimental problems, as MMPs are vital to survival [34]. There have been additional problems in its use, some of which include problems with oral bioavailability, toxicity, and metabolic stability [34,35]. Despite the unsuccessful attempts, knowledge of MMPs continues to evolve and the use of new and future technological advances, including use of CRISPR-*Cas*9 and MMP-activatable optical probes, make the use of MMP as a pharmaceutical target more hopeful [34,35]. If and when a successful pharmaceutical agent is discovered targeting MMPs, having a good understanding of the specific MMPs involved in TMD progression could provide an expedited route to applying the therapy to TMD treatment.

More studies with larger sample sizes are needed to analyze the involvement of specific MMPs in TMD. With more concrete evidence of its role, and because of the nature of the enzymes, MMPs could prove to provide a better understanding of the progression of TMD and be a valuable pharmaceutical target for therapy.

Conflicts of Interest: No conflicts of interest.

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