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## Expression of MMP-13 in Human Temporomandibular Joint Disc Derangement and Osteoarthritis

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## Abstract

**Objective:** MMP-13 performs digestion of collagen, which is a primary component of the temporomandibular joint (TMJ) articular disc. This study evaluated the expression of MMP-13 in patients with anterior disc displacement with (ADDwR) and without reduction (ADDwoR), and in the presence of TMJ osteoarthritis.

**Methods:** Thirty-nine human temporomandibular joint disc samples were collected and divided in two ways: ADDwR (21 samples), ADDwoR (10 samples), and a control group (8 samples); and with osteoarthritis (10 samples) and without osteoarthritis (29 samples). Immunostaining of the TMJ discs was statistically compared between the groups.

**Results:** There was no statistically significant difference for the area of MMP-13 immunostaining between the control group, ADDwR, and ADDwoR, nor between groups with and without osteoarthritis.

**Conclusion:** This study suggests MMP-13 is not significantly involved in collagen degradation in human TMJ disc displacement or osteoarthritis.

Keywords: Temporomandibular disorder, disc derangement, osteoarthritis

## Introduction

Temporomandibular joint derangement (TMD) is a common disease that affects many people around the world, with a major prevalence in females [\[1-4\]](#). The most commonly found disorder in the temporomandibular joint (TMJ) is the abnormal positioning of the articular disc [\[1,5-8\]](#). The two most frequent types of disc displacement are anterior disc displacement with (ADDwR) and without reduction (ADDwoR). In ADDwR, the disc returns to its normal position during mouth opening, and it goes back to its displaced position when the mouth closes completely, which is clinically represented by an articular click. Hence, in ADDwoR, the disc is unable to return to its normal position, which leads to a decrease in mouth opening and is usually painful [\[9,10\]](#).

The disc displacement may contribute to the progression of TMJ derangement and could lead to osteoarthritis of the TMJ, which is characterized by the abnormal remodeling of osseous structures of the joint, frequently accompanied by pain, limiting functional capability [\[11-14\]](#).

Previous studies have shown that alteration of the disc structure may impact the expression of some mediators related to apoptosis and inflammatory process, and they could be associated with TMD progression [\[15-26\]](#). The articular disc of the TMJ is formed basically by proteoglycan aggregates and collagen fibers that are composed mainly of type 1 and 2 collagen; its physiologic maintenance is through a balance between degradation of collagen fibers performed by matrix metalloproteinase (MMP) and their inhibitors, tissue inhibitor of matrix metalloproteinase (TIMP) [\[26-28\]](#).

In this study, the hypothesis was that MMP-13 might be involved in the progression of TMD. Therefore, the present investigation was designed to evaluate, through immunohistochemistry, the expression of MMP-13 in TMJ articular discs of ADDwR and ADDwoR patients. Moreover, the presence of TMJ osteoarthritis was also investigated to better understand the relationship between TMD advanced stages and MMP-13 expression.

## Materials and methods

### Sample selection

A sample of 39 temporomandibular joint discs was collected from 27 patients, with a mean age of 33.59 years old (17 to 57 years), for study at the Evangelico School Hospital, Curitiba, in the Southern region of Brazil (Table 1). This study was approved by the Ethical Committee on Research at Pontifical Catholic University of Paraná, according to Resolution 196/96 of the National Health Council and approved under registration number 104. Subjects were not included in the study if presenting: use of orthodontic appliances, chronic usage of anti-inflammatory drugs, history of diabetes, hepatitis, HIV infection, immunosuppressive chemotherapy, history of any disease known to severely compromise immune function, current pregnancy or lactation, dentofacial deformity, major jaw trauma, previous TMJ surgery, or previous steroid injection in the TMJ.

Patient	Gender	Age (yrs)	Diagnosis	Affected side		Wilkes Stage
				Right	Left	
1	F	33	ADDwR	X		III
2	M	27	CFx		X	
3	M	33	CFx	X		
4	F	26	ADDwR	X		III
4	F	26	ADDwR		X	III
5	F	43	CH		X	
6	F	17	CH		X	
7	F	30	ADDwR		X	III
8	F	25	ADDwR		X	III
8	F	25	ADDwR	X		III
9	F	37	ADDwR	X		III
9	F	37	ADDwR		X	III
10	M	42	CFx	X		
11	F	20	ADDwR		X	III
12	F	23	ADDwoR		X	V
12	F	23	ADDwoR	X		V
13	F	36	ADDwR	X		III
13	F	36	ADDwR		X	III
14	F	38	ADDwR	X		III
14	F	38	ADDwR		X	III
15	F	22	ADDwR	X		III
15	F	22	ADDwR		X	III
16	F	26	ADDwoR	X		IV
16	F	26	ADDwoR		X	IV
17	F	32	ADDwoR		X	IV
17	F	32	ADDwoR	X		V
18	F	45	ADDwoR	X		V
19	F	35	ADDwoR		X	IV
19	F	35	ADDwoR	X		IV
20	F	24	ADDwoR		X	V
21	F	34	ADDwR		X	III
22	F	57	ADDwR		X	III
23	F	18	CFx		X	
23	F	18	CFx	X		
24	M	46	ADDwR		X	III
24	M	46	ADDwR	X		III
25	F	40	CH		X	
26	F	56	ADDwR	X		III
27	F	42	ADDwR	X		III

Table 1. Baseline clinical characteristics of the control and study groups with and without TMJ dysfunction, according to Wilkes stage.

Subjects completed personal medical history questionnaires and, within a protocol approved by an Institutional Review Board, signed a consent form after being advised of the nature of the study. All patients were asked to complete a pain questionnaire, and a clinical examination was performed according to Clinical Practice Guidelines for TMJ surgery of the American Association of Oral Maxillofacial Surgeons. The patients were considered to be affected and were treated surgically when presenting painful clinical signs of disc displacement after unsuccessful nonsurgical treatment for at least six months.

Out of the eight control joints, five were condyle fractures (CFx), confirmed by radiographs and CT scan; the patients had to undergo surgery for the fracture reduction. Three joints displayed active condyle hyperplasia (CH), diagnosed by radiographs. All patients had a panorex; the patients with condyle fracture had a CT scan, and most of the patients in the study group had an MRI.

The sample was divided as follows:

- (1) Joints without any signs of disc displacement (control group;  $n = 8$  disc specimens);
- (2) Joints presenting anterior disc displacement with reduction (ADDwR;  $n = 21$  disc specimens);
- (3) Joints presenting anterior disc displacement without reduction (ADDwoR;  $n = 10$  disc specimens).

Joints were clinically categorized according to the presence or absence of disc displacement and, secondarily, according to the presence or absence of osteoarthritis (according to Wilkes classification) [29].

Joints' selection for osteoarthritis analysis was based on the primary diagnosis of severe TMJ internal derangement (ID). The stages of TMJ ID were classified into mild, intermediate, and severe, according to Wilkes classification, based on clinical, surgical, and pathological stages [29]. Mild ID (Wilkes stage III) is characterized by simple disc displacement without any morphological alteration of the disc and with or without osseous shift. The intermediate stage (Wilkes stage IV) is characterized by disc displacement and morphological deformity and/or osseous remodeling changes. Severe derangement (Wilkes stage V) is characterized by perforations of the disc attachments and osseous shift and/or osteoarthritis changes (sclerosis, osteophyte formation, articular surface flattening, depression and/or cystic alterations) [29]. Joints from the control group and those classified as Wilkes III were considered not presenting osteoarthritis, and joints classified as Wilkes IV or V were included in the osteoarthritis group, as follows:

- (1) Joints without osteoarthritis (control group + Wilkes stage III;  $n = 29$  disc specimens);
- (2) Joints with osteoarthritis (Wilkes stage IV and V;  $n = 10$  disc specimens).

Table 1 shows the baseline characteristics of the sample.

### Surgical technique

TMJ surgery was performed by the same surgeon, according to the technique described by Mehra and Wolford [30].

First, the displaced disc was freed by the surgeon entering the upper and lower joint spaces and lysing adhesions. At this point, a small hole was placed through the lateral-posterior pole of the condyle from a posterior to anterior direction. The Mitek bone-cleat introducer was

inserted and pushed into the bone, where two small coils unlocked and attached the cleat to the inner surface of the condyle cortical bone. A non-resorbable 2–0 or 3–0 suture was placed through the hole and through the disc at the junction of the posterior and intermediate bands, and the disc was tied down to the condylar neck. The deformity of the disc precluded repositioning it into the ideal position, and re-contouring the thickened disc with a scalpel was necessary (this scalpelled material constitutes the specimen).

This procedure was conducted for all patients with disc displacement and the control group. In the CFx patients, the disc displaced by fracture was repositioned, and in the CH patients, the disc was sutured to prevent disc displacement caused by the gap that was created after the high condylectomy. Postsurgical physical therapy was indicated at the discretion of the surgeon.

Histological sections obtained by scalpel of disc excess were prepared for observation of the *in situ* expression of MMP-13 by immunohistochemistry.

## Immunohistochemistry

The TMJ disc sections were deparaffinized with xylol (2 × 10 min) and rehydrated with absolute ethylic alcohol (3 × 1 min) and 80% ethylic alcohol (1 × 1 min). Endogenous peroxidase activity was quenched by treatment with H<sub>2</sub>O<sub>2</sub> (5% in methanol) for 10 min. Target Retrieval Solution™ (Dako, DK-2600 Glostrup, Denmark) was used prior to slide staining for heat-inducing epitope retrieval (for formalin-fixed, paraffin-embedded material), according to the manufacturer's instructions. The sections were incubated with monoclonal MMP-13 antibody (Abcam PLC, Cambridge, UK), diluted 1:50 in phosphate-buffered saline (PBS), 0.1% bovine serum albumin (BSA). For negative controls, the primary antibody was not added. PBS was used instead. The secondary antibody, Advance™ (Dako, DK-2600 Glostrup, Denmark), was applied for 30 min, according to the manufacturer's instruction.

The immunoreactions were visualized by incubating the sections using 3,3' diaminobenzidine (DAB) chromogen (OriGene, Rockville, MD, USA), (1 drop in 1 mL distilled water). The sections were lightly counterstained with Harris haematoxylin for 5 min, and finally mounted. Immunostaining was considered to be specific to MMP-13 because immunoreactivity was not observed in the negative controls.

The color morphometry method was used to analyze the anti-MMP-13 immunostained area in the TMJ disc tissue. For this purpose, images of consecutive fields were captured by a 20× objective lens coupled with the BX50 Olympus microscope with a Sony camera, Model DXC-107A, and image analysis was performed with specific software called Image Pro Plus software (Media Cybernetics Inc., Rockville, MD, USA). This software allows an observer to select and paint the positive areas to obtain an image model and make the mask for the other stained slides, the area of the positive reaction being automatically calculated. This procedure was performed by a single examiner in a blind manner. The data were entered into a spreadsheet, and Microsoft Excel (Redmond, WA, USA) was used to obtain the statistical analysis. The variable area was measured in square micrometers (µm<sup>2</sup>) and was obtained with the mean of all positive areas.



## Statistical analysis

To compare the groups (control, ADDwR and ADDwoR) regarding area, the non-parametric Kruskal-Wallis analysis was considered. To compare groups with and without osteoarthritis, the non-parametric Mann-Whitney test was employed. To meet the symmetric condition of the variable, data of area were previously submitted to a logarithmic transformation. The  $p$  value  $<0.05$  was considered statistically significant. Data were analyzed with IBM SPSS Statistics v.20.0 software (IBM Corporation, Armonk, NY, USA).

## Results

Expression of MMP-13 was observed at cytoplasm level.

Expression of MMP-13 in TMJ sample ADDwR, ADDwoR and control

Significant differences were not found in the expression of MMP-13 in TMJ discs between the three groups for the variable area ( $p = 0.288$ ) (Table 2).

Variable	Group	n	Mean	Median	Minimum	Maximum	Standard deviation	p-value*
Area	Control	8	17428	7292	1432	52714	19534	
	With reduction	21	11155	5947	108	54225	13058	
	Without reduction	10	6364	2466	418	19862	6951	0.288

Table 2. MMP-13 area of immunostaining ( $\mu\text{m}^2$ ) in the discs of the control and study groups with and without TMJ dysfunction.

Expression of MMP-13 in TMJ discs of patients with and without osteoarthritis

All joints with ADDwoR presented osteoarthritis. On the other hand, almost all joints without osteoarthritis presented ADDwR.

Statistically significant differences were not found in the expression of MMP-13 in TMJ discs between the groups with and without osteoarthritis for the variable area ( $p = 0.185$ ) (Table 3).

Variable	Group	n	Mean	Median	Minimum	Maximum	Standard deviation	p-value*
Area	With osteoarthritis	10	6364	2466	418	19862	6951	
	Without osteoarthritis	29	12885	6933	108	54225	15011	0.185

Table 3. Differences between groups with and without osteoarthritis, with respect to area of *in situ* expression ( $\mu\text{m}^2$ ) of MMP-13 cytokine.

## Discussion

In the last few years, the expression of matrix metalloproteases and some others markers, such as Fas Ligand (FasL) and ADAM metallopeptidase domain 17 (ADAM-17), were shown in the progression of TMJ ID using TMJ discs and synovial fluid [15–26].

The articular disc of the TMJ is formed by proteoglycan aggregates and collagen types 1 and 2. But the TMJ's disc is a fibrocartilage, different from other joints in the body (hyaline cartilage), and this disc is composed mostly of type 1 collagen rather than type 2, whereas hyaline cartilage has no type 1 collagen [5,10,13]. A balance between degradation of collagen fibers performed by matrix metalloproteinase (MMP) and their tissue inhibitor of metalloproteinase (TIMP), are responsible for functional remodeling of the TMJ [21,26–28].

MMPs have been reported to be involved in the cleavage of cell surface receptors and the release of apoptotic ligands (such as the Fas ligand). They play an important role in tissue remodeling associated with various physiological or pathological processes such as morphogenesis, angiogenesis, tissue repair, cirrhosis, arthritis, and metastasis [21,27,28].

Loreto et al. [21] showed that MMP-7 and MMP-9 are expressed in arthritic joints and provided evidence of a role for those MMPs in TMJ ID disc damage, with higher expression being detected in the posterior rather than in the anterior and intermediate bands of ADDwR and ADDwoR discs.

Almeida et al. [24], in a study using MMP-2 and MMP-9, did not find a statistically significant difference between the variable area of MMP-9 expression in the disc with or without disc displacement, as determined by immunohistochemical analysis. However, an elevation of MMP-2 expression in the discs of patients with ADDwoR (more severe alteration) was identified.

One of the most important metalloproteinases involved in degradation of collagen within the cartilage is MMP-13 (collagenase-3), a metalloproteinase of the collagenase group, which performs preferential digestion of type 2 collagen over type 1 and 3 collagens [26–28]. Leonardi et al. [26] found correlation of an increased MMP-13 immunoreactivity in TMJ diseased disc tissue with the increased severity of the histopathological changes; however that study was performed with cadavers' discs.

In this study, the hypothesis is that MMP-13 may be involved in the progression of TMD, since other studies have already demonstrated the correlation of MMPs with this progression.

Significant differences were not observed between the groups control and with or without anterior disc reduction of the articular disc, with respect to the variable area for the expression of MMP-13 measured by immunohistochemical examination. This lack of expression could be due to the composition of the TMJ disc, which is mainly collagen type 1, and MMP-13 is less effective at breaking down type 1 collagen than type 2 collagen.

Osteoarthritis is characterized by deterioration and abrasion of articular cartilage. Some papers have demonstrated the association of MMPs (MMP-7, MMP-9, MMP-13) with osteoarthritis, an inflammatory disorder of movable joints, in the degenerative process of joints included in the TMJ [\[21.27.28\]](#).

Schlopov et al. [\[31\]](#) suggested a key role of MMP-13 and MMP-8, as well as MMP-1 in osteoarthritis.

This study has some limitations, such as the restrictive sample size; however this still seems to be the biggest sample size so far in TMJ studies, to the authors' knowledge. This reduced number refers to the fact that only a low number of patients must be submitted to surgical treatment.

In this study, significant differences between the groups with and without osteoarthritis with respect to the variable area for the expression of MMP-13 measured by immunohistochemical examination were not observed.

## Conclusion

In conclusion, the expression of MMP-13 was not associated with TMD and osteoarthritis in the study population.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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