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ORIGINAL ARTICLE

Tumor necrosis factor mediates temporomandibular joint bone tissue resorption in rheumatoid arthritis

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Abstract

Objective. To investigate if TNF, IL-1 or their endogenous controls, in relation to ACPA, are associated with radiological signs of ongoing temporomandibular joint (TMJ) bone tissue resorption and disc displacement in RA patients. ***Methods.*** Twenty-two consecutive outpatients with TMJ of RA were included. Systemic inflammatory activity was assessed by DAS28. The number of painful regions in the body and ESR, CRP, RF and ACPA were analyzed. TMJ synovial fluid and blood samples were obtained and analyzed for TNF, TNFsRII, IL-1ra, IL-1sRII and ACPA. The ratios between the mediators and their endogenous control receptors were used in the statistical analysis. Magnetic resonance imaging was performed in closed- and open-mouth positions and evaluated regarding disc position and presence of condylar and temporal erosions of the TMJ. ***Results.*** A high TNF level in relation to TNFsRII in TMJ synovial fluid correlated to the degree of TMJ condylar erosion. A high IL-1ra level in relation to TNF in TMJ synovial fluid was also correlated to the degree of TMJ condylar erosion. The total degree of TMJ condylar erosion was correlated with the number of painful regions. ***Conclusion.*** This study indicates that TNF in TMJ synovial fluid mediates TMJ cartilage and bone tissue resorption in RA. The study also suggests that the degree of endogenous cytokine control is of importance for development of bone tissue destruction.

Key Words: *TMJ, erosion, MRI, disc displacement, cytokines, rheumatoid arthritis*

Introduction

Approximately 35–50% of rheumatoid arthritis (RA) patients experience clinical signs of temporomandibular joint (TMJ) arthritis [1,2]. The most common clinical findings are pain in the TMJ area on movement or loading, joint sounds and impaired jaw function. In addition, radiographic signs such as cartilage and bone tissue destruction are common [1,3,4].

Magnetic resonance imaging (MRI) has proved valuable for assessing bone tissue changes in TMJ RA [5–7] and reported to occur in 45–71% of RA patients [3,8]. The radiographic sign of erosion is generally considered an indicator of active bone resorption and ongoing inflammatory activity [8,9]. In addition, TMJ disc displacement is common and associated with TMJ RA [10].

The pro-inflammatory cytokines tumor necrosis factor (TNF) and interlukin-1β (IL-1β) play major roles in the inflammatory process in RA [11,12]. Increased TNF levels are found in TMJ synovial fluid from patients with TMJ arthritides [13–15]. In synovial tissue, TNF contributes to and modulates the development of arthritis, including the destruction of cartilage and bone tissue and the sensitization of nociceptors [12,16–18]. TMJ bone tissue resorption has been associated with increased synovial fluid concentrations of pro-inflammatory cytokines [13].

IL-1β is present in the synovial tissue and fluids of RA patients and contributes to bone tissue and

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Table I. Demographic and background data for 33 patients with temporomandibular joint (TMJ) involvement of rheumatoid arthritis.

		Mean	SD	% abn	*n*
Age	*years*	47	9		22
Gender	*F/M*				20/2
Duration					
General disease	*years*	6	5		22
TMJ symptoms	*years*	3	3		22
Systemic disease activity					
Disease activity score (28)		4.09	1.11		22
Number of painful regions	*0–9*	10	4		22
Erythrocyte sedimentation rate	*mm/hr*	42	22	80	22
C-reactive protein	*Mg/L*	9	3	53	22
Rheumatoid factor	*lU/ml*	30	9	84	22
ACPA	*U/L*	17	8	42	22
Thrombocyte particle count	10^9*/L*	311	44	9	22
Medication					
NSAID	%		100		
DMARD	%		100		
Glucocorticoid	%		4		
Anti-TNF	%		27		

% abn: percentage of observations with abnormal values (when applicable), n: number of observations, M: males, F: females, IU: international units, ACPA: anit-citrullinated peptide antibodies, NSAID: non-steroidal antiinflammatory drug, DMARD: disease-modifying antirheumatic drug, Anti-TNF: biologic drug specifically targeting tumor necrosis factor. The following values were considered abnormal: rheumatoid factor >14 IU, C-reactive protein >4 mg/L, erythrocyte sedimentation rate >20 mm/h, and thrombocyte particle count $>300 \times 10^9$/L. The disease activity score for 28 joints was assessed at the time of clinical examination.

cartilage destruction in TMJ arthritis [7,19]. Patients with chronic inflammatory joint disease and detectable IL-1β levels in TMJ synovial fluid exhibit a greater extent of radiographic changes than patients with undetectable IL-1β [3,20,21]. Interlukin-1 receptor antagonist (IL-1ra) is a member of the IL-1 family and its release is strongly associated with IL-1β release and related to the severity of TMJ arthritis [13,15,19,22,23].

The strong, and to a large extent overlapping, pro-inflammatory effects of TNF and IL-1β are counterbalanced by endogenous inhibitors that control the effects of these potent cytokines [24]. Soluble TNF and IL-1 receptors (TNFsRI, TNFsRII, IL-1sRI and IL-1sRII) act as inhibitors by binding to and inactivating the respective cytokines and by removing the cytokines from the inflammation site. Tenderness to TMJ palpation in RA has been related to a deficiency in local cytokine control (personal communication). A deficiency in cytokine control has previously been found to also be associated with tissue degradation [25].

Autoantibodies to citrullinated proteins (ACPA) are highly specific for RA and today of the diagnostic classification [26,27]. Presence of ACPA in blood is associated with more destructive disease course and higher disease activity [27].

Aim

The aim of the present study was to investigate if TNF, IL-1 or their endogenous controls, in relation to ACPA, are associated with radiological signs of ongoing TMJ bone tissue resorption and disc displacement in RA patients.

Materials and methods

Patients

Twenty-two RA outpatients at the Department of Rheumatology at Dr Baksh Hospital, Jeddah, Saudi Arabia were included in the study (Table I). The patients were consecutively invited at their first visit or during a follow-up visit in the rheumatology clinic, regardless of whether they had TMJ symptoms or not.

The inclusion criteria were RA diagnosis according to the 1987 criteria of the American College of Rheumatology [28]. Exclusion criteria were age younger than 20 years, current malignancies, TMJ surgery or trauma within 1 year and less than 6 months since an intra-articular corticosteroid injection in the TMJ.

The project was approved by the ethics committee of the Ministry of Health, Jeddah, Saudi Arabia (H-02-J-002), which allowed this project to be conducted at the Dr Baksh Hospital. Each subject

provided his or her informed consent before participation.

Clinical examination

Each patient was clinically examined by one calibrated operator (NA) who had no knowledge about the patients' general or rheumatologic history before examination. The clinical examination procedure has been used in several previous studies [8,29]. General information about age, sex, time since RA diagnosis, duration of TMJ symptoms, smoking habits and medication was recorded.

The disease activity score 28 (DAS28) was obtained from the attending rheumatologist on the same day as the TMJ examination. The DAS28 combines data from the swollen joint count, tender joint count, ESR and the patient's self-evaluation of general health. A high disease activity corresponds to DAS28 >5.1, low disease activity to DAS28 <3.2 and remission to DAS28 <2.6 [30,31].

The patients were asked about ongoing pain present in nine uni- or bilateral joint regions in addition to the TMJ (neck, shoulders, elbows, hands, upper back, lower back, hips, knees and feet) and the number of painful joint regions was recorded (number of painful regions; score = 0–22).

The degree of anterior open bite was used as a clinical marker of the degree of TMJ cartilage and bone tissue destruction and was assessed by recording the occlusal contacts on each side upon hard biting in the intercuspid position. 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 the scores on the right and left sides was used in the analysis as an estimation of the degree of anterior open bite.

Temporomandibular joint synovial fluid sampling

TMJ synovial fluid sampling was performed according to the technique of Alstergren et al. [32]. This is a scientifically validated and routine method that was developed and used since 1995 by the main researcher. The technique enables determination of the true synovial fluid concentration of investigated mediators after saline washing of the joint. Due to technical and procedural difficulties in Saudi Arabia, the hydroxocobalamin concentration in the samples could not be determined. Therefore, the ratios between cytokines and their endogenous control mediators were calculated and used in the statistical analysis. The samples were centrifuged (1500 g for 10 min at 4°C) and the supernatants were transferred into other tubes (specific for each substance to be analyzed) and stored at 80°C until analysis.

Magnetic resonance imaging of the temporomandibular joint

A MRI examination of the TMJ region was performed in closed and open mouth positions at First Scan Clinic, Jeddah, Saudi Arabia. For the closed mouth position, the patients were asked to close the mouth with their teeth in light contact. For the open mouth position, the patients opened their mouths as wide as possible and a stepped plastic bite-block was placed between the upper and lower incisors for support.

Bilateral TMJ MR images were obtained within 1 week after the clinical examination. A 1.5 Tesla Siemens Magnetom Sonata Vision (Siemens, Erlangen, Germany) was used to acquire the images, using a bilateral TMJ surface coil. Sagittal proton density (PD) (TR mean 1940, TE 23) and T1-weighted (TR mean 856, TE 10) as well as PD coronal (TR mean 2487, TE 22) data were acquired. A minimum of nine sections with 2.0–2.5 mm thickness of each joint were obtained in sagittal and coronal views.

One odontological radiologist (AP) with extensive experience of interpreting TMJ MRIs interpreted the images blinded to clinical findings of the patients. The MRI sections were evaluated for disc position and for presence of erosions within the condylar and temporal portions of the TMJ. For that purpose, the condyle was divided into three areas: lateral, central and medial. The temporal components were divided into three areas: posterior, central and anterior. Erosion was defined as a loss of continuity of the articular cortex/margin, according to Ahmad et al. [33]. Presence of erosions was recoded as absent or present for each area. The erosion score was defined as the sum of the presence of erosions in the three parts of the condyle and the three parts of the temporal (score 0–6 per joint; 0–3 per condyle or temporal part; Figure 1). The disc positions were defined and classified according to Ahmad et al. [33] into five categories;

(1) *normal*: disc location is normal on closed and open-mouth images;
(2) *disc displacement with reduction*: disc location is displaced on closed-mouth images but normal in open-mouth images;
(3) *disc displacement without reduction*: disc location is displaced on closed-mouth and open-mouth images;
(4) *indeterminate*: disc location is not clearly normal or displaced in the closed-mouth position; and
(5) *disc not visible*: neither signal intensity nor outlines of the disc makes it possible to define the disc structure in the closed-mouth or open-mouth images.

Blood sampling and laboratory procedures

Immediately after the clinical examination, 5 mL venous blood was collected in uncoated tubes that

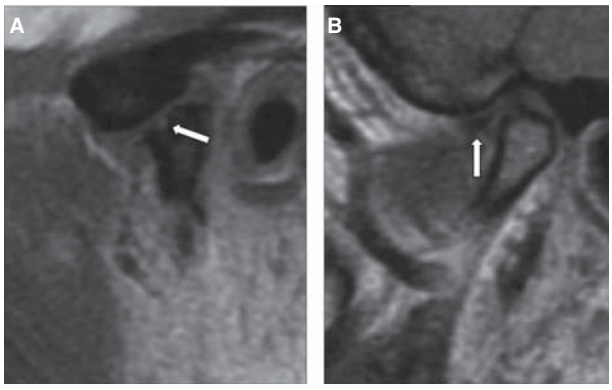

Figure 1. Examples of temporomandibular joint (TMJ) erosion and disc displacement in two patients with rheumatoid arthritis, as assessed by magnetic resonance imaging (MRI). (A) TMJ erosion on the superior–anterior surface of the right condyle (sagittal view, T1-weighted image in closed mouth position) and (B) anterior disc displacement in the right TMJ (sagittal view, T1-weighted image in closed mouth position).

were left at room temperature to coagulate for 1 h and then centrifuged (10 min in 4°C at 1500 g). The supernatant (serum) was stored at 80°C until analysis. The ESR, CRP, ACPA and RF concentrations as well as the TPC were determined by the accredited Saudi Laboratories at the Ministry of Health Research Center (Jeddah, Saudi Arabia).

ESR was analyzed by the Westergren method and levels below 20 mm/h for females and below 13 mm/h for males were considered normal. CRP was analyzed with the particle-enhanced turbidimetric test (Cobas Integra analyzer, Roche, Mannheim, Germany). CRP levels below 5 mg/L were considered normal. ACPA was analyzed by an enzyme antibody immunoassay (EL-anti-CCP/2TM; TheraTest Laboratories Inc, Lombard, IL). Levels ≥11 U/mL were considered ACPA positive. RF was analyzed by the direct latex fixation test (Architect ci4100, Abbott Laboratories, Abbott Park, IL) and levels below 14 IU/mL were considered normal. TPC was analyzed by the ADVIA® 2120i System with an Autoslide streamlined workflow (Siemens Medical Solutions USA, Inc., Malvern, PA) and the normal reference range was 150–400 10^9/L.

The concentrations of cytokines and cytokine receptors were determined in the TMJ synovial fluid and blood serum was analyzed using commercially available kits (Human Tumor Necrosis Factor [TNF] ELISA Kit, Human sTNFR2 ELISA Kit, Human Interleukin I Receptor Antagonist [lL-I Ra] ELISA Kit and Human sTNFR2 ELISA Kit; all from Wkea Med Supplies Corp, Changchun, China).

Statistics

Parametric statistics were used. The ratio between TNF and TNFsRII concentrations in TMJ synovial fluid and the erosion scores were not normally distributed. We consider the relatively small sample size to motivate the use of parametric statistics in the present study since, although not fully known, the distributions of the TNF/TNFsRII ratio and erosion scores are likely to be normally distributed in a larger sample of these patients. For descriptive statistics, mean and standard deviation (SD) are reported. For analytical statistics, the student's independent *t*-test was used to calculate the significance of differences between groups and the Pearson correlation coefficient was used to calculate the significance of the correlations between variables. Multiple regression was used to calculate the significance for relations between the dependent variable erosion score and the independent variables. For relationships between variables related to the joint, both TMJs in each patient were used in the statistical analysis. To investigate the relationships between joint-related and individual-related variables, the mean of the TMJ (right and left sides) was used. No attempt was made to adjust for multiple testing since this study partly had an exploratory aim and the intention was to minimize the risk of type II errors. A probability level of $p < 0.05$ was considered significant.

Results

Magnetic resonance imaging findings

Table II shows the MRI findings regarding TMJ disc position and erosions. A total of 2% of the joints displayed disc displacement with reduction, 20% displayed disc displacement without reduction and 64% had a normal disc position.

The majority of erosions were found on the condyle. Erosions were observed in 50 (38%) of the 132 examined TMJ condyle areas compared to the temporal portion where only four (3%) of the 132 areas displayed erosive signs ($p = 0.001$). Twenty-four per cent of the erosions were found in the medial portions of the condyle, 29% were found in the lateral portion and the highest proportion, 53%, was found in the central portion of the condyle.

Total erosion score on the condyle and the total erosion score in the temporal portion were related ($r = 0.65$, $n = 44$, $p < 0.001$). There was no significant difference in the presence of erosions between joints with a normal disc position and joints exhibiting disc displacement with reduction.

Temporomandibular joint erosions in relation to synovial fluid mediators

Table III shows the TMJ synovial fluid and serum concentrations of each mediator.

High concentration of TNF in relation to TNFsRII in the TMJ synovial fluid correlated to TMJ condylar erosion score ($r = 0.32$, $n = 44$, $p = 0.036$; Figure 2).

Table II. Temporomandibular joint (TMJ) findings in magnetic resonance imaging in 22 patients (44 TMJs) with rheumatoid arthritis.

	n	%
DISC POSITION		
Normal	28	64
Disc displacement without reduction	1	2
Disc displacement with reduction	9	20
Indeterminate or disc not visible	6	14
EROSIONS		
Condyle		
Medial		9
Central		18
Lateral		11
Sum		**38**
Temporal part		
Posterior		4
Central		0
Anterior		0
Sum		**4**

n: number of observations.

Table III. Temporomandibular joint (TMJ) synovial fluid levels and blood serum levels of cytokines, cytokine receptors and serotonin in patients with rheumatoid arthritis.

		Mean	SD	*n*
Clinical finding				
Anterior open bite	0–9	0.14	0.35	22
Ratios between TMJ synovial fluid mediators				
TNF/TNFsRII		0.72	0.37	44
TNF/CRP		21	15	44
TNF/RF		5.4	3.8	44
TNF/ACPA		9.1	5.1	44
IL-1ra/IL-1sRII		1.9	1.2	44
IL-1ra/TNF		2.2	1.2	44
IL-1ra/5-HT		3.7	2.2	44
Serotonin/TNF		0.81	0.69	44
Serotonin/CRP		16	14	44
Serotonin/ACPA		6.7	6.3	44
Blood serum levels				
TNF	*pg/mL*	149	119	22
TNFsRII	*pg/mL*	267	213	22
IL-1ra	*pg/mL*	240	122	22
IL-1sRII	*pg/mL*	136	61	22
Serotonin	*pg/mL*	111	80	22

n: number of observations, PMV: pain on movement vertical, PMR: pain on movement retrution, PM: pain on movement, TNF: tumor necrosis factor, TNFsRIktumor necrosis factor receptor II, CRP: C-reactive protein, RF: rheumatoid factor, ACPA: anti-citrullinated protein antibodies, IL-1ra: interleukin 1 receptor antagonist, IL-1sRII: interleukin 1 receptor II.

The erosion score on the medial part of the condyle and the posterior temporal area correlated with TNF concentration in relation to TNFsRII concentration in the TMJ synovial fluid ($r = 0.31$, $n = 44$, $p = 0.042$ and $r = 0.40$, $n = 44$, $p = 0.007$).

Multiple regression did not reveal any significant contribution by the independent variables TNF/TNFsRII and IL-1ra/IL-1sRII vs the dependent variable erosion score.

Temporomandibular joint erosions in relation crepitus

Crepitus was correlated to total erosion score in the temporal part ($r = 0.40$, $n = 44$, $p = 0.008$) and to erosion score on the medial area of the condyle ($r = 0.50$, $n = 44$, $p = 0.001$).

Temporomandibular joint erosions in relation to systemic inflammatory activity

The total (right + left) score of the TMJ condylar erosion as well as the total score of TMJ temporal erosions correlated with the number of painful regions ($r = 0.61$, $n = 22$, $p = 0.003$ and $r = 0.56$, $n = 22$, $p = 0.007$). The number of painful regions correlated to DAS28 ($r = 0.63$, $n = 22$, $p = 0.001$).

Differences between ACPA-positive and negative patients

In serum, 86% of the patients were ACPA positive, whereas 48% of the TMJ synovial fluid samples were ACPA positive.

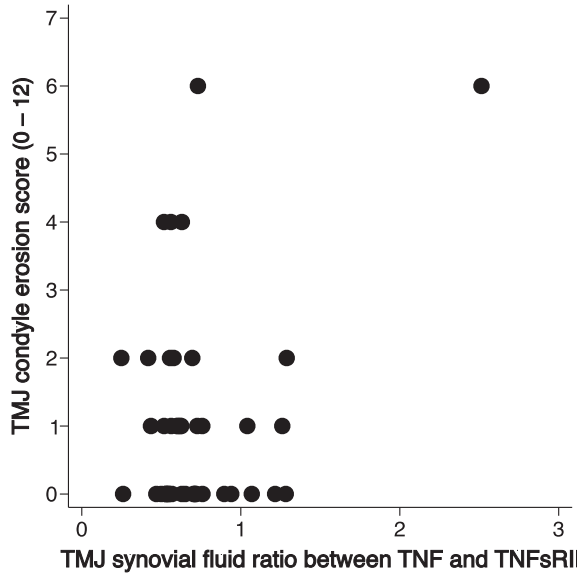

Figure 2. Scatter plot showing the ratio between the concentrations of tumor necrosis factor (TNF) and soluble TNF receptor II (TNFsRII) in temporomandibular joint (TMJ) synovial fluid in relation to extent of TMJ condyle erosions in 22 patients with rheumatoid arthritis ($r = 0.31$, $n = 44$, $p = 0.042$).

In serum, ACPA positive patients had higher concentration of IL-1sRII ($p = 0.004$). In ACPA-positive TMJ synovial fluid, the ratio between TNF and IL-1ra was significantly higher than in ACPA-negative patients ($p = 0.001$).

Influence of medication

Patients on anti-TNF medication had a significantly lower ratio between IL-1ra and IL-1sRII concentrations in TMJ synovial fluid than patient without anti-TNF medication ($p = 0.048$).

Discussion

This study shows that excess concentrations of TNF in the TMJ synovial fluid in relation to its endogenous control, as assessed by TNFsRII, is associated with ongoing inflammatory activity resulting in TMJ bone tissue resorption.

A high TMJ synovial fluid concentration of TNF in relation to TNFsRII was associated with erosive changes of the TMJ cartilage and bone tissue. TNF plays a major role in RA, not the least by promoting cartilage and bone tissue destruction [9]. TNF stimulates release of matrix metalloproteinases and other proteolytic enzymes that degrade proteoglycans. TNF also has potent effects on bone metabolism by stimulating osteoclast activity while inhibiting osteoblast formation of new bone tissue. Our finding also indicates that the relation between these pro- and anti-inflammatory factors to some extent determines the local inflammatory activity, including TMJ bone tissue resorption. Insufficient endogenous control of TNF, as represented by a low TMJ synovial fluid concentration of TNFsRII in relation to TNF, may therefore be a risk factor for development of structural TMJ changes. This has been reported before where insufficient systemic endogenous control of TNF was found to contribute to TMJ pain and tissue destruction in RA [34]. A recent study found that deficient TNF control by TNFsRII was related to TMJ pain in RA (personal communication). Insufficient formation of soluble TNF receptors may, thus, contribute to the development or maintenance of inflammation [35]. It is, however, not possible in the present study to determine which factor is the most important, high TNF or low TNFsRII concentrations, for TMJ bone tissue resorption.

Our MRI findings indicate that changes in the temporal portion are found in TMJs with more severe inflammatory activity involving bone tissue changes. Erosions were only occasionally observed in the temporal TMJ portion, but these were associated with erosive changes on the condyle. Our findings regarding erosions in the condylar and temporal parts are supported by several previous studies, both using MR and computerized tomography [9,36].

Approximately one-fifth of the investigated joints showed disc displacement. This finding was unexpected because the prevalence in the included patients was apparently lower than in the normal population where symptom-free disc displacement is found in ~34% [37]. Additional studies are, therefore, needed to clearly determine whether a causal relationship exists between disk displacement and rheumatic TMJ involvement. Degeneration of connective tissue, including disc and disc attachments, as well as increased intra-articular friction due to impaired quality of the synovial fluid, has been suggested as possible causes of disc displacement in arthritis [37,38].

This study used MRI to detect disc displacement and erosive changes of the articular bone tissue. MRI has been proven to be a valid and reproducible method for these assessments and PD and T1-weighted sections were appropriately used for analysis of disc position and presence of erosions. The method used for obtaining the sagittal and coronal images was not optimal, as the images were not corrected in relation to the horizontal axis of the condyle. This might result in an under-estimation of bony changes. Since T2-weigthed images were not obtained in this study, the presence of joint effusion or edema could not be investigated.

In the present study, the ratios between concentrations of pro- and anti-inflammatory cytokines as well as ACPA, RF and CRP in TMJ synovial fluid were calculated. This was due to the unfortunate technical problems that prevented measurement of vitamin B12 absorbance, which in turn precluded conclusions from true/absolute TMJ aspirate concentrations. However, the ratios are fully comparable between joints and have been used before. For example, Jouvenne et al. [22] showed that the relation between pro- and anti-inflammatory cytokines is important for inflammatory activity. The overall significance of ratios is, on the other hand, a complex matter. The ratios used in this study do not comprise all possible control factors for each investigated cytokine, but solely one factor that, on the other hand, is biologically important. In addition, immune system activation may stimulate a general release of both pro- and anti-inflammatory with weak clinical significance of their respective relations.

IL-1ra concentration in plasma has been found to be related to several indices of disease activity and joint destruction [27], particularly with CRP. That study suggested that IL-lra, although an acute-phase protein with anti-inflammatory properties, could be used as a biologic marker of disease activity in RA. Increased concentration of IL-lra may, thus, reflect increased production and activity of IL-1β [27].

Both TNF and ACPA have separately been associated to structural joint damage [35]. Patients ACPA-positive in TMJ synovial fluid had higher TNF concentrations in TMJ synovial fluid in relation

to IL-1ra concentrations than ACPA-negative patients. This suggests that the presence of ACPA in synovial tissues to a great extent affects TNF production and release. ACPA activates the immune system and can, therefore, be expected to contribute to TNF release. TMJ synovial fluid levels of ACPA have never been reported before. In this study, 48% of the TMJ synovial fluids samples showed presence of ACPA, which supports the fact that ACPA contributes to local inflammatory activity.

ACPA positivity in blood may discern erosive RA patients from non-erosive cases early [39]. ACPA positivity in blood is associated with progressive radiographic joint destruction in patients with recent-onset RA [40]. The presence of ACPA in blood indicates a higher inflammatory activity, in part possibly due to elevated TNF levels [39,41]. In our study 86% of the patients had presence of ACPA in blood, compared to ~72% of the Western European countries [42]. However, in a study on Egyptian RA patients, the proportion of ACPA-positive patients was found to be 84% [43], which is similar to what was found in this study on a similar RA population.

Patients on anti-TNF medication had a lower ratio between IL-1ra and IL-1sRII in TMJ synovial fluid. Although this study did not detect any relation between IL-1ra or IL-1sRII and bone tissue changes in the TMJ, this finding indicates that the anti-TNF medication influences the cytokine balance also for other cytokines than TNF. This was, however, expected and shown before [44].

The patients included were diagnosed with RA according to the 1987 ACR criteria and were all out-patients to one of the largest rheumatological clinics in Jeddah. The age, gender distribution, the prevalence of RF and ACPA and the systemic inflammatory activity give reasons to believe that our patients are representative for the local RA community in the greater Jeddah area. In general, the patients were diagnosed with RA diagnosis at the mean age of 41 years, which corresponds well to many studies in various parts of the world [45].

In this study, all 33 RA patients that attended the clinic during the time when the operator was present at the clinic were asked to participate in this study. However, 11 patients declined, which was why 22 patients were included. However, the number of included patients is a limitation of the study and the reason for the cautious interpretation of the results. However, our findings support the biologically plausible role of TNF and its endogenous control in bone tissue destruction, found in other studies [3,8,9,20]. The validated synovial fluid sampling methodology is nowadays a routine method for obtaining TMJ synovial fluid samples and a technique that enables determination of the true synovial fluid concentration. It has been used extensively for determination of cytokine concentrations in TMJ (and knee joint) synovial fluid [32].

All patients in this study used anti-inflammatory medication as well as DMARDs. In addition, 27% were on anti-TNF therapy, while only one patient used oral corticosteroids. DMARDs and anti-TNF-therapy can be expected to modify the disease process, including reducing bone tissue resorption, whereas NSAID therapy cannot. Nevertheless, we included a real-life sample of RA patients where most patients are pharmacologically treated. These patients can still have ongoing bone tissue destruction in certain joints, despite the medication, but there is likely a reduction of total bone tissue changes in patients taking DMARDs or anti-TNF.

In conclusion, this study indicates that TNF in TMJ synovial fluid mediates TMJ cartilage and bone tissue resorption in RA. The study also suggests that the degree of endogenous cytokine control is of importance for development of bone tissue destruction.

Conclusion

Intra-articular TNF mediates TMJ cartilage and bone tissue resorption in RA. The degree of endogenous cytokine control seems to be of importance for development of bone tissue destruction.

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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