

Temporomandibular Joint Pressure Pain Threshold Is Systemically Modulated in Rheumatoid Arthritis

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***Aims:** To investigate the relative importance of systemic and local inflammatory mediators (serotonin: 5-HT; tumor necrosis factor: TNF; soluble interleukin-1 receptor II: IL-1sRII) in the modulation of temporomandibular joint (TMJ) pressure pain threshold in patients with seropositive or seronegative rheumatoid arthritis (RA) and to investigate to what extent TMJ pressure pain threshold is related to other TMJ pain parameters. **Methods:** Sixty patients with seropositive RA for rheumatoid factor and 74 patients with seronegative RA involving the TMJ were investigated regarding synovial fluid and plasma levels of IL-1sRII, 5-HT, and TNF as well as erythrocyte sedimentation rate, C-reactive protein, thrombocyte particle count, and rheumatoid factor in blood. TMJ resting pain, movement pain, tenderness, and palpebral pain reflex to digital palpation and TMJ pressure pain threshold were examined. **Results:** Statistical analyses indicated that TMJ pressure pain threshold was only correlated to systemic factors. TMJ movement pain was in turn mainly correlated to systemic mediators in the seropositive patients but to local mediators in the seronegative patients where synovial fluid IL-1sRII was positively correlated to TMJ pain on mouth opening. Seropositive patients had higher systemic inflammatory activity but lower TMJ movement pain intensities than seronegative patients. **Conclusion:** The results indicate that TMJ pressure pain threshold is modulated by systemic rather than local inflammatory mediators and suggest that it is unrelated or only weakly related to other TMJ pain entities in RA patients. A rheumatoid factor-dependent systemic modulation, in combination with local factors, seems to account for TMJ pain in RA patients. J OROFAC PAIN 2008;22:231–238.*

Key words: pain, pain threshold, serotonin, temporomandibular joint, tumor necrosis factor

Clinically temporomandibular joint (TMJ) pain comprises resting pain, pain on internal mechanical stimulation (eg, pain on movement), and pain on external mechanical stimulation (eg, pain on pressure). The pressure pain threshold over the TMJ has been shown to be lower in patients with rheumatoid arthritis (RA) than in healthy individuals¹ and seems to be regulated by systemic or central mechanisms rather than local factors in TMJ arthritis.^{2–5} The mechanisms behind reduced TMJ pressure pain threshold and its relation to other TMJ pain entities are therefore of particular interest to study.

Table 1 Demographic Data for 134 Patients with TMJ RA

	Median	IQR	n
Seropositive for the rheumatoid factor			
Age (y)	55	16	60
Gender (M/F)			12/48
Duration of general joint involvement (y)	8	13	59
Duration of local TMJ involvement (y)	4	7	48
Seronegative for the rheumatoid factor			
Age (y)	45	24	71
Gender (M/F)			8/66
Duration of general joint involvement (y)	10	11	70
Duration of local TMJ involvement (y)	4	6	63

IQR = 75th to 25th percentile; M = males; F = females.

RA is a chronic and systemic inflammatory disease that frequently affects the TMJ,⁶⁻⁸ sometimes to a severe extent. TMJ pain due to involvement of RA may be modulated by systemic mechanisms (ie, circulating mediators acting on the synovial tissues or pain-associated mechanisms in the central nervous system) as well as local mechanisms (ie, mediators released in the synovial tissues or neurogenic inflammatory reflexes), since RA is a systemic disease that expresses a major part of its pathology in the synovial tissues.^{9,10} However, the relative contribution of systemic and local factors for the modulation of joint pain in RA has not yet been determined. As has been shown previously, the proinflammatory amine serotonin (5-HT)¹⁰ and cytokine tumor necrosis factor (TNF)^{5,11} as well as the soluble anti-inflammatory interleukin-1 receptor II (IL-1sRII),^{12,13} among other mediators, such as eicosanoids and glutamate,^{14,15} are involved in the pathophysiology of RA. On a clinical basis, determination of the relative influence of systemic and local factors has a substantial interest for choice of treatment, since the effect of systemic treatment with, eg, TNF blockers has been shown to be rather variable in reducing TMJ pain.^{16,17} It would be of additional interest to know which factors the different pain parameters, including the TMJ pressure pain threshold, are related to in order to evaluate their diagnostic ability.

Approximately 80% to 90% of RA patients are seropositive for the rheumatoid factor,¹⁸ which is a platelet-activating immune complex that elicits immune reactions in the synovial tissues. Seropositive patients have higher systemic inflammatory activity and poorer prognosis^{19,20} than seronegative RA patients, and these 2 groups have been shown to differ not only regarding general inflammatory activity but also local TMJ pain

intensity,¹⁰ which suggests interesting but so far undetermined differences between these 2 patient groups regarding their TMJ pain profile.

The aims of this study were to investigate the relative importance of systemic and local inflammatory mediators (5-HT, TNF, IL-1sRII) in the modulation of TMJ pressure pain threshold in patients with seropositive or seronegative RA and to investigate the extent to which TMJ pressure pain threshold is related to other TMJ pain parameters.

Materials and Methods

Patients

One-hundred thirty-four patients, 114 women and 20 men, with RA according to the diagnostic classification of the American Association of Rheumatology²¹ were included (Table 1). Further inclusion criteria were pain or tenderness of the TMJ as an indication of involvement by RA. The patients were consecutively referred to the clinic from rheumatologists in the Stockholm area; TMJ pain was the most frequent reason for referral. Disease activity and duration are described in Tables 1 and 2. All patients had TMJ pain despite treatment with a variety of systemic medications. The patients were categorized as seropositive or seronegative according to the presence or absence of abnormal levels of rheumatoid factor in blood.

This study was approved by the ethical committee at Huddinge University Hospital, Huddinge, Sweden (142/02 and 176/91).

Assessment of Subjective Symptoms and Clinical Signs

The pressure pain threshold over the palpable lateral pole of the TMJ condyle with the patient's mandible in a rest position and that over the glabella on the frontal bone was determined with a single measurement by a handheld electronic pressure algometer (Somedic), consisting of a pressure transducer probe connected to a pistol grip with a display unit. The tip of the pressure transducer has a flat, circular rubber tip with an area of 1.0 cm². A linearly increasing pressure rate of 50 kPa/s^{1,22,23} was applied until the subject responded to the first pain sensation by pressing a button on a device connected to the probe that froze the pressure pain threshold level on the display. The pressure pain threshold was defined as the minimum pressure needed to evoke a painful sensation recognizable by the subject.

Table 2 Clinical, Synovial Fluid and Blood Variables in 60 Patients with Seropositive RA and 74 Patients with Seronegative RA

	Seropositive*					Seronegative**					P
	Median	IQR	n	% > 0	% abn	Median	IQR	n	% > 0	% abn	
General disease activity											
No. of painful joint regions (0 to 9)	6	4	60	100	NA	4	4	73	96	NA	< .001
Erythrocyte sedimentation rate (mm/first h)	32	18	54	100	70	16	20	68	100	25	< .001
C-reactive protein (mg/L)	14	34	57	68	67	0	15	71	46	39	.001
Thrombocyte particle concentration (10 ⁹ /L)	340	118	43	100	26	292	80	64	100	14	< .001
Rheumatoid factor	83	180	50	100	100	0	0	72	0	0	< .001
TMJ pain intensity score											
At rest	21	51	54	87	NA	33	39	65	92	NA	NS
On maximum mouth opening	16	46	49	59	NA	30	33	60	83	NA	.042
No. of painful mandibular movements (0 to 4)	2	2	59	76	NA	3	1	74	89	NA	.003
Pressure pain threshold											
TMJ (kPa)	149	90	60	100	NA	146	75	74	100	NA	NS
Glabella (kPa)	259	197	42	100	NA	234	136	54	100	NA	NS
TNF											
Synovial fluid (pg/mL)	0	17	12	25	25	12	55	14	14	14	NS
Plasma (pg/mL)	17	14	34	97	76	13	13	54	87	52	.031
5-HT											
Synovial fluid (nmol/mL)	46	2576	12	75	75	33	8995	11	82	82	NS
Serum (nmol/mL)	808	486	34	100	18	832	647	57	100	28	NS
Plasma (nmol/mL)	21	41	28	100	46	22	28	50	100	32	NS
Platelet-rich plasma (nmol/mL)	600	634	21	100	NA	1024	1585	12	100	NA	NS
IL-1sRII											
Synovial fluid (pg/mL)	1618	1866	13	8	NA	2889	6369	11	9	NA	NS
Plasma (pg/mL)	13518	4472	29	100	38	12232	3429	32	100	19	NS

*For the rheumatoid factor.

Pain intensity was assessed with a 100-mm visual analog scale, and the pressure pain threshold was assessed over the palpable lateral pole of the TMJ condyle. IQR = 75th to 25th percentile, % > 0 = percentage of observations exceeding 0, % abn = percentage of observations exceeding normal levels. NA = not applicable; NS = not significant. Rheumatoid factor was expressed in international units, and levels above 20 units were considered abnormal.

The patients were asked about rheumatic complaints in 9 joint regions besides the TMJ (neck, shoulders, elbows, hands, upper back, lower back, hips, knees, and feet) and the number of involved joint regions was recorded, for a maximum score of 9.

A 100-mm visual analog scale (VAS; score, 0 to 100) with endpoints marked with “no pain” and “worst pain ever experienced” was used to assess the current degree of TMJ pain intensity at rest and on maximum mouth opening.

TMJ pain upon mandibular movements (maximal voluntary mouth opening, ipsilateral and contralateral laterotrusion and protrusion) was scored with 1 unit per movement, causing TMJ pain on each side (score, 0 to 4).

Synovial Fluid Sampling

TMJ anesthesia was achieved by blocking the auriculotemporal nerve posterior to the neck of the mandible with 2.0 mL 2% lidocaine (Xylocain,

Astra-Zeneca) and a standard disposable needle (diameter = 0.40 mm). The TMJ was punctured with another standard disposable needle (diameter = 0.65 mm) inserted into the posterior part of the upper joint compartment. TMJ synovial fluid samples were obtained by using a push-and-pull technique²⁰ to wash the joint cavity with saline. The washing solution, which consisted of 78% saline (NaCl 9 mg/mL, Pharmacia Upjohn) and 22% hydroxocobalamin (Behepan 1 mg/mL; Pharmacia Upjohn), was slowly injected into the posterior part of the upper joint cavity approximately 1 mL at a time and then aspirated. The total volume of the injected washing solution was 4 mL. The hydroxocobalamin was included to determine the amount of synovial fluid in the aspirate by comparing the spectrophotometric absorbance of the aspirate and that of the washing solution. The synovial fluid volume recovered was then calculated. Only samples that fulfilled previously established sample quality criteria were included in the statistical analysis.²⁴

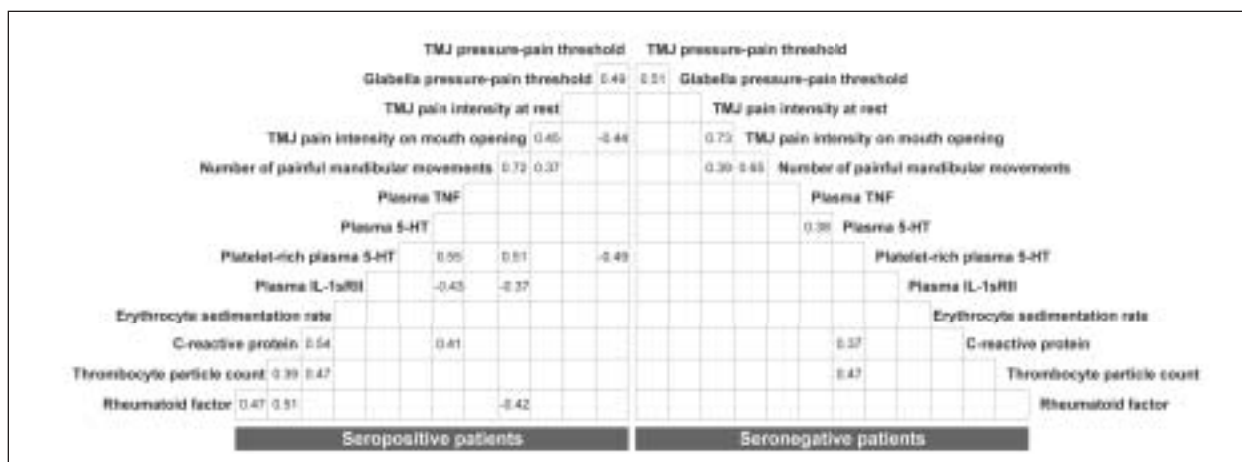


Fig 1 Significant ($r_s > 0.35$ and $P < .05$) Spearman's rank correlation coefficients in 60 patients with seropositive rheumatoid arthritis and 74 patients with seronegative rheumatoid arthritis.

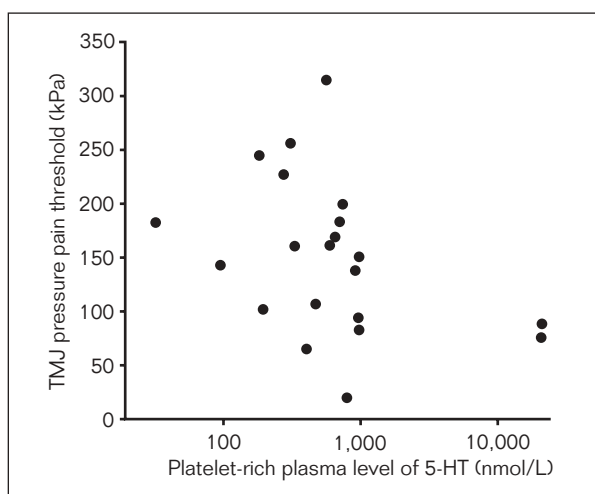


Fig 2 Relation between platelet-rich plasma level of 5-HT (nmol/L) and TMJ pressure pain threshold in 21 patients with seropositive RA ($r_s = -0.49$, $n = 21$, $P = .023$).

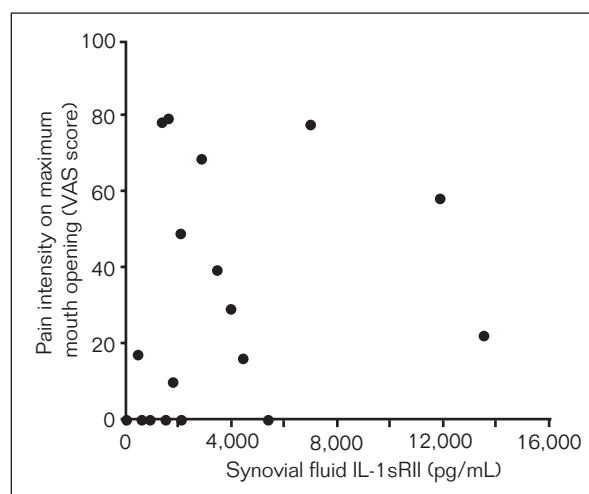


Fig 3 Relation between TMJ synovial fluid level of IL-1sRII and TMJ pain intensity on maximum mouth opening in 21 patients with seropositive RA ($r_s = 0.48$, $n = 21$, $P = 0.28$).

Blood Sampling

Venous blood was collected in a sodium citrate tube (0.105 mol/L) to determine the erythrocyte sedimentation rate and in an EDTA tube that was immediately cooled and centrifuged (1500 g for 10 minutes at $+4^{\circ}\text{C}$) and then frozen (-70°C) and later examined for platelet-rich 5-HT as well as TNF and IL-1sRII in plasma. A separate EDTA tube was processed as described but was centrifuged for 30 minutes instead of 10 minutes; that tube was also examined for 5-HT in platelet-poor plasma. In addition, venous blood was collected without addi-

tives for analysis of serum concentrations of 5-HT, thrombocyte particle count, rheumatoid factor, and C-reactive protein. The tube for determination of serum concentration of 5-HT was left at room temperature for 60 minutes for coagulation and thereafter centrifuged (1500 g for 10 minutes at $+4^{\circ}\text{C}$). The serum was then removed and frozen (-70°C) until analysis. Rheumatoid factor titers below 15 IE/mL and C-reactive protein levels below 10 mg/L were considered as zero values according to the standard procedures of the Department of Clinical Chemistry at Karolinska University Hospital, Huddinge, Sweden.

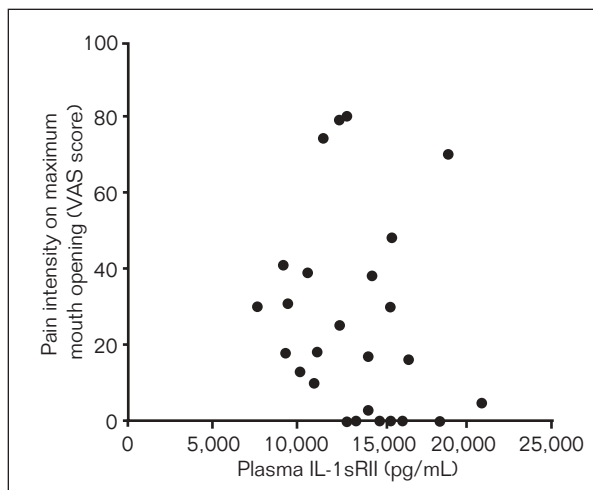


Fig 4 Relation between plasma level of IL-1sRII and TMJ pain intensity on maximum mouth opening in 29 patients with seropositive RA ($r_s = -0.37$, $n = 29$, $P = 0.48$).

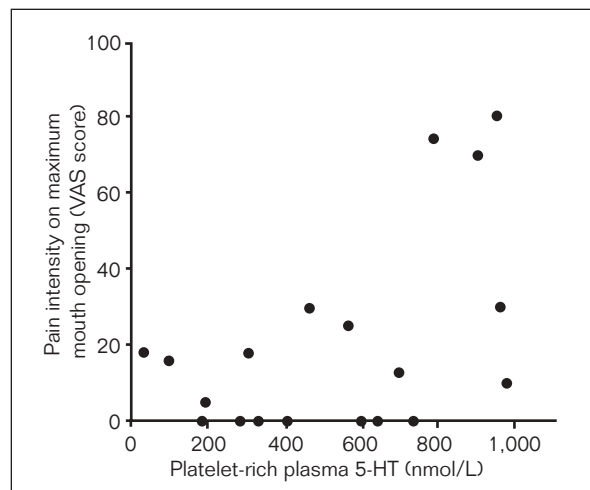


Fig 5 Relation between platelet-rich plasma level of 5-HT (nmol/L) and TMJ pain intensity on maximum mouth opening in 21 patients with seropositive RA ($r_s = 0.51$, $n = 21$, $P = .017$).

Analysis of Mediators

The concentrations of all investigated mediators and receptors were determined by commercially available enzyme-linked immunoassays with highly specific antibodies to detect the mediators (5-HT: Kit nr 0642, Immunotech International; TNF: TNF α EASIA, Medgenix, B 6220 Fleurus; IL-1sRII: Quantikine Immunoassays, R&D Systems). The 25th/75th percentile plasma levels of TNF, 5-HT, and IL-1sRII in healthy individuals are 8/12 pg/mL, 10/30 nmol/L, and 11442/14790 pg/mL, as assayed in the authors' laboratory. The corresponding 25th/75th percentiles of serum 5-HT in healthy individuals are 584/1186 as assayed in the authors' laboratory. TNF and 5-HT are undetectable in TMJ synovial fluid in healthy individuals.

Definition of Terms

Local modulation was defined as changes in TMJ pain parameters by effects of inflammatory mediators released from cells in the TMJ synovial tissues on cell-surface receptors in the TMJ synovial tissues.

Systemic modulation was defined as changes in TMJ pain parameters by effects of inflammatory mediators circulating in the blood on cell-surface receptors in the TMJ synovial tissues, effects of inflammatory mediators circulating in the blood on cell-surface receptors in the central nervous system, or effects of pain mechanisms in the central nervous system.

Statistical Analyses

Nonparametric methods were applied for all statistical analyses. Median and interquartile range (75th percentile to 25th percentile; IQR) were used for descriptive statistics. The seropositive and seronegative patients were divided into 2 age groups according to the median age (50 years) of all patients. Missing data account for the lower number of observations reported for some variables within each group in the Results section as well as in Tables 1 and 2. The significance of the differences between groups was tested with the Mann-Whitney test. Correlations between variables were tested for significance by the Spearman's ranked sign test. A probability level of less than .05 was considered significant.

Results

The clinical, synovial fluid and blood variables are presented in Table 2. Significant correlations between the pain variables as well as inflammatory mediators and markers in the 2 main groups, ie, seropositive and seronegative patients, are presented in Fig 1. Additional data from all patients combined as well as the influence of the background factors gender and age are presented in the text. Figure 2 shows the relation between platelet-rich plasma level of 5-HT and TMJ pressure pain threshold in seropositive patients ($r_s = -0.49$, $n = 21$, $P = .023$).

Influence of Age on Pressure Pain Threshold and Inflammatory Mediators

TMJ. The seropositive patients younger than 50 years of age showed a positive correlation between pressure pain threshold and C-reactive protein ($r_s = 0.48$, $n = 21$, $P = .027$).

Seronegative patients younger than 50 years of age showed a positive correlation between TMJ pressure pain threshold and plasma level of 5-HT ($r_s = 0.45$, $n = 29$, $P = .014$).

Glabella. In the seronegative patients younger than 50 years of age the glabella pressure pain threshold was positively correlated to 5-HT in plasma ($r_s = 0.42$, $n = 29$, $P = .022$).

Relation Between TMJ Pain on Mandibular Movement and Inflammatory Factors

In all patients, the TMJ pain intensity on maximum mouth opening was positively correlated to the synovial fluid level of IL-1sRII ($r_s = 0.48$, $n = 21$, $P = .028$; Fig 3). In the seropositive patients, the plasma levels of IL-1sRII and platelet-rich plasma level of 5-HT were correlated to TMJ pain intensity on maximum mouth opening ($r_s = -0.37$, $n = 29$, $P = .048$ and $r_s = 0.51$, $n = 21$, $P = .017$, respectively; Figs 4 and 5).

Influence of Age on Number of Painful Mandibular Movements and Inflammatory Mediators. Number of painful mandibular movements was positively correlated to the synovial fluid level of IL-1sRII ($r_s = 0.68$, $n = 24$, $P < .001$) in all patients combined for the entire study sample.

In the seropositive patients younger than 50 years of age, the number of painful mandibular movements was negatively correlated with erythrocyte sedimentation rate ($r_s = -0.59$, $n = 20$, $P = .006$).

Differences Between Seropositive and Seronegative RA Patients

The seropositive and the seronegative patients differed for several variables. The seropositive patients were older ($P = .001$) and had higher plasma levels of TNF ($P = .031$), a higher erythrocyte sedimentation rate ($P < .001$), a higher C-reactive protein count ($P = .001$), and a higher thrombocyte particle concentration ($P < .001$) than the seronegative patients. On the other hand, the seronegative patients reported higher TMJ pain intensity on mouth opening ($P = .042$) and a higher number of painful mandibular movements ($P = .003$; Table 2).

There were no significant differences in pressure pain threshold or TMJ synovial fluid levels of 5-HT, TNF, or IL-1sRII between seropositive and seronegative RA patients.

Discussion

This study indicates that the TMJ pressure pain threshold is determined by systemic rather than local mediators in RA. In addition, seropositive and seronegative patients differ not only in terms of systemic inflammatory activity, as could be expected, but also regarding TMJ pain on mandibular movement. Seronegative patients do have lower systemic inflammatory activity, as expressed by the inflammatory markers erythrocyte sedimentation rate, C-reactive protein, and thrombocyte particle concentration, than seropositive patients but similar or even higher intensity of TMJ pain, which indicates foremost local mechanisms behind the TMJ pain in seronegative patients. However, TMJ pain in both seropositive and seronegative RA patients seems to be influenced by systemic serotonergic factors.

Pressure Pain Threshold

TMJ pressure pain threshold seems to be modulated mainly by systemic mechanisms mediated by circulating 5-HT, since low TMJ pressure pain threshold was associated with a high level of 5-HT in platelet-rich plasma in seropositive patients and low 5-HT plasma level in seronegative patients younger than 50 years. Moreover, the TMJ pressure pain threshold was related to the glabella pressure pain threshold in both groups, which supports a systemic modulation. Indeed, patients with pain from fibromyalgia/whiplash, endometriosis, low back pain, or RA have been reported to have lower pressure pain threshold for 8 investigated sites compared to healthy individual controls, which supports an association between a general painful condition and a generalized reduced pressure pain threshold.⁴

In the seropositive patients, TMJ pressure pain threshold was related to the systemic inflammatory activity as expressed by C-reactive protein, which in turn was related to TNF in plasma. This further supports a systemic inflammatory modulation of TMJ pressure pain threshold in these patients. In the seronegative patients, on the other hand, TMJ pressure pain threshold was associated with 5-HT in plasma. These findings indicate a difference between seropositive and seronegative patients

in the character of systemic modulation of pressure pain threshold. In fact, high 5-HT plasma level in seronegative RA patients before treatment with intra-articular injection of the 5-HT₃ receptor blocker granisetron was shown to predict a reduction of the TMJ pressure pain threshold.²⁵

The degree of local TMJ inflammatory activity, as indicated by the investigated inflammatory mediators in the synovial fluid, did not influence the TMJ pressure pain threshold in any of the groups. In a previous study, intra-articular injection of glucocorticoid was not found to influence TMJ pressure pain threshold despite improvements in TMJ pain at rest and movement.^{3,5} One explanation for the lack of treatment effect on TMJ pressure pain threshold could therefore be that systemic factors, including the peripheral serotonergic system, play a major role in determining the threshold.

Assessment of TMJ pressure pain threshold with an algometer affects the periarticular tissues between the skin surface and the lateral aspect of the joint more than the joint proper, which may explain why systemic rather than intra-articular mediators predominantly modulate this pain entity. Thus, the results of the present study indicate that TMJ pressure pain threshold has a very limited value as a tool for assessment of intra-articular pain conditions of inflammatory nature in the TMJ.

Resting Pain

No clinically relevant association between local TMJ inflammatory activity and resting pain intensity could be found in this study, as indicated by the absence of significant relations to synovial fluid mediator levels in both seropositive and seronegative patients, which is in agreement with previous studies.^{26,27} The investigated mediators do not seem to influence or modulate TMJ resting pain in RA to a significant extent.

Pain on Mandibular Movement

TMJ pain intensity on maximum mouth opening and number of painful mandibular movements are pain parameters provoked by internal mechanical stimulation. A combination of the local factor synovial fluid IL-1sRII and the systemic factors platelet-rich plasma level of 5-HT, plasma level of IL-1sRII, erythrocyte sedimentation rate, and rheumatoid factor seem to modulate TMJ pain intensity in RA. High TMJ pain intensity on mouth opening in the seropositive group was thereby asso-

ciated with high platelet-rich plasma level of 5-HT but low titer of rheumatoid factor and low plasma level of IL-1sRII. A high level of 5-HT in platelet-rich plasma suggests a high total blood content of 5-HT as well as a high degree of thrombocyte activation, which both have been associated with the clinical activity of RA.^{7,28,29} The association between TMJ movement pain and low plasma level of IL-1sRII indicates that an insufficient endogenous systemic control of IL-1b contributes to TMJ pain.¹³ The relation between rheumatoid factor and TMJ movement pain is difficult to explain but has been previously reported.¹⁰ Plasma 5-HT, IL-1sRII, and rheumatoid factor titer were not significantly related, which suggests an independent influence of these factors.

Difference Between Seropositive and Seronegative Patients

The seropositive patients with TMJ involvement had higher systemic inflammatory activity than the seronegative patients, which is expected and has been shown in many previous studies.^{7,10,20,30} One explanation could be that rheumatoid factor has an aggravating influence on the disease process both systemically and locally, eg, by its platelet-activating properties and its ability to trigger potent immune responses. The finding that the seronegative patients had more pain is intriguing but is nevertheless in agreement with previous results.¹⁰

In conclusion, the results from this study indicate that TMJ pressure pain threshold is modulated by systemic rather than local inflammatory mediators and suggest that it is unrelated or only weakly related to other TMJ pain parameters in RA patients. A rheumatoid factor-dependent systemic modulation, in combination with local factors, seems to account for TMJ pain in RA patients.

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