

Insufficient Endogenous Control of Tumor Necrosis Factor- α Contributes to Temporomandibular Joint Pain and Tissue Destruction in Rheumatoid Arthritis

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ABSTRACT. Objective. To investigate whether pain and tissue destruction in the temporomandibular joint (TMJ) of patients with rheumatoid arthritis (RA) are influenced by plasma levels of the proinflammatory cytokine tumor necrosis factor- α (TNF- α) or the soluble receptor TNFsRII.

Methods. Fifty-one patients with RA were included. TMJ resting pain intensity, pain intensity upon mandibular movement, tenderness to palpation, pressure-pain threshold, and presence of anterior open bite were assessed. Venous blood was obtained for analysis of TNF- α , TNFsRII, and inflammatory markers.

Results. A total of 29 patients had TMJ pain and 22 patients had anterior open bite. In the group of patients with TMJ pain, 12 had anterior open bite and 17 did not. In the patients without TMJ pain 10 patients had anterior open bite and 12 did not. Patients with or without anterior open bite did not differ regarding any investigated variable. Plasma TNF- α and TNFsRII were positively correlated in the total patient sample. TNFsRII was negatively correlated with degree of anterior open bite in patients with TMJ pain but positively correlated with TMJ pressure-pain threshold in patients with elevated plasma TNF- α .

Conclusion. Our results indicate that insufficient systemic endogenous control of TNF- α seems to contribute to TMJ pain and tissue destruction in RA. (J Rheumatol 2006;33:1734-9)

Key Indexing Terms:

ARTHRITIS

CYTOKINE RECEPTORS

RHEUMATOID ARTHRITIS

TEMPOROMANDIBULAR JOINT

TUMOR NECROSIS FACTOR- α

Rheumatoid arthritis (RA) is a severe chronic disease with persistent inflammation, especially in joints. The characteristic pain and progressive cartilage and bone tissue destruction are the major causes of disability for patients with RA¹.

Proinflammatory cytokines, in particular tumor necrosis factor- α (TNF- α) and interleukin-1 β (IL-1 β), are major contributors to this disease². In RA, TNF- α is often present in high levels at the site of inflammation. It is also present in the blood and seems thereby to be responsible for systemic effects³. TNF- α elicits cartilage and bone degradation as well as pain by direct action but also by inducing production of other cytokines like IL-1 β and IL-6⁴⁻⁶. In synovial tissue, TNF- α exerts a cascade of effects that may lead to development of arthritis, including sensitization of nociceptors and destruction of cartilage and bone tissue^{2,4,5,7}. High levels of TNF- α in synovial fluid (SF) have been associated with temporomandibular joint (TMJ) pain⁶. High plasma levels of

TNF- α have been associated with anterior open bite, which is a consequence of cartilage and bone tissue destruction in this joint, and radiographic signs of bone destruction in the TMJ⁸.

The strong and often overlapping proinflammatory effects of TNF- α and IL-1 β are counterbalanced by endogenous inhibitors that protect the organism from harmful local and systemic effects⁹. Soluble TNF and IL-1 receptors (TNFsRI, TNFsRII, IL-1sRI, and IL-1sRII) act as inhibitors by binding to and inactivating respective cytokines as well as by removing cytokines from the inflammation site. Indeed, synovitis is believed to result when a cytokine imbalance develops, either from excess production of proinflammatory cytokines or from inadequate mobilization of endogenous antiinflammatory mechanisms¹⁰⁻¹². For example, blocking TNF- α with soluble TNF receptors improves signs and symptoms of RA and inhibits progression of erosions in a majority of patients with RA¹³ by reducing levels of several cytokines and other inflammatory mediators¹⁴.

We investigated whether pain and tissue destruction in the TMJ of patients with RA are influenced by plasma levels of the proinflammatory cytokine TNF- α or the soluble receptor TNFsRII.

MATERIALS AND METHODS

Patients. A total of 51 patients, 41 seropositive and 10 seronegative for rheumatoid factor (RF), with RA according to the classification criteria of the American Rheumatism Association¹⁵ were included (Table 1). They were

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Table 1. Distribution of age, gender, and duration of general and TMJ symptoms in 51 patients with RA with or without current TMJ pain. Results are expressed as percentage of total patient sample in each subgroup.

	No Current TMJ Pain			Current TMJ Pain			p
	Median	IQR	n	Median	IQR	n	
Age, yrs	52	18	22	53	18	29	
Gender, M/F			8/14			4/25	
Duration, yrs							
General	10	8	22	13	12	29	0.021
TMJ	0	2	22	4	7	29	
RF positivity, n (%)			20 (91)			16 (55)	
Medication, n (%)							
NSAID			17 (77)			18 (62)	
DMARD							
Methotrexate			22 (100)			23 (79)	
Salazopyrine						1 (3)	
Auranofin						1 (3)	
Combination			0 (0)			2 (7)	
Glucocorticoid			12 (55)			12 (41)	

IQR: interquartile range; n: number of observations; RF: rheumatoid factor; DMARD: disease modifying antirheumatic drugs; NSAID: nonsteroidal antiinflammatory drugs.

referred to the clinic from rheumatologists in the Stockholm area. Patients were allocated into groups with (n = 29) or without (n = 22 patients) TMJ pain according to the American Association of Orofacial Pain¹⁶ diagnostic criteria (Table 1). Inclusion criteria for the TMJ pain group were TMJ resting pain or TMJ pain upon mandibular movement. Four patients were not receiving any current medication; 47 patients were receiving stable longterm medication (Table 1) including nonsteroidal antiinflammatory drugs, disease modifying antirheumatic drugs, or oral glucocorticoids. There was no difference in the distribution of medication between patients with or without TMJ pain. None of the patients was on anti-TNF or anti-IL-1 medication. This study was approved by the ethical committee at Huddinge University Hospital (Karolinska Institutet 03-204).

Assessment of subjective symptoms and clinical signs. Each patient was clinically examined by one of the 2 authors immediately before blood sampling with the operators blinded to medical data at examination. Operators were calibrated to each other and according to the clinical examination routine used in other studies¹⁶⁻²⁰.

Examination comprised the following variables: (1) Patients were asked about pain in 9 joint regions besides the TMJ (neck, shoulders, elbows, hands, upper back, lower back, hips, knees, and feet) and the number of painful joint regions was recorded (score 0-9). (2) A 100 mm visual analog scale (ACO, Stockholm, Sweden; score 0-100) with endpoints marked "No pain" and "Worst pain ever experienced" was used to assess current degree of overall body pain intensity as well as TMJ pain intensity at rest and on maximum mouth opening for each TMJ. (3) A score (0-4) for tenderness to digital palpation of the TMJ was adopted that involved evaluation of the lateral and posterior aspect of the joint on each side. For each site, one unit was scored if the patient reported tenderness upon palpation and 2 units if the palpation in addition caused a palpebral reflex. Pressure pain thresholds to linearly increasing pressure over the lateral aspect of the TMJ and over glabella on the frontal bone were assessed with an electronic algometer with a 1 cm² blunt rubber tip and a rate of increasing pressure of 50 kPa/s (Somedic Sales AB, Sollentuna, Sweden). TMJ pain upon mandibular movements (maximal and voluntary mouth opening, ipsilateral and contralateral laterotrusion, and protrusion) were recorded separately for each TMJ. One unit was scored for each movement causing TMJ pain on each side (score 0-4). (4) The degree of anterior open bite was used as a clinical marker of the degree of cartilage and bone destruction in the TMJ and was assessed by recording the occlusal contacts on each side upon hard biting in intercuspid position (2 × 8 mm, Occlusions-Prüf-Folie, GHM Hanel Medizinal, Nürtingen, Germany). The following

scores were used on each side: 0: occlusal contacts including the canine; 1: no contacts anterior to the first premolar; 2: no contacts anterior to the second premolar; 3: no contacts anterior to the first molar; 4: no contacts anterior to the second molar; and 5: no occlusal contact. The sum of scores on the right and left sides was used in the analysis as an estimation of the degree of anterior open bite. None of the patients in our study was edentulous.

Blood sampling. Venous blood was collected and used for determination of RF, erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP), and plasma levels of TNF- α and TNFsRII. RF titers below 15 IE/ml and CRP levels below 10 mg/l were considered zero values according to standard procedures of the Department of Clinical Chemistry at Karolinska University Hospital, Huddinge, Sweden.

Analysis of mediators. Plasma levels of all investigated cytokines and receptors were determined using commercially available enzyme linked immunoassays in which highly specific antibodies were used to detect the mediators (TNF- α : TNF- α EASIATM and TNFsRII: EASIAh TNF-RIITM, Medgenix, B 6220 Fleurus, Belgium). Median (75th/90th percentile) plasma levels of TNF- α in healthy individuals was 6 (12/18) pg/ml as assayed in our laboratory. According to the manufacturers, normal plasma level to be expected for TNFsRII in healthy individuals is 829-2262 pg/ml (average 1500 pg/ml).

Statistics. Nonparametric methods were applied for all statistical analyses. Median and interquartile range (75th-25th percentile; IQR) were used for descriptive statistics. To enable statistical analysis of side related variables with variables related to the individual, the sum of the right and left scores for the side-related variables was used.

A more detailed statistical analysis was performed with the patients allocated to 2 groups according to their plasma levels of TNF- α : patients with elevated (> 12 pg/ml, i.e., > 75th percentile of 37 healthy individuals analyzed in our laboratory) or normal (\leq 12 pg/ml) plasma TNF- α levels.

The significance of the differences between groups was tested with Mann-Whitney's U-test or ANOVA on ranks (Kruskal-Wallis test). Correlations between variables were tested for significance by the Spearman's ranked sign test. Chi-square test was used to calculate the significance of differences in RF between patients with or without TMJ pain. A probability level of less than 0.05 was considered as significant.

RESULTS

Clinical and blood variables are shown in Table 2. A total of 29 patients were classified with TMJ pain and 22 patients had

Table 2. Clinical and serological variables in 51 patients with RA with or without current TMJ pain.

	No Current TMJ Pain			Current TMJ Pain			p
	Median	IQR	n	Median	IQR	n	
Painful joint regions, no.	6	1	21	6	2	29	
Mouth opening capacity, mm	48	8	22	39	10	29	< 0.001
Pain intensity at rest							
General	42	20	22	47	19	29	
TMJ	NA			39	74	29	
Tenderness to palpation	0	1	22	2	3	29	< 0.001
Pressure pain threshold, kPa							
Glabella	408	160	22	312	180	29	0.018
TMJ	500	223	21	383	192	29	0.013
Pain intensity upon joint movement							
Maximum mouth opening	NA			39	44	29	
Number of painful movements	NA			3	3	29	
Anterior open bite, score	0	3	22	1	2	29	
Patients with anterior open bite, n (%)			10 (45)			12 (41)	
Inflammatory mediators in plasma, pg/ml							
TNF- α	18	12	22	15	15	29	
TNFsRII	2675	860	22	2300	853	29	
Markers of inflammatory activity							
Erythrocyte sedimentation rate, mm/h	30	15	20	34	20	28	
C-reactive protein, g/l	18	36	20	16	56	28	
Platelet count, $10^9/l$	391	279	20	345	140	29	

IQR: interquartile range; NA: not applicable (variables used to allocate patients to “No TMJ pain” and “TMJ pain” groups); number of painful joint regions; pain intensity at rest as assessed with a 100-mm visual analogue scale; tenderness to palpation: score of tenderness to digital palpation of the lateral and posterior aspect of the TMJ (0–8); pressure pain threshold: for linearly increasing pressure over glabella or over the lateral aspect of the TMJ (kPa); pain intensity upon maximum mouth opening as assessed with a 100-mm visual analogue scale; number of painful movements (0–8).

anterior open bite. In the group with TMJ pain, 12 patients had anterior open bite and 17 did not. In the group without TMJ pain, there were 10 patients with and 12 without anterior open bite (Table 2). Patients with or without anterior open bite did not differ significantly regarding any other investigated clinical or blood variable.

TMJ pain in relation to clinical findings. Patients with TMJ pain had longer duration of general disease ($p = 0.021$; Table 1) and lower pressure-pain threshold over the glabella and TMJ ($p = 0.018$ and $p = 0.013$, respectively; Table 2); smaller maximum mouth opening capacity ($p < 0.001$; Table 2); and more tenderness to digital palpation of the TMJ ($p < 0.001$; Table 2) than patients without TMJ pain. Patients with TMJ pain had lower frequency of RF seropositivity (16/29, 55%) than those without pain (20/22, 91%, $n = 51$, $p = 0.006$).

Inflammatory mediators in relation to temporomandibular joint pain. Plasma levels of TNFsRII were above normal in 15 patients and positively correlated to TMJ pressure-pain threshold ($r_s = 0.58$, $n = 15$, $p = 0.025$; Figure 1) in patients with elevated TNF- α (> 12 pg/ml) in plasma.

Inflammatory mediators in relation to TMJ tissue destruction. In patients with TMJ pain, plasma TNFsRII was negatively correlated to the degree of anterior open bite ($r_s = -0.41$, $n = 29$, $p = 0.026$; Tables 2 and 3; Figure 2A). This relationship was stronger in the subgroup of patients with TMJ pain and

normal plasma TNF- α ($r_s = -0.54$, $n = 14$, $p = 0.047$; Tables 2 and 3; Figure 2B).

Inflammatory mediators and markers. Plasma TNF- α and TNFsRII were positively correlated in the total patient sample

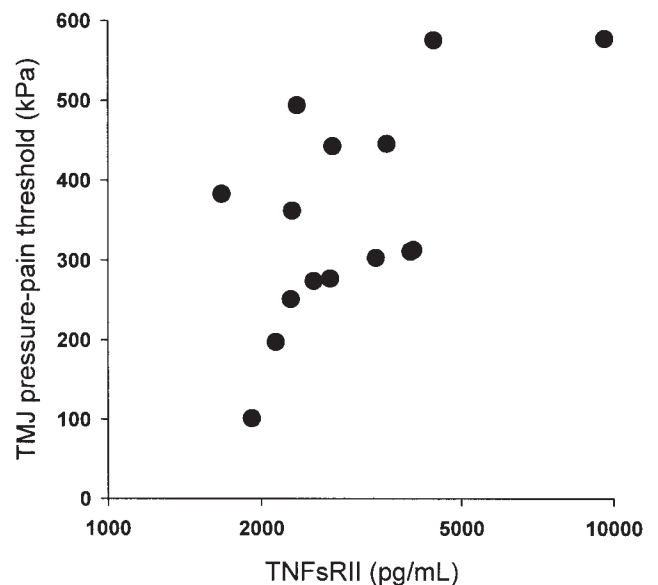


Figure 1. Scatter-plot showing the relationship between plasma TNFsRII and TMJ pressure-pain threshold ($r_s = 0.58$, $n = 15$, $p = 0.025$) in 15 patients with RA and TMJ pain.

Table 3. Degree of anterior open bite (0–9), as a clinical sign of TMJ tissue destruction, in relation to plasma TNF- α and TNFsRII in 29 patients with RA and TMJ pain.

	Low TNF- α			High TNF- α		
	Median	IQR	n	Median	IQR	n
Low TNFsRII	2	6	11	1	1	5
High TNFsRII	0	0	3	0	1	10

($r_s = 0.58$, $n = 51$, $p < 0.001$) as well as in patients with ($r_s = 0.48$, $n = 29$, $p = 0.007$) and without TMJ pain ($r_s = 0.76$, $n = 22$, $p < 0.001$). The ratio between plasma TNFsRII and TNF- α levels was negatively correlated to the TNF- α level ($r_s = -0.84$, $n = 51$, $p < 0.001$).

In patients with TMJ pain, plasma TNFsRII was positively correlated with CRP ($r_s = 0.38$, $n = 28$, $p = 0.048$).

DISCUSSION

Our study indicates that insufficient systemic endogenous control of TNF- α , as represented by TNFsRII in plasma, is associated with TMJ pain and tissue destruction in RA.

In patients with TMJ pain, high plasma TNFsRII was associated with lower degree of anterior open bite, which is a clinical sign of destructive changes of TMJ cartilage and bone tissue. At the same time there was no difference in plasma TNF- α between patients with and without anterior open bite. Our results therefore indicate that insufficient endogenous control of TNF- α , as represented by low plasma TNFsRII, is a risk factor for development of structural changes of the TMJ. Systemic levels of endogenous antiinflammatory mediators such as TNFsRII thus seem to influence the extent of structural joint

damage in RA. Since TNFsRII is considered one of the most important factors involved in endogenous control of proinflammatory cytokines in RA¹⁴, insufficient formation of soluble TNF receptors may result in development or maintenance of inflammation due to reduced blocking of TNF- α ²¹. Indeed, relief of TMJ pain in patients with RA as a response to anti-TNF- α treatment with infliximab has been found to be associated with increased levels of antiinflammatory cytokines and receptors in plasma as well as SF after treatment¹⁷.

The degree of anterior open bite did not differ between patients with and without TMJ pain, and plasma TNF- α was not found to be related to the degree of anterior open bite. This finding could, however, be explained by temporal variations in local pain and inflammatory activity that may be unrelated to persistent anterior open bite. In addition, other pro- and antiinflammatory mediators may contribute to the modulation of joint tissue breakdown in these patients. For example, the influence of TNFsRI, IL-1 β , IL-1ra, IL-1sRI, IL-1sRII, and IL-6 was not investigated, but these mediators probably contribute to modulation of the local inflammatory response^{2,7,9}. Another explanation could be that systemic inflammatory activity was low in general and unrelated to the degree of anterior open bite, which is a result of a local inflammatory process. Patients were all receiving longterm stable treatment with various combinations of nonsteroidal antiinflammatory drugs, disease-modifying antirheumatic drugs, and oral glucocorticoids, which could explain the low systemic inflammatory activity. Local inflammatory rather than systemic processes may thus be mainly responsible for the development and maintenance of TMJ tissue destruction and anterior open bite²².

Remarkably, no association between TNFsRII and anterior

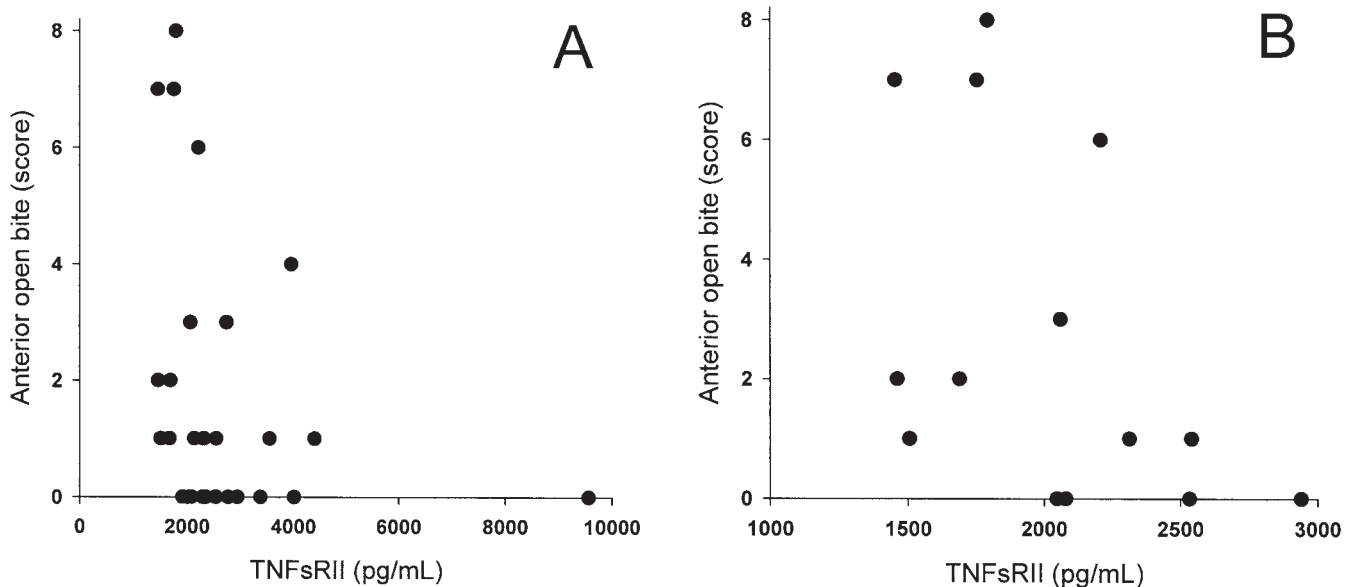


Figure 2. Scatter-plot showing the relationship between plasma TNFsRII and anterior open bite (score 0–9). (A) Twenty-nine patients with RA and TMJ pain [median (IQR) TNF- α : 15 (15) pg/ml ($r_s = -0.41$, $n = 29$, $p = 0.026$)] compared to (B) 14 of these patients with normal (< 12 pg/ml) plasma TNF- α [median (IQR) plasma TNF- α : 10 (4) pg/ml; $r_s = -0.54$, $n = 14$, $p = 0.047$].

open bite was found in patients without TMJ pain, which is difficult to explain. One explanation could be that these patients had low local inflammatory activity at the time of examination, while irreversible tissue changes that developed during previous episodes of inflammation are still present. Another explanation could be that tissue destruction is unrelated to inflammation or at least that tissue destruction can occur without inflammation^{23,24}.

Besides reduction of tissue destruction, antiinflammatory effects of TNFsRII regarding the TMJ seem to include anti-nociception since high plasma TNFsRII was associated with high TMJ pressure-pain thresholds. High TNF- α levels in TMJ SF have been found to be associated with TMJ pain and tenderness upon palpation⁶. Since plasma TNF- α appears to be involved in TMJ pain it is likely that TNFsRII is able to reduce or inhibit analgesic effects of TNF- α . This was also true for TNF- α inhibition with infliximab¹⁷.

The TNFsRII level was in general more than 200 times higher than the corresponding TNF- α level in patients with low plasma TNF- α . This ratio tended to be lower in patients with high plasma TNF- α . Production and release of TNF- α and TNFsRII increase during inflammation^{21,23-25}, which explains the higher TNFsRII level in patients with high plasma TNF- α . However, a considerable concentration excess of natural soluble TNF receptors is necessary for inhibition of the biological actions of TNF- α and it seems that production of the soluble receptor becomes insufficient when the TNF- α levels rise above a certain level. However, balance between the increase of TNF- α and TNFsRII in inflammation varies largely, even among patients with the same disease at the same stage. This individual balance of TNF- α and TNFsRII might explain part of the variation in individual disease progression.

Patients with anterior open bite did not differ from those without regarding any of the investigated variables. Our study thus suggests that none of the investigated blood variables are useful to identify individuals at risk for destructive processes in the TMJ when pain is absent as a warning signal. However, this patient group would be very important to identify for early intervention with anti-TNF- α treatment, for example.

Fewer patients with TMJ pain were positive for RF versus patients without TMJ pain, suggesting that neither TMJ pain nor RF is related to degree of anterior open bite since the degree of anterior open bite was similar in the groups with and without TMJ pain. In addition, the apparent lack of relationship between TMJ pain and anterior open bite further suggests that TMJ pain and tissue destruction are modulated by mechanisms that are mostly unrelated. The relationship between positive RF and TMJ pain or vice versa is, however, difficult to explain from a mechanistic point of view, but seropositive patients with RA have previously been found to have higher general pain intensity but less severe TMJ symptoms (resting pain intensity, pain intensity on maximum mouth opening, and number of painful mandibular movements) than seronegative patients²⁶.

In conclusion, our results indicate that insufficient systemic endogenous control of TNF- α seems to contribute to TMJ pain and tissue destruction in RA.

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