

## TMJ Osteoarthritis/Osteoarthrosis and Immune System Factors in a Japanese Sample

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### ABSTRACT

**Objective:** To determine whether there is an association between temporomandibular joint (TMJ) osteoarthritis/osteoarthrosis (OA) and immune system factors in a Japanese sample.

**Materials and Methods:** The records of 41 subjects (7 men, aged  $22.0 \pm 3.8$  years; 34 women, aged  $24.8 \pm 6.3$  years) and 41 pair-matched controls (7 men, aged  $22.1 \pm 2.3$  years; 34 women, aged  $24.8 \pm 6.4$  years) based on age and gender were reviewed. Information on medical history included local or systemic diseases, details on medication type and use, and the presence of allergies and asthma. Dental history questions referred to details regarding past oral injuries. The validity of the hypothesis, defining allergies and asthma as risk factors in OA, was tested by using a logistic regression analysis.

**Results:** The incidence of allergy was significantly higher in the TMJ OA ( $P = .008$ ), with a mean odds ratio of 4.125 and a 95% confidence interval of 1.446–11.769.

**Conclusion:** These results suggest that allergy may be a risk factor in association with TMJ OA in this Japanese sample.

**KEY WORDS:** TMJ OA; Risk factors; Allergy; Asthma

### INTRODUCTION

Arthritis refers to inflammation of the articular surfaces of a joint. Osteoarthritis (OA) is one of the most common forms of arthritis affecting the temporomandibular joint (TMJ) and has been referred to as a degenerative joint disease.<sup>1</sup>

Although the precise causes of OA are unknown, its

most common etiologic factor is generally thought to be overloading of the articular structures of the joint.<sup>2-4</sup> When bony changes are active, the condition is often painful. When the actual cause of OA can be identified, the condition is referred to as secondary osteoarthritis. On the other hand, when the cause cannot be determined, it is referred to as primary osteoarthritis.<sup>1</sup> In either case, as functional remodeling occurs, the condition becomes stable, although the bony changes still remain. This condition is referred to as osteoarthrosis and is nature's way of adapting to the functional demands of the system.<sup>1</sup> Radiographic changes are commonly detected in osteoarthritis/osteoarthrosis.

The TMJ is believed to be in a constant state of remodeling (cellular and extracellular matrix turnover).<sup>5</sup> The primary goal of remodeling is to maintain functional and mechanical relationships between articulating surfaces of the joint. Remodeling is an essential biological response to normal functional demands, ensuring homeostasis of joint form and function and an optimal occlusal relationship between the two dental arches. In addition, remodeling may take place when changes occur either in the adaptive capacity of the host or when mechanical stresses are placed on the joint structures. Host factors (ie, age, systemic dis-

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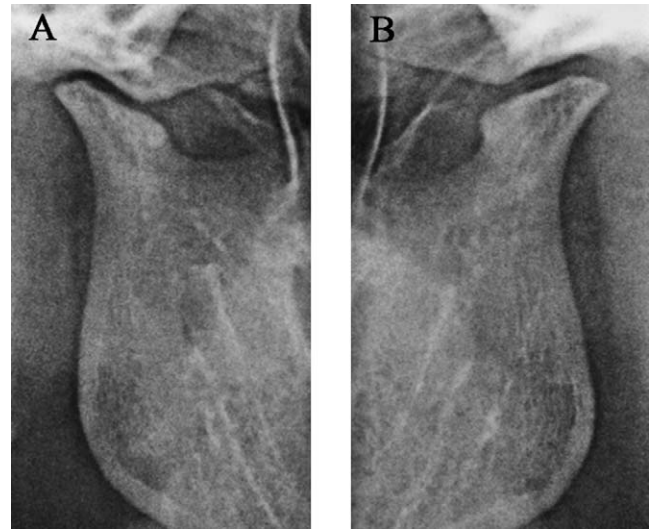
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ease, hormones) may contribute to dysfunctional remodeling of the TMJ, even when the biomechanical stresses are within a normal physiological range.<sup>6,7</sup> Alternatively, excessive mechanical stress may provoke dysfunctional remodeling in the absence of predisposing host factors.<sup>5,6</sup> The exact molecular mechanisms of degenerative TMJ disease, however, are unknown. Three mechanisms (direct mechanical injury, hypoxia-reperfusion injury, and neurogenic inflammation) of injury have been suggested.<sup>6</sup> All of these changes can lead to a net loss of tissue by increasing degradation processes (catabolic) and inhibiting synthetic processes (anabolic) in affected articular tissues.

Neurogenic inflammation has been cited as a possibly mediating condylar morphologic change.<sup>8</sup> Traction or compression of peripheral nerve terminals in the joint may evoke a release of neuropeptides (substance P, calcitonin gene-related peptide [CGRP]) into the surrounding tissues. These neuropeptides are vasoactive. When mechanically strained, these neuropeptides are released from nerve endings adjacent to blood vessels, causing local hypotension, leading to plasma extravasation and migration of leukocytes out of capillaries. These migratory cells initiate an inflammatory reaction, typified by the synthesis and secretion of chemokines, cytokines, growth factors, and colony-stimulating factors. These signal molecules attract osteoclast and osteoblast progenitor cells to the affected area, thus sustaining the inflammatory process. In this fashion, inflammation governs the remodeling of the TMJ. In addition, inflammatory cytokines can increase the synthesis of these neuropeptides in a positive feedback mechanism.<sup>9-11</sup> Therefore, the inflammatory process produced by the stimulation of peripheral nerve terminals in the TMJ can lead to a self-perpetuating cycle. Consequently, the presence of primed leukocytes in the peripheral blood, which originate in diseased organs such as lungs and joints, supports the notion of a possible association between TMJ OA and pathological conditions that affect and/or involve the immune system.

It has been reported that immune system factors are associated with excessive dental root resorption<sup>12-14</sup> and excessive alveolar bone resorption.<sup>15,16</sup> However, no report exists regarding the relationship between TMJ OA and immune system factors. In lieu of the reports linking signal molecules derived from immune cells with enhanced root resorption and bone remodeling in mechanically loaded dental and paradental tissues, we hypothesize that individuals who have medical conditions that affect the immune system, such as allergies and asthma, may be at a high level of risk for TMJ OA. The objective of this study was to determine whether there is an association between TMJ OA and



**Figure 1.** Examples of temporomandibular joint (TMJ) osteoarthritis. (A) Right side of TMJ. (B) Left side of TMJ.

the presence of systemic diseases that affect the immune system in a Japanese sample.

## MATERIALS AND METHODS

This study was a retrospective analysis of existing radiographs and was performed in accordance with the guidelines of the Helsinki Declaration (1996).

The sample was selected from the case files of the Department of Orthodontics, Faculty of Dentistry, Kyushu University, Fukuoka, Japan, which included more than 2000 documented individual records. These records contained a pretreatment questionnaire, medical history, and pretreatment dental panoramic and transcranial radiographs. The questionnaire included the documentation of TMJ pain, TMJ sounds, and mandibular restriction of mouth opening.

Determination of the TMJ OA status of each patient was established by an examination of the pretreatment radiographs. Individuals aged 16 years or older were assigned to the TMJ OA group when bilateral condylar bony changes (flattening, osteophyte, and erosion) were detected. The radiographs were interpreted by an experienced radiologist, who implemented the TMJ OA definitions and scoring system published by Muir and Goss.<sup>17</sup> We determined scores of 1 and 2 corresponding to mild bony change and gross bony change, respectively, as constituting TMJ OA (Figure 1). Eighteen cases, in which radiographic interpretation was ambiguous, and two rheumatoid arthritis cases were excluded from this study.

In this population, 41 individuals were found to have bilateral TMJ OA. In this group, 7 subjects were male (aged  $22.0 \pm 3.8$  years) and 34 were female (aged  $24.8 \pm 6.3$  years). A control group was selected from

**Table 1.** Comparison of Means and Standard Deviations of Age in the TMJ OA and Control Groups<sup>a</sup>

	No. of Subjects	Age, y
TMJ OA group		
Male	7	22.0 ± 3.8
Female	34	24.8 ± 6.3
Total	41	24.3 ± 6.0
Control group		
Male	7	22.1 ± 2.3
Female	34	24.8 ± 6.4
Total	41	24.5 ± 6.0

<sup>a</sup> TMJ indicates temporomandibular joint; TMJ OA, temporomandibular joint osteoarthritis/osteoarthritis.

the remaining patients of this population who did not display bilateral radiographic evidence of TMJ OA. Each individual in the control group was pair matched to another in the TMJ OA group based on age and gender. In the control group, 7 subjects were male (aged 22.1 ± 2.3 years) and 34 were female (aged 24.8 ± 6.4 years; Table 1). Student's *t*-tests were used to compare the mean difference in age between the TMJ OA and the control groups. No significant difference in the mean age was found between the two groups.

Subjects or their legal guardians recorded answers to a questionnaire prior to the onset of treatment. The questionnaire sought information on personal demographics, medical history, and dental history. Information in the medical history included local or systemic diseases (ie, bone disorders, heart disease, blood disease, liver disease, kidney disease, and respiratory disease), details on medication type and use, the presence of allergies (ie, allergic rhinitis, allergic urinary, allergic response to food or metal, pollen allergy, and atopic dermatitis) and asthma. Dental history questions referred to details regarding previous dental treatment and information about past oral injuries.

**Statistical Analysis**

The validity of our hypothesis was tested by the logistic regression analysis using the Stat View 5.0 program (SAS Institute Inc, Cary, NC). This analysis is a variation of ordinary regression, applicable when the observed outcome is restricted to two values, which represent the occurrence or nonoccurrence of an outcome event (TMJ OA). It produces a formula that predicts the probability of the occurrence as a function of the independent variables. Logistic regression also produces odds ratios associated with each predictor variable (trauma, allergy, asthma, systemic disease, medication use). The result is the odds of an event occurring divided by the probability of the event not occurring.

**Table 2.** Prevalence of Subjective TMJ Pain and TMJ Sounds in the TMJ OA and Control Groups<sup>a</sup>

	TMJ OA Group	Control Group
TMJ pain, %	34.1	5.9
TMJ sounds, %	70.7	19.5

<sup>a</sup> TMJ indicates temporomandibular joint; TMJ OA, temporomandibular joint osteoarthritis/osteoarthritis.

**RESULTS**

The prevalence of the subjective signs and symptoms of TMJ dysfunction in TMJ OA and control groups is shown Table 2. The prevalence of bilateral TMJ OA was 2.1%. The distribution of each risk factor in the TMJ OA and control groups is shown in Table 3. The logistic regression analysis is shown in Table 4. The incidence of allergy was significantly higher in the TMJ OA group (*P* = .008), with a mean odds ratio of 4.125 and 95% confidence interval of 1.446–11.769. The incidences of the other factors were not significant between the two groups.

**DISCUSSION**

TMJ OA, which is a degenerative disease common to human general joints, is defined for the TMJ as deterioration of the articular cartilage layer with structure changes of subchondral bone. Factors that influence the host remodeling capacity of the TMJ may include advancing age and hormonal factors.<sup>7</sup> It is reported that progressive resorption occurred in a young age group (second and third decade).<sup>18–21</sup> Occurrence at this age is secondary to reduced host adaptive capacity and diminished cellular density in the articular cartilages.<sup>22,23</sup> Furthermore, females are more likely to be afflicted with OA than males are.<sup>24,25</sup> Females might be predisposed to dysfunctional remodeling of the TMJ, and this female preponderance for dysfunctional remodeling of the TMJ suggested a potential role of sex hormones (ie, estrogen, prolactin) as modulators of this response.<sup>18</sup> Based on that premise, in this study, each individual in the control group was pair matched

**Table 3.** Distribution for Each Risk Factor in the TMJ OA and Control Groups

Risk Factor	TMJ OA Group			Control Group		
	Male	Female	Total	Male	Female	Total
Trauma	1	3	4	2	3	5
Allergy	3	16	19	2	5	7
Asthma	0	4	4	1	2	3
Systemic disease	1	7	8	1	2	3
Medication use	0	5	5	0	2	2

<sup>a</sup> TMJ indicates temporomandibular joint; TMJ OA, temporomandibular joint osteoarthritis/osteoarthritis.

**Table 4.** Logistic Regression Analysis of Each Risk Factor

Risk Factor	$\chi^2$	P Value	Odds Ratio	95% Confidence Interval
Trauma	0.530	.818	0.840	0.189–3.722
Allergy	7.020	.008	4.125	1.446–11.769
Asthma	0.246	.620	1.551	0.274–8.771
Systemic disease	1.933	.164	2.635	0.672–10.325
Medication use	0.670	.413	2.164	0.341–13.744

to another in the TMJ OA group based on age and gender.

TMJ OA still bristles with unclear points regarding the involved cellular and tissue mechanisms underlying this pathological process. However, one biological pathway of TMJ OA has been identified as neurogenic inflammation.<sup>5,6</sup> Traction or compression of the nerve-rich regions of the TMJ may result in the release of neuropeptides from the peripheral terminals into the affected tissue. Some neuropeptides, such as substance P and CGRP, may stimulate the production and release of proinflammatory cytokines (ie, interleukin-1 [IL-1], tumor necrosis factor [TNF]) by local cell populations.<sup>26–30</sup> These cytokines may in turn stimulate the production, release, and/or activation of the matrix-degrading enzyme as well as activate both phospholipase A<sub>2</sub> and cyclooxygenase, leading to the production of prostaglandins and leukotrienes. Prostaglandins, such as PGE<sub>2</sub>, may sensitize peripheral nerve terminals in the region, leading to a continued release of proinflammatory neuropeptides. This interaction may potentially lead to a self-perpetuating cycle that can amplify the inflammatory response. In this disease state, the delicate balance between catabolic and anabolic events is perturbed, resulting in a net loss of articular tissue. Furthermore, the levels of several cytokines, including IL-1 $\beta$ , IL-6, TNF- $\alpha$ , IL-8, and interferon- $\gamma$ , were reported to be increased in synovial fluid samples taken from patients with temporomandibular disorders, and these cytokines may play a role in the pathogenesis of synovitis and degenerative changes of the cartilaginous tissue and bone of the TMJ.<sup>31</sup> Therefore, it is reasonable to hypothesize that patients with local or systemic diseases that involve the immune system may be susceptible to TMJ OA because at least some of their circulating leukocytes are primed to produce high levels of inflammatory mediators and growth factors.

Allergy is associated with a set of abnormal genetically regulated immune responses to a variety of allergens. Allergic individuals are characterized by the excessive production of IgE, antibodies to the allergens, and many major classes of cytokines, which have been organized into different categories according to their major functional activities.<sup>32</sup>

In this study, we found that allergy might be an etiological factor in TMJ OA. Our finding supports the hypothesis that allergies may be high-risk factors for TMJ OA. Similarly, we hypothesized that asthma might be one of the high-risk factors in TMJ OA because circulating lymphocytes from asthma patients produce large amounts of interleukins 2, 4, and 5.<sup>33</sup> However, we did not find a significant association between the two pathologies. This statistical finding does not preclude the existence of an association between asthma and TMJ OA because only a few patients with asthma were included in our sample (four patients with asthma in the TMJ OA group; three patients with asthma in the control group). Therefore, additional research on a larger sample appears to be warranted.

One limitation of this study was that determination of the TMJ OA status of each patient was established by examination of dental panoramic radiographs. It has been suggested that bony tissues are best imaged with computed tomography (CT) scan.<sup>34</sup> The greatest advantage of the CT scan is that it images both hard and soft tissue.<sup>35</sup> However, the disadvantages of the CT scan are that it is time consuming, expensive, and a procedure with high radiation exposure.

Although there is a controversy regarding the utility of the dental panoramic radiographic imaging in both general practice and when evaluating the TMJ,<sup>36</sup> the panoramic and transcranial radiographs have been widely used in dental offices, providing useful diagnostic images for screening purposes.<sup>37</sup> The accuracy of determining bony changes by using panoramic radiographs was reported to be from 71% to 84%.<sup>38,39</sup> Therefore, the validity and impact of the results should be interpreted with caution.

In this study, the subjects were grouped into the TMJ OA group when the bilateral bony changes (flattening, osteophyte, and erosion) were obvious in the panoramic and transcranial radiographs according to the definitions and scoring system published by Muir and Goss.<sup>17</sup> Recently, it was reported that cone beam CT is one of the best choices for imaging diagnosis of the TMJ OA.<sup>40</sup> Cone beam CT, which reproduces multiple images, including axial, coronal, and sagittal planes of the joint, provides a complete radiographic investigation of the bony components of the TMJ. However, these images were not available to us at the time of this investigation.

## CONCLUSION

- Allergy may be a risk factor in association with TMJ OA in this Japanese sample. However, the small size of our sample precluded the exposure of additional physiological and medical conditions that may

contribute, alone or in concert with other factors, to the etiology of TMJ OA.

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### Erratum

Vol. 75, No. 5, September 2005, page 793.

“Effects of preoperative ibuprofen and naproxen sodium on orthodontic pain”.

Omar Polat, Ali Ihya Karaman and Ercan Durmus.

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**TABLE 1.** Groups With Mean Age and Sex Distribution

Group No.	Preoperative Analgesic	Preoperative Dose	Mean Age	No. of Boys	No. of Girls
1	Placebo	1 tablet	<b>16.15 ± 5.7</b>	10	10
2	Ibuprofen	400 mg	17 ± 7.0	13	7
3	Naproxen sodium	550 mg	15 ± 2.2	14	6

**TABLE 2.** Mean Pain Scores and Standard Deviations of the Experimental Groups<sup>a</sup>

Groups	2 h	6 h	At night	24 h	2 d	3 d	7 d
<b>Chewing</b>							
Placebo	<b>3.92 ± 3.18</b>	<b>5.18 ± 3.07</b>	<b>5.99 ± 2.88</b>	<b>4.47 ± 2.97</b>	<b>3.27 ± 2.81</b>	<b>3.27 ± 2.81</b>	<b>1.06 ± 0.80</b>
Ibuprofen	2.18 ± 2.68	3.49 ± 3.04	4.96 ± 3.97	5.46 ± 3.82	5.01 ± 3.10	4.94 ± 3.07	1.55 ± 2.49
Naproxen sodium	1.43 ± 2.66	1.62 ± 2.40	2.81 ± 2.76	3.41 ± 3.27	3.60 ± 3.16	2.48 ± 3.09	0.36 ± 1.12
<b>Biting</b>							
Placebo	<b>5.41 ± 2.78</b>	<b>5.73 ± 3.71</b>	<b>6.34 ± 2.93</b>	<b>6.69 ± 2.84</b>	<b>4.49 ± 1.95</b>	<b>3.78 ± 2.95</b>	<b>1.93 ± 1.72</b>
Ibuprofen	2.15 ± 2.44	4.56 ± 3.50	5.08 ± 3.56	6.08 ± 3.38	5.54 ± 2.83	4.38 ± 3.03	1.79 ± 2.54
Naproxen sodium	2.54 ± 3.15	4.86 ± 2.02	5.11 ± 3.20	5.11 ± 3.20	5.53 ± 3.22	4.69 ± 3.29	0.89 ± 1.67
<b>Fitting front teeth</b>							
Placebo	<b>3.81 ± 3.03</b>	<b>5.83 ± 3.13</b>	<b>6.55 ± 2.84</b>	<b>6.63 ± 2.91</b>	<b>5.11 ± 2.88</b>	<b>4.58 ± 2.87</b>	<b>2.57 ± 1.97</b>
Ibuprofen	2.03 ± 2.52	4.09 ± 3.69	5.68 ± 3.66	6.27 ± 2.75	6.24 ± 3.34	4.88 ± 3.62	4.88 ± 3.62
Naproxen sodium	1.39 ± 2.72	2.75 ± 2.89	4.03 ± 2.76	5.32 ± 2.81	6.30 ± 3.10	5.30 ± 3.97	1.68 ± 2.72
<b>Fitting back teeth</b>							
Placebo	<b>3.41 ± 3.01</b>	<b>5.20 ± 3.07</b>	<b>5.34 ± 3.07</b>	<b>5.22 ± 3.32</b>	<b>3.44 ± 2.97</b>	<b>2.24 ± 2.09</b>	<b>1.44 ± 1.46</b>
Ibuprofen	2.20 ± 2.19	2.21 ± 2.19	3.50 ± 3.41	4.90 ± 3.92	3.76 ± 3.38	3.34 ± 3.21	1.22 ± 2.38
Naproxen sodium	1.16 ± 2.59	1.19 ± 2.29	2.08 ± 2.78	2.95 ± 2.93	3.41 ± 2.81	2.42 ± 3.47	0.70 ± 2.24

<sup>a</sup> Values are mean ± SD.