TMJ Pain and Crepitus Occur Early Whereas Dysfunction Develops Over Time in Rheumatoid Arthritis

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Aims: To investigate inflammatory mediator levels in TMJ synovial fluid (SF) and blood and to investigate clinical TMJ symptoms in relation to general and TMJ symptom duration in patients with rheumatoid arthritis (RA). Methods: Examination of 80 TMJs (68 patients; median age 55 years; 85% women) included the following variables: TMJ pain at rest, maximum mouth opening, and palpation; jaw movement capacity; number of painful movements; crepitus; and degree of anterior open bite. Levels of tumor necrosis factor (TNF), TNF soluble receptor II, interleukin 1β, IL-1 receptor antagonist, IL-1 soluble receptor II, and serotonin in TMJ SF and blood; systemic disease activity; and duration of general and TMJ symptoms were assessed. General symptom duration ≤ 2 years was considered early RA. Results: TMJ symptoms predominantly developed within 5 years following general symptom onset. Logistic regression analysis showed that number of involved joints, general pain, maximum mouth opening, anterior open bite, and TNF plasma levels combined explained 46% of the distinction between early and established RA. Furthermore, TMJ pain at rest and maximum mouth opening, contralateral laterotrusion, painful movements, crepitus, and SF TNF levels combined explained 35% of the distinction. In these analyses, higher general pain and maximum mouth opening, TMJ pain on maximum mouth opening, and crepitus were associated with early RA. Conclusion: This study indicates that TMJ pain and crepitus in RA usually occur within 2 years following general symptom onset. Pain-related dysfunction and structural changes develop with time. TNF in plasma and TMJ SF are associated with this development. This makes early (clinical) recognition of pain and inflammation important, enabling early treatment to minimize later irreversible damage. J Oral Facial Pain Headache 2020;34:398–405. doi: 10.11607/ofph.2718

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Synovial inflammation is one of the key characteristics of rheumatoid arthritis (RA). Many of the changes that occur in the inflamed synovium can be observed in the synovial fluid (SF), which contains cytokines that play important roles in the inflammatory response. Proinflammatory cytokines have even been found to be present prior to clinical symptom onset. Also, the levels of several cytokines in early inflammatory arthritis seem to be higher than in patients with established RA. RA symptoms usually debut bilaterally in small peripheral joints, but may involve other joints as well, including the TMJ. TMJ pain, as well as TMJ cartilage and bone tissue destruction, have been strongly associated with increased SF levels of the cytokines tumor necrosis factor (TNF) and interleukin 1-beta (IL-1β).

Because of the positive effects of early diagnosis and treatment on disease outcomes, identifying patients with early RA is of great importance. Insight into a possible difference between patients with early and established RA regarding inflammatory mediators in TMJ SF and clinical TMJ symptoms could be crucial in order to develop better diagnostic procedures and management of TMJ involvement in RA. Rheumatologists and dentists share the possibility of diagnosing and managing RA cases with TMJ involvement at an early stage to improve prognosis.
Therefore, the aim of the current study was to investigate the inflammatory mediator levels in TMJ SF and blood and the clinical TMJ symptoms in relation to the duration of local and general symptoms in patients with RA.

Materials and Methods

Patients
A total of 68 patients (58 women and 10 men) with RA, diagnosed according to the 1987 classification criteria of the American College of Rheumatology, were included in this study. Fifty-one patients (75%) were positive for the rheumatoid factor (RF). These patients were referred to the specialist clinic for Orofacial Pain and Jaw Function by rheumatologists in the area of Stockholm, Sweden, mainly because of TMJ pain. The patients were included and examined between 1993 and 2007. Systemic pharmacologic treatment of the general disease was provided by the referring rheumatologist. For a subset of 15 patients, specific data on pharmacologic treatment were available: 9 patients received a disease-modifying anti-rheumatic drug (DMARD; the majority being methotrexate) (4 of whom received it in combination with biologic anti-TNF treatment); 2 patients received anti-TNF treatment only; and 4 patients received nonsteroidal anti-inflammatory drug (NSAID) only. No specific data were available for the other 53 patients; however, when taking into account the period of inclusion for this study, all participants were presumably treated by either an NSAID, DMARD, anti-TNF, or a combination of these treatments.9

Table 1 describes the included patient sample.

This project was approved by the regional ethical committee at Karolinska Institutet, Stockholm, Sweden (176/91; 310/97; 142/02; 03-2004) according to the Declaration of Helsinki. Written informed consent was obtained from all study participants.

Assessment of Subjective Symptoms and Clinical Signs
To assess aspects of the degree of general disease, patients were asked about musculoskeletal complaints in nine joint regions besides the TMJ (neck, shoulders, elbows, hands, upper back, lower back, hips, knees, and feet), resulting in a score from 0 to 9. Pain intensity of general symptoms was assessed using either a visual analog scale (VAS) or a numeric rating scale (NRS), both with the end points “no pain” (score of 0) and “worst pain ever experienced” (score of 10). Minimal influence on the results was expected by the mix of visual and numeric scales due to the high correspondence between the two scale types.10

Local TMJ pain intensity at rest was assessed using either a VAS or NRS. Tenderness on digital palpation reported by the patient, or a palpebral reflex, was recorded as present or absent for the lateral aspect of the TMJ using 20-N pressure.

Maximum voluntary mouth opening was measured in millimeters between the right central incisors, and pain intensity on mouth opening was recorded on either the VAS or NRS. The number of painful mandibular movements (maximum voluntary mouth opening, protrusion, and ipsilateral and contralateral laterotrusion; maximum score = 4) was counted for each TMJ.

Pressure pain threshold (PPT) was measured by linearly increasing pressure of approximately 50 kPa/second to the lateral aspect of the TMJ, with an algometer with a 1-cm² rubber tip. The PPT was defined as the minimum pressure needed to evoke a painful sensation recognizable by the patient.

Crepitus was recorded as present if crepitus was palpable or audible in at least one of three maximum-mouth-opening movements.

The degree of anterior open bite (AOB) 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 of occlusal foil in the intercuspid position (2 x 8 µm, Occlusions-Prüf-Folie, GHM Hanel Medizinal). The following scores were used in the assessment of AOB 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 the scores for the right and left sides was used in the analysis as an estimation of the degree of AOB. None of the patients in the present study were edentulous, and the score thus ranged from 0 to 9. A score of 9 (4 + 5) means that only one contact between two opposing teeth exists on one side.

All clinical examinations were performed by two experienced examiners (P.A. and S.K.), and the two examiners were calibrated regularly throughout the years in order to prevent drift. The calibration was both theoretical and clinical.

**TMJ SF Sampling**

All SF samples were obtained by the same two experienced and specially trained operators (P.A. and S.K.) according to Alstergren et al as follows. Anesthesia of the TMJ was achieved by blocking of the auriculotemporal nerve with 2.0 mL Xylocaine (lidocaine 2%, Astra). The TMJ was punctured with a standard disposable needle (diameter = 0.6 mm) inserted into the posterior part of the upper joint compartment. TMJ SF samples were obtained by washing the joint cavity with saline using a push-and-pull technique performed with two syringes, one used for the washing solution to be injected and the other for aspiration. The syringes were connected to the arthrocenesis needle by a three-way stopcock. The injected washing solution consisted of 78% saline (NaCl 9 mg/mL, Kabi Pharmacia) and 22% Behepan (hydroxocobalamin, 1 mg/mL, Kabi Pharmacia), which was injected slowly into the joint cavity in 1-mL portions and aspirated after approximately 20 seconds. This procedure was repeated three times, and the total washing solution volume used was 4 mL. The Behepan was included in order to measure the amount of synovial fluid in the aspirate. The absorbance of the aspirate and a sample of unused washing solution were compared in a spectrophotometer (UV-160A, Shimadzo) at 350 nm with a capillary tube system consisting of a capillary tube of quartz (3 μL/sample) and a capillary tube holder (Shimadzo). The detection limit regarding dilution of the washing solution to be injected and the other for aspiration was completely compensated for this procedure. The absorbance was calculated using the following formula, where \( C_{SF} \) = SF concentration, \( C_{Asp} \) = aspirate concentration, \( Abs_{Asp} \) = aspirate absorbance, and \( Abs_{Wash} \) = washing solution absorbance:

\[
C_{SF} = \frac{C_{Asp}}{1 + \frac{Abs_{Asp}}{Abs_{Wash}}}
\]

During and after the arthrocentesis, blood contamination of the aspirate was estimated visually according to the following scale: no visible blood contamination; hardly visible blood contamination; clearly visible blood contamination; and blood-like appearance of the aspirate. After aspiration, the weight of the sample was immediately measured by a balance (JW-120, Adam Equipment), and the sample was then centrifuged (1,500 g for 10 minutes at 4°C). Hemolysis was then recorded as absent or present. Twelve mL of the supernatant (ie, four capillary tubes) were used for absorbance measurement. The aspirate and washing solution absorbances were compared, and a dilution factor (Absorbance\text{Aspirate} / Absorbance\text{Washing solution}) was calculated for each sample. The same procedures, apparatus, and protocols were used for analysis of absorbance, as well as for the sample handling, throughout the study period.

**Sample Quality Criteria**

In order to ensure that only high-quality samples were used in the statistical analysis, included samples had to meet the sample quality criteria according to Alstergren et al, which exclude samples with hemolysis, clearly visible blood contamination, aspirate weight < 0.5 g, and a dilution factor of > 0.98.

**Blood Sampling**

Venous blood was collected and used for determination of RF level, erythrocyte sedimentation rate, serum level of C-reactive protein, and plasma or serum levels of inflammatory mediators. RF titers below 15 IE/mL and C-reactive protein levels below 10 mg/L were considered as “0” values according to the standard procedures of the accredited laboratory at the Department of Clinical Chemistry at Karolinska University Hospital.

**Analysis of Mediators**

The TMJ SF and blood plasma concentrations of TNF, TNF soluble receptor II (TNF\text{sR}II), IL-1β, IL-1 receptor antagonist (IL-1ra), IL-1 soluble receptor II (IL-1\text{sR}II), and serotonin (5-HT) were determined using commercially available enzyme-linked immunoassays, in which highly specific antibodies were used to detect the mediators (TNF, TNF\text{sR}II, IL-1β, IL-1ra, IL-1\text{sR}II; R&D Systems; serotonin: Serotonin EIA-kit, Immunotech A Coulter Company). The serotonin assay for SF concentrations was modified to be applicable at concentrations between 1.6 and 5,000 nmol/L. To compensate for hydroxocobalamin interaction with the assay, the SF aspirates were read against a standard curve with hydroxocobalamin included. The small hydroxocobalamin interaction was completely compensated for by this procedure.

Although data were collected over a period of several years, possible drift in performance is expected...
to be of minor and insignificant extent, since the commercially available assays are quality controlled by the manufacturer in order to ensure consistent performance. The same assay was used for each mediator during the study period.

**TMJ Arthritis**

Probable and definite TMJ arthritis were defined according to Alstergren et al.14 In the present study, TMJ arthritis was considered present if the joint fulfilled at least the criteria for probable arthritis, being a combination of pain on maximum mouth opening and contralateral laterotrusion of < 8 mm. These simple measures are not trend-dependent or influenced by new insights or techniques since exactly the same clinical procedures were used, and therefore the criteria, although published in 2018, are applicable to the data currently described as well.

**Statistical Analyses**

Nonparametric statistics were used throughout the study because the majority of variables was either not normally distributed or not measured on an interval scale. For descriptive statistics, median values and 25th/75th percentiles are presented.

For joint-related variables where there were bilateral data, the joints were considered as two separate statistical units. This enabled a statistical analysis that tested the combination of local SF levels of inflammatory mediators and local TMJ symptoms from the same joint in relation to general and TMJ symptom duration.

To calculate the significance of correlations, the duration of general and local TMJ symptoms (in years) was used as a scale variable, and variables were tested with Spearman rank correlation test.

For logistic regression analysis based on general symptom duration, patients were grouped in either early RA, defined as general symptom duration of \( \leq 2 \) years, or established RA. This dichotomized variable was then used as a dependent variable in the statistical model. For independent variables, the same stepwise backwards procedure was applied.

A probability level of \( P < .05 \) was considered significant.

**Results**

**Clinical Examination Including Laboratory Variables**

Table 2 shows the investigated clinical, SF, and blood variables.

SF samples were collected from 80 joints. Twelve patients had bilateral samples. Detectable levels of TNF were found in 14 out of 58 (24%) samples, and detectable levels of IL-1β were found in 12 out of 75 (16%) samples.

Fifty-four joints were diagnosed with either probable or definite arthritis.
Symptom Duration

Figure 1 shows the distribution of patients by years between the onset of general and TMJ symptoms. The majority of patients developed TMJ symptoms within 5 years or even prior to the onset of general symptoms. There was a positive correlation between the duration of general symptoms and the duration of TMJ symptoms ($R_s = .638, n = 60, P < .001$; Fig 2), where duration of TMJ symptoms was consistently shorter.

Relationship Between Duration of Symptoms vs Clinical, Blood, and TMJ SF Variables

Table 3 shows the significant correlations between duration of general and TMJ symptoms and the investigated variables.

When comparing patients with early RA to patients with established RA, the combination of number of involved joints, general pain intensity, maximum voluntary mouth opening, degree of anterior open bite, and plasma levels of TNF explained 46% of the distinction between the groups ($P = .012$). Higher general pain intensity and greater maximum mouth opening capacity were associated with early RA, whereas a larger number of involved joints, higher degree of anterior open bite, and higher plasma levels of TNF were associated with established RA. Furthermore, the combination of current TMJ pain intensity at rest, pain intensity on maximum voluntary mouth opening, laterotrusion to the contralateral side, number of painful movements, crepitus, and SF levels of TNF explained 35% of the difference between early RA and established RA ($P = .019$). Here, a higher TMJ pain intensity on maximum mouth opening and crepitus were associated with early RA.

Besides comparing patients based on general symptom duration, a similar analysis was performed to compare patients with short and long duration of TMJ symptoms. In this analysis, the combination of TMJ pain intensity on maximum mouth opening, number of painful jaw movements, and SF levels of TNF explained 15% of the distinction between the groups ($P = .041$). Higher TMJ pain intensity on maximum mouth opening was associated with short duration of TMJ symptoms, whereas a higher number of painful jaw movements and higher SF levels of TNF were associated with persisting TMJ symptoms.
Discussion

This study indicates that in RA patients with TMJ symptoms, the onset of these symptoms predominantly occurs in the first 5 years following general symptom onset. Early RA seems to be associated with high general and TMJ pain intensity and early TMJ cartilage degradation. On the other hand, established RA seems to be associated with high general and TMJ disease activity; TMJ cartilage and bone tissue destruction; high systemic and local TNF levels; and reduced TMJ function. In addition, short duration of TMJ symptoms seems to be associated with TMJ pain, but at the same time with low TMJ disease activity and low local TNF levels.

In the present study, early general RA symptoms were associated with high general pain intensity, TMJ pain intensity on maximum mouth opening, TMJ crepitus, and greater maximum mouth opening capacity, but also with a low number of involved joints, low degree of AOB, and low plasma levels of TNF. Both general and TMJ pain intensity thus seem to be higher in early RA, which is consistent with the higher systemic inflammatory activity usually found in early RA. Also, early RA was found to be associated with a small number of involved joints. This is likely because involvement of joints increases with disease duration and is preceded by increased systemic inflammatory activity. High TMJ pain intensity, but also a low number of painful jaw movements and greater maximum mouth opening capacity, were associated with early RA. TMJ pain on mouth opening may therefore be regarded as an early sign of TMJ involvement in RA, but does not seem to occur in conjunction with the lower maximum mouth opening capacity in established RA.

TMJ crepitus was associated with early RA, suggesting that destruction of TMJ cartilage—and perhaps also of bone tissue—occurs early and in parallel with TMJ pain. This is in accordance with the findings of Hajati et al, where radiographic signs of bone tissue resorption of the TMJ were found in the majority of an early RA cohort, and the presence of crepitus could predict TMJ bone tissue resorption in early RA. Futhermore, both TMJ pain on maximum mouth opening and crepitus have been found to be associated with TMJ arthritis, which may explain this finding. TNF in plasma and TMJ SF have previously been associated with TMJ pain and tissue destruction, but in the present study, TNF in both plasma and TMJ SF were found to be low in early RA. This was interesting but somewhat surprising, since TNF is known to be involved in early RA, which is supported by the potent treatment effects of anti-TNF therapy also in early RA. Certainly, the immune system reactions involved in RA are highly complex and involve many other inflammatory mediators, but TNF is an important aspect of joint inflammation. Patients with early inflammatory arthritis who subsequently developed RA have been found to have a distinct but transient SF cytokine profile, indicating a change in cytokine profile with the duration of the disease. In established RA, TNF has been associated with TMJ cartilage and bone tissue destruction, as assessed by computerized tomography, as well as the potential clinical consequence of AOB. Indeed, AOB was associated with established RA in the present study as well.

Degree of AOB was used as a clinical sign of TMJ tissue destruction, which may be a severe clinical problem for the patient as well as the dentist. The degree of AOB was higher in established RA, supporting a progressive disease course. These findings of both early tissue damage and a progressive disease course are supported by the findings of Uchiyama et al, where a prevalence of 69% was found for bone changes as assessed by MRI in RA patients with a disease duration of < 5 years, and the increasing number of bony changes was significantly correlated with the duration of the general disease. The progressive disease course, together with the higher TMJ pain intensity and presence of crepitus in early RA, further strengthens the obvious need for early detection of TMJ involvement in RA. Furthermore, and from a functional point of view, the degree of AOB and lower maximum mouth opening capacity found in established RA suggest that early recognition and treatment of TMJ inflammation is important.

In the present study, TMJ symptoms occurred close to the onset of general symptoms for most patients, which has been shown before. In three patients (4%), the TMJ symptom onset was before the onset of general symptoms. The duration of general symptoms was strongly associated with duration of TMJ symptoms, which further corroborates that TMJ involvement occurs early in the general disease course. The strong relationship between duration of general and TMJ symptoms also explains the similar findings in the logistic regression analysis in both early general and early TMJ symptom cases.

The limitations of this study that may influence the generalizability and conclusions of the results, further discussed below, include limitations in how well the patients could recall the onset of general and TMJ symptoms, the fact that the patients were referred to the clinic by rheumatologists because of TMJ symptoms, and that the seropositivity was determined only by the presence of RF. In addition, a limited number of samples had detectable SF concentrations or a sufficient sample volume to analyze all inflammatory mediators of interest; bilateral data were available in a number of, but not all, cases; and the medication profile does not fully correspond to current guidelines.

The patients were asked to recall the first year they experienced general and TMJ symptoms. For some patients, particularly patients with a long duration of
symptoms, recollection of onset may be difficult; however, the present authors consider the data for patients with shorter duration of symptoms to be sufficiently accurate. Limited influence is therefore expected when using a cut-off point of 2 years when allocating patients to groups of early and longer symptom duration.

The patients were referred to the specialist clinic by rheumatologists because of TMJ complaints. The study population is thus not fully representative of the entire RA population. However, the aim of this study was not to report on the prevalence or incidence of TMJ involvement in the RA population. The paper does, on the other hand, give an insight into the characteristics of TMJ symptoms in relation to symptom duration.

The patients were allocated to groups based on duration of symptoms rather than duration of RA diagnosis. Actually, the duration of symptoms was of primary interest in this study, as it adds to understanding of when in the disease course the TMJ symptoms first occurred. Furthermore, this study focuses on early RA—including the period preceding RA diagnosis—just as can be found in many recent publications.

Seropositivity was determined solely by the presence or absence of RF. The current determination of seropositivity includes assessment of anti-citrullinated protein antibody (ACPA) levels. When the data for this study were collected, ACPA assays were not available. However, the proportions of RF seropositivity and seronegativity in the study sample (75% seropositivity) very well resemble the general RA population, where 50% to 80% were reported to be positive for RF, ACPA, or both, with most ACPA-positive patients also being positive for RF.

There was a limited number of samples with detectable SF concentrations of TNF and IL-1β, and the majority of samples had insufficient sample volume to analyze all inflammatory mediators of interest, which limits the analysis based on SF content. However, all included samples fulfilled the sample quality criteria, ensuring high-quality SF data that the authors consider to be of great importance.

Data from both joints were included for some, but not all, individuals, which makes the analysis of data a statistical challenge. When comparing joint-related variables, each joint was used as one statistical unit. Otherwise, the individual was used as the unit. The alternative would be to use only one joint for each individual, but this would mean losing valuable data, and the present authors believe that there is no justifiable way to choose which joint to use.

For most patients, no specific data on the pharmacologic treatment were available, which is a limitation of the study to some degree. It is therefore not feasible to analyze a possible confounding effect of RA medication on the investigated variables. Furthermore, the medication profiles of the patients do not fully correspond to current guidelines, because at the time of data collection the systemic pharmacologic treatment did not yet include biologics. Developments in treatment strategies over the last decades have substantially changed the course of RA, nowadays frequently resulting in remission of the disease. The possible effects on the TMJ of this improved systemic RA treatment would be an interesting topic for research. However, the aim of this study was to specifically investigate patients with TMJ symptoms, despite systemic treatment or not, rather than investigating the prevalence of TMJ symptoms in the total RA population or the effects of systemic treatment on the TMJ. Although information on systemic treatment could complement the analysis, the authors therefore argue that the lack of it does not devaluate the results that concern the present aim substantially. Furthermore, recent studies still report a high prevalence of TMJ involvement in RA. This suggests that, despite the greatly improved treatment modalities, the TMJ remains a joint that is important to monitor.

Conclusions

This study indicates that TMJ pain and crepitus in RA usually occur early in the disease; ie, within 2 years following general symptom onset. Pain-related dysfunction worsens and structural changes develop with time, and the presence of TNF in plasma and TMJ SF is associated with this development. This presumably makes early (clinical) recognition of pain and inflammation important, enabling early treatment to minimize later irreversible damage.

Key Findings

- This paper reports on TMJ symptoms in patients with early RA—a topic with limited description in the current literature—and compares them to patients with established RA.
- Most RA patients with TMJ symptoms develop these symptoms within 5 years following general symptom onset.
- TMJ pain and crepitus are associated with early RA.
- Pain-related dysfunction worsens and structural changes develop with time.

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