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Temporomandibular joint pain and tissue destruction in relation to inflammatory activity in rheumatoid arthritis

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To my beloved family

Temporomandibular joint pain and tissue destruction in relation to inflammatory activity in rheumatoid arthritis

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ABSTRACT

The general aim of this thesis was to study temporomandibular joint (TMJ) pain and bone tissue destruction in patients with rheumatoid arthritis (RA), in particular: pro- and anti-inflammatory cytokines, systemic inflammatory activity, and the impact of TMJ pain on daily activities and quality of life.

This thesis comprises three parts. The aim of the first part was to investigate the impact of TMJ pain and inflammation on daily activities and quality of life in relation to systemic inflammatory activity. The aim of the second part was to investigate how local and systemic cytokine levels of tumor necrosis factor (TNF) and interleukin 1 (IL-1) interact to modulate TMJ pain in RA. And the aim of the third study was to investigate the relationship between inflammatory mediators in TMJ synovial fluid and blood versus bone tissue destruction by magnetic resonance imaging (MRI) of the TMJ.

Each study in this thesis examined subjects from the same group of patients with a recent RA diagnosis. In the first study, 33 patients participated; in the second, 26; and in the third, 22. Each study performed similar clinical examinations. The patients rated their TMJ pain (resting, movement, loading and on palpation) on a scale from 0 to 10 and underwent MRI examination to assess signs of TMJ erosions. We obtained and analyzed TMJ synovial fluid samples for TNF, IL-1ra, anti-citrullinated protein antibodies (ACPA), and rheumatoid factor (RF) and blood samples for erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ACPA and RF. Studies I and II used non-parametric statistics (Mann-Whitney U-test, Spearman correlation) while Study III used parametric statistics (student's *t*-test and Pearson correlation). A probability level of less than 0.05 was considered as significant.

The first study found that TMJ pain intensity, together with systemic inflammatory activities, plays an important role in the impact of TMJ pain on daily living and quality of life in RA. The second study found that a high TNF to TNFsRII ratio in the synovial fluid of the TMJ was associated with TMJ pain on palpation in patients with RA. High levels of TNF were found

to be associated with high levels of TNFsRII; however, increases in local cytokine control in the presence of elevated levels of TNF was likely insufficient to control or inhibit the inflammatory process. Presence of ACPA in TMJ synovial fluid was associated with elevated TNF levels but not with TNFsRII levels. The third study found that TNF in TMJ synovial fluid modulates TMJ bone tissue resorption in patients with RA. However, bone tissue destruction was associated with a low degree of endogenous cytokine control.

In conclusion, TNF, including its endogenous control system, seems to be involved in TMJ inflammation, which results in TMJ pain and tissue destruction. In turn, TMJ pain has a negative impact on daily living and quality of life in patients with RA.

Key words
ACPA, Arthritis, Bone tissue erosion, Cytokines, Erosion, Inflammatory activity, Interleukin-1, Magnetic resonance imaging, Pain, Quality of life, Rheumatoid arthritis, Temporomandibular joint, Tumor necrosis factor.

LIST OF SCIENTIFIC PAPERS

I. Ahmed N, Mustafa H, Catrina A, Alstergren P. Impact of temporomandibular joint pain in rheumatoid arthritis. Mediators of Inflammation. 2013;2013:597419

II. Ahmed N, Catrina A, Alyamani A, Mustafa H, Alstergren P. Deficient cytokine control modulates temporomandibular joint pain in rheumatoid arthritis. Submitted to European Journal of Oral Sciences.

III. Ahmed N, Pettersson A, Catrina A, Mustafa H, Alstergren P. Temporomandibular joint bone tissue changes in rheumatoid arthritis. Acta Odontologica Scandinavica. 2014; Dec 17:1-9

CONTENT

LIST OF ABBREVIATIONS

ACPA	Anti-citrullinated protein antibodies
CBCT	Cone-beam computed tomography
CT	Computed tomography
CRP	C-reactive protein
DAS28	Disease activity score (28 joints)
ESR	Erythrocyte sedimentation rate
HLA-DR	Human leukocyte antigen DR
IgM	Immunoglobulin M
IL-1	Interleukin 1
IL-1ra	Interleukin 1 receptor antagonist
IL-1sRII	Soluble interleukin-1 receptor II
IL-6	Interleukin-6
MRI	Magnetic resonance imaging
NRS	Numerical rating scale
RA	Rheumatoid arthritis
RF	Rheumatoid factor
TMJ	Temporomandibular joint
TNF	Tumor necrosis factor
TNFsRII	Soluble tumor necrosis factor receptor II
TPC	Thrombocyte particle count

DEFINITIONS

Local inflammation	Inflammatory mechanisms with local effects at the inflammatory site
Systemic inflammation	Inflammatory mechanisms with peripheral and/or central effects mediated by factors present in the circulatory system
Peripheral sensitization	Sensitization of peripheral nociceptors by local mechanisms
Central sensitization	Increased excitability of nociceptive neurons and pain-related centers in the central nervous system

INTRODUCTION

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic, progressive, systemic, and inflammatory autoimmune disease. It develops in a genetically susceptible host for whom environmental factors like smoking can contribute to its initiation and development (1). RA has a world-wide prevalence of 0.5-1.0% (2-4) and is about three times more common in females than in males (5).

CLINICAL PRESENTATION

RA primarily involves the musculoskeletal system, often in a bilateral manner, in which the most commonly affected joints are the metacarpophalangeal joints, wrists, proximal interphalangeal joints, metatarsophalangeal joints, shoulders, knees, ankles, and elbows. RA is characterized by abnormal immune system reactions that result in synovial inflammation with pain, synovial hyperplasia, autoantibody production (such as anti–citrullinated protein antibodies [ACPA] and rheumatoid factor [RF]), and cartilage and bone tissue destruction. RA not only affects the musculoskeletal system but can also cause cardiovascular, pulmonary, psychological, and skeletal diseases (1).

Clinically, the most characteristic, but far from only symptom of RA is joint and muscle pain. Patients with RA also present with fatigue; stiffness in the joints and muscles, especially in the early morning or after being ill for a period of time; low-grade fever; and muscle weakness. These patients may also develop joint deformity over time, due to cartilage and bone tissue destruction, and rheumatoid nodules in the skin triggered by the inflammatory process (6).

CLINICAL COURSE

RA often begins bilaterally in small, peripheral joints with larger joints becoming involved over time. The disease course can range from brief and self-limiting to prolonged and progressive (7). Also, the severity of the

disease may vary from mild to severe. The most common pattern of onset is gradual with a polycyclic progression (7) (Fig. 1).

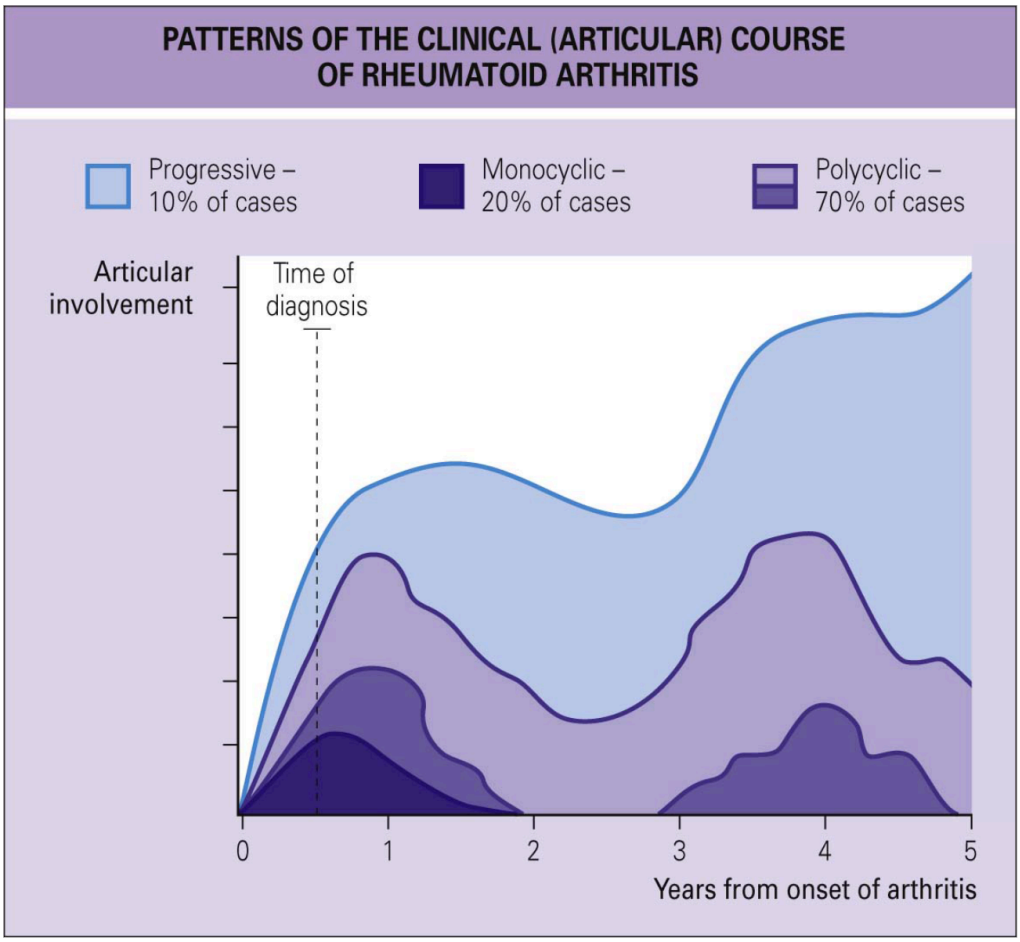

Figure 1. Patterns of the clinical articular course of rheumatoid arthritis over five years in adult patients with early-diagnosed rheumatoid arthritis. The figure shows three major patterns of the articular course of rheumatoid arthritis based on clinical findings. (Reprinted with permission from Mosby Elsevier)

There is currently no definite consensus regarding the prognostic factors for RA. Research has shown that radiographic damage at the beginning of the disease is an important predictor of clinical outcomes and radiographic progression (8). In the first years after symptom onset, joint destruction often begins very early and progresses rapidly. In the later stages of the disease, the severity of bone and cartilage damage has

functional implications, with many studies demonstrating the association between increasing joint destruction and progressive decline in physical function over time (9).

Serological markers may predict the progression of the disease. Presence of rheumatoid factor (RF) is associated with general radiographic progression (10, 11). Presence of anti-citrullinated protein antibodies (ACPA) is another, independent predictor of radiographic damage (11, 12).

GENERAL PATHOGENESIS AND RISK FACTORS

The pathogenesis of RA is not completely understood. External factors, such as cigarette smoking, infection, or trauma, seem to trigger an autoimmune reaction resulting in synovial hypertrophy and chronic joint inflammation along with the potential for extra-articular manifestations in genetically susceptible individuals (13).

The risk of developing RA depends on genetic and environmental factors. Recent theories of the genetic factors of RA propose that antigens in RA are modified by a process called citrullination. This process involves post-translational modification of the amino acid arginine to citrulline. This modification breaks the tolerance that permits antibody formation against these antigens. Therefore, genetic risk factors in RA affect both ACPA-positive and ACPA-negative forms of the disease (14). On the other hand, environmental risk factors such as smoking predominate the development of RA, but their effects seem limited to patients with the ACPA-positive form of the disease (15). Other possible environmental risk factors include coffee intake, low vitamin D levels, use of oral contraceptives, and low socioeconomic status, though supporting evidence for these other factors is weak (16).

In the synovium, synovial cell hyperplasia and endothelial cell activation are early events in the pathologic process that progresses to uncontrolled chronic inflammation and consequent cartilage and bone destruction in RA. Activated CD4+ T cells, B cells, mononuclear phagocytes, fibroblasts, osteoclasts, and neutrophils play major cellular roles in the pathophysiology of RA. On a molecular level, patients with RA have shown

abnormal production and release of numerous cytokines like tumor necrosis factor (TNF), interleukin 1 beta (IL-1β), and interleukin 6 (IL-6); chemokines; and other inflammatory mediators, such as serotonin(17, 18).

In addition, $CD4^+$ T cells may inappropriately recognize the human leukocyte antigen-DR (HLA-DR) autoantigen on the surface of antigen-presenting cells. This activates the T cell, stimulating a release of cytokines that directly activates synovial macrophages (18). Additionally, T cells also activate B cells, which release antibodies, including RF. This may then lead to formation of immune complexes, resulting in activation of the immune system including further release of proinflammatory cytokines (19).

Cells such as activated synovial macrophages, for instance, release large amounts of TNF and IL-1 into the synovium. These cytokines stimulate synoviocytes and chondrocytes in the cartilage to release matrix metalloproteases such as collagenase and other proteases which, in turn, degrade components of the cartilage matrix. Increased synoviocyte proliferation culminates in an overgrowth of synovial tissue, known as pannus (20-22). TNF and IL-1 also play pivotal cytokine-mediated roles in the destruction of bone and cartilage in RA by activating osteoclasts to resorb bone. In addition, IL-1 impairs bone and cartilage repair (18, 23).

The inflammatory process is usually tightly regulated, involving both mediators that initiate and maintain inflammation and mediators that shut the process down. In states of chronic inflammation, an imbalance between these two mediator types leaves inflammation uncontrolled, resulting in cellular damage. In the case of RA, this damage is manifested by the destruction of cartilage and bone (24).

CYTOKINES

Cytokines are extracellular peptides that influence nearly every cell type via surface receptors. Their essential role is activation and maintenance of immune system mechanisms including the inflammatory reaction. They also act as mediators of pathology in infectious, inflammatory, and immune diseases (25, 26). Cytokines are involved in processes like inflammation and modulation of bone remodeling and turnover. Cytokines

play important roles in the pathology of RA by mediating acute and chronic inflammation and the destruction of cartilage and bone tissue. There are proinflammatory cytokines and anti-inflammatory cytokines, receptors, and factors that constitute the endogenous cytokine control system (23, 27, 28). The activity of cytokines is often redundant, with the same functions being modulated by different cytokines. Cytokines are often released in a cascade: one cytokine will stimulate its target cells to produce and release other cytokines as well as more of the initiating cytokine in a positive feedback loop. However, certain cytokines can also act synergistically or antagonistically (29).

TNF and IL-1 play a central role in inflammatory responses as shown by the effect of clinical administration of their antagonists, such as monoclonal antibodies to TNF (e.g., infliximab or adalimumab), TNFsRII (e.g., etanercept), and the IL-1 receptor antagonist (IL-1ra, e.g., anakinra). These antagonists block a variety of acute and chronic responses, and some are now used to treat RA as well as other chronic inflammatory diseases.

In RA, TNF and IL-1 levels are increased both locally in the synovium and synovial fluid and systemically in the blood (25, 30), where they have been associated with pain as well as cartilage and bone tissue destruction (Fig. 2).

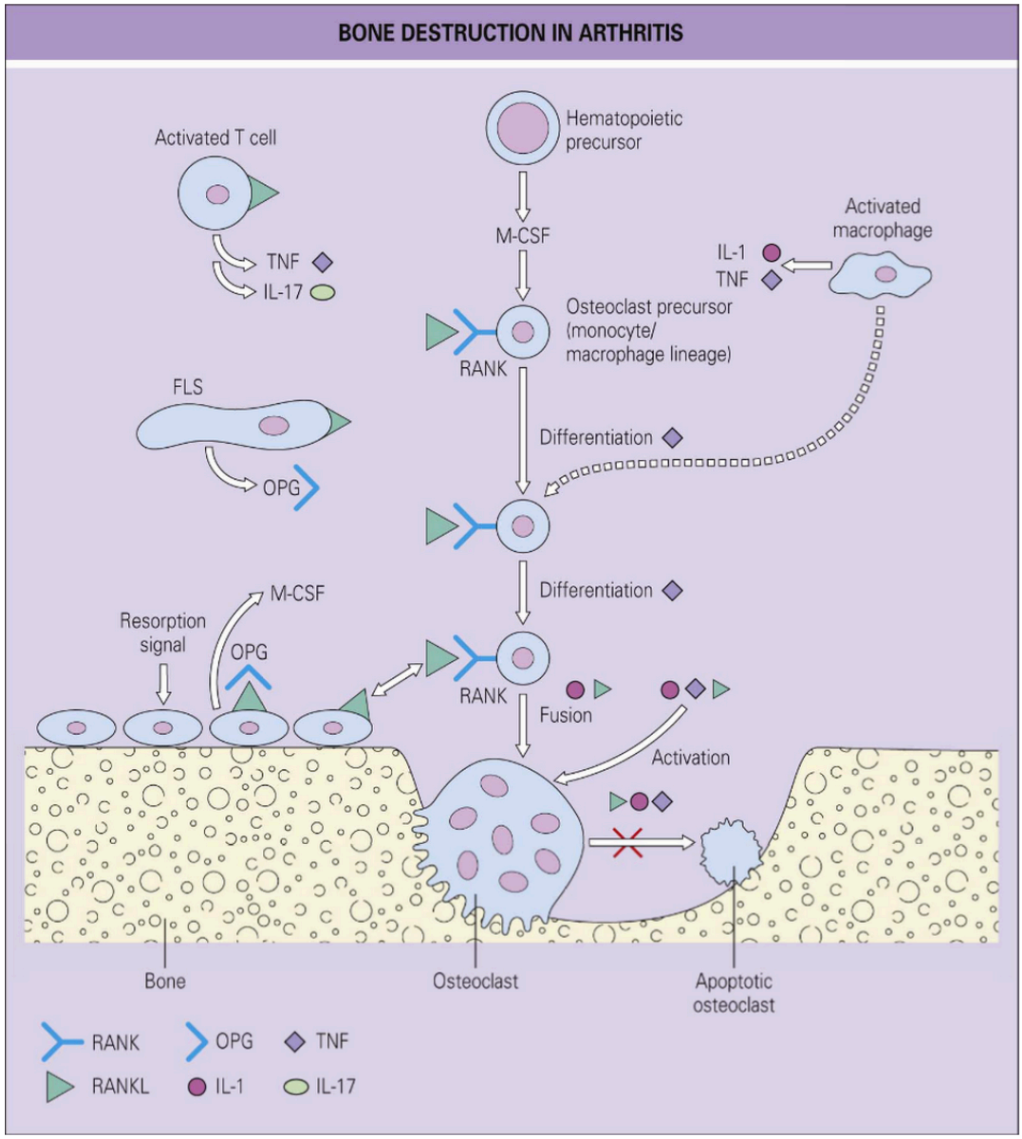

Figure 2. Mechanisms of bone tissue destruction in arthritis. Cells from rheumatoid arthritis (RA) synovium produce factors that influence osteoclast differentiation and activation in various ways. Activated macrophages produced tumor necrosis factor (TNF) and interleukin 1 (IL-1). This TNF promotes bone destruction by upregulating the production of RANKL and the macrophage colony-stimulating factor from osteoblasts, and by augmenting differentiation into osteoclasts. The bone tissue is destroyed by the result of massive infiltration of immune cells, proliferative vessels, and increased numbers of osteoclasts. (Reprinted with permission from Mosby Elsevier).

Tumor necrosis factor

Tumor necrosis factor (TNF) seems to play a dominant role in directing the inflammatory process and immune response. TNF is mainly produced by activated T-cells and macrophages in the inflamed synovium (31, 32) and modulates the inflammatory response. Moreover, TNF regulates the production of other proinflammatory cytokines such as IL-1 and IL-6 (33). Patients with RA have increased TNF in their synovial fluid and in the membrane (34).

TNF can promote pain. Nociceptive pain in joints occurs with the activation and sensitization of neurons through TNF and IL-1 (35). TNF promotes inflammation, activation of chemokines, and upregulation of other receptors (35). This results in modification of the neurons of the ganglia causing chronic persistent pain (36). TNF also promotes inflammation by stimulating fibroblasts to express adhesion molecules, such as intercellular adhesion molecule 1 (37). These adhesion molecules interact with their respective ligands on the surface of leukocytes, resulting in increased transport of leukocytes to inflammatory sites, including the joints in patients with RA (24). Independent of its role in inflammation, TNF can regulate osteoclast differentiation and function either directly or indirectly (38, 39). Individuals with RA have elevated levels of TNF in their synovial fluid as well as their plasma, and they play an important role in the inflammation and bone tissue destruction that are hallmarks of RA (29).

Interleukin-1

The IL-1 family members (IL-1α, IL-1β, IL-1ra) are very potent cytokines. IL-1 and TNF share multiple proinflammatory effects and both potentiate each other (40). IL-1ra binds with high avidity to IL-1 receptors but does not activate cells (41). IL-1ra is strongly associated with IL-1β release and is related to the severity of TMJ arthritis (42-46).

IL-1β is produced by activated macrophages and synovial fibroblasts and is also produced by activated monocytes and osteoblasts during inflammation (46, 47). The effects of IL-1β on osteoclasts and osteoblasts,

including osteoclast differentiation and activation, can induce and maintain bone resorption (48).

IL-1 correlates with high disease activity and joint destruction (49, 50). A detectable level of IL-1β in the TMJ synovial fluid may be an indicator of bone tissue destruction in polyarthritic conditions (49). Moreover, inflammatory activity in RA knee joints is also related to local level of IL-1β (51). Low levels of IL-1ra in TMJ synovial fluid are associated with TMJ pain on movement, probably due to insufficient IL-1β control by IL-1ra (52, 53).

Soluble TNF and IL-1 receptors

Levels of the anti-inflammatory TNFsRII and IL-1sRII increase dramatically during inflammation. Cell-surface type II IL-1 receptors act as decoy receptors with anti-inflammatory effects (54). In RA, these receptors have been found in the blood and synovial fluid (55) while elevated levels of IL-1sRII have been found in plasma and synovial fluid (47, 52, 56). High levels of IL-1sRII in the TMJ synovial fluid have been associated with only a minor degree of joint destruction or none at all (57). Anti-inflammatory cytokines are present in TMJ synovial fluid in chronic arthritis (55).

SYSTEMIC INFLAMMATORY ACTIVITY

The erythrocyte sedimentation rate (ESR), together with the CRP levels provide a basis for estimating systemic inflammatory activity in RA. These markers are associated with the occurrence, progression, and prediction of articular bone tissue resorption in patients with RA (58-62).

Erythrocyte sedimentation rate

Along with other factors, cytokine release increases the ESR. The ESR is one of several useful measures for assessing the severity of RA, especially in later stages (58, 63, 64). A high ESR has been associated with difficulty in performing physical activities. Elevated ESRs also indicate a poor prognosis in systemic inflammatory disease (63). However, ESR has limited prognostic value as a single marker in early RA (65, 66). For example, an evaluation of the prognostic value of the ESR for radiographic

progression in patients with RA found that the value was too low to be used as a single prognostic marker in clinical practice (67).

C-reactive protein

CRP is an acute phase protein produced in the liver upon stimulation by increased levels of cytokines in the blood, such as TNF, IL-1, and IL-6 (68). CRP is sensitive to inflammation and, as such, inflammation triggers rapid production and release of CRP, which also decreases rapidly when inflammation subsides.

Several studies have shown a relationship between CRP levels and radiographic joint damage, in hand joints for example (67, 69). High CRP is related to radiographic progression of TMJ bone tissue resorption in patients with RA (70, 71).

Disease Activity Score 28

DAS28, which includes a 28-joint count of tender or swollen joints, is a routine measure in both clinical practice and research (72). DAS28 combines data from the swollen joint count, tender joint count, CRP levels or the ESR, and the patient's self-evaluation of general health. It excludes assessment of the foot and ankle joints because, in these joints, tenderness and swelling may be confused with other disorders (72, 73).

SEROLOGICAL BIOMARKERS

Rheumatoid factor

RF is an Immunoglobulin M (IgM) autoantibody against the fragment crystallizable (FC) portion of human IgG (74). It can be detected in 60-80% of patients with RA and is a well-recognized predictor of a poor prognosis in RA (75-77). RF contributes to the disease by activating the immune system in the synovial tissues (78); RF binds to the Fc portion of IgG, thereby activating the immune system via antigen-presentation cells and by activating platelets that release, for example, serotonin upon activation (74)

In the TMJ, radiographic signs of bone tissue resorption in the late phase of RA (79) are related to RF levels in serum. One study on patients with

recent-onset RA shows that the presence of RF predicted more severe disease outcomes (80). High disease activity and presence of RF were the strongest factors predicting a poor prognosis in patients with RA (67).

Antibodies against citrullinated proteins

ACPA are present in the vast majority of patients with established RA (97%) (81). These autoantibodies recognize proteins or peptides where the amino acid arginine is changed into citrulline through a process of posttranslational modification, mediated by peptidyl arginine deiminase enzymes. High calcium levels can activate these enzymes through inflammation or by smoking for example (82, 83). Citrullinated proteins are present in various inflamed tissues, including the synovial tissue of patients with RA (84, 85). ACPA activates the immune system when it detects a citrullinated peptide (86).

The temporomandibular joint in rheumatoid arthritis

TMJ involvement in RA is common with a prevalence of 30-65%, depending on patient selection, diagnostic criteria, and techniques used (87-89). The most important clinical consequences of TMJ in RA are pain, TMJ clicking and locking, limitation in opening the mouth (90), and functional disability, such as pain during jaw movement and loading or an anterior open bite due to TMJ bone tissue resorption. Involvement of the TMJ in RA can restrict jaw function due to movement-related pain or limitation of condylar translation. An anterior opening of the bite due to articular cartilage and bone tissue destruction may also develop. These consequences may have a significant impact on the daily activities and quality of life of the affected patients (91).

Temporomandibular joint pain

RA pain arises from peripheral and central mechanisms (92). In RA, peripheral nociceptors are activated and sensitized by inflammatory mediators like cytokines released at the inflammatory site. Central pain mechanisms are also involved in RA pain (92). Inflamed joints, as well as remote nonarticular sites, show general reductions in pressure and thermal pain thresholds and also increases in pain sensitivity (92). Because RA is a systemic disease that expresses a major part of its

pathology in the synovial tissues, systemic mechanisms, as well as local mechanisms, can modulate TMJ pain in RA. Proinflammatory cytokines such as TNF, as well as soluble anti-inflammatory cytokines such as IL-1sRII, are involved in the pathophysiology of RA. Alstergren et al. (52) show that, in RA, the TMJ pressure pain threshold depends on systemic, rather than local, mediators. The study also shows that seropositive and seronegative patients differ not only concerning systemic inflammatory activity, as would be expected, but also in TMJ pain on mandibular movement. Moreover, 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. Thus, the TMJ pressure pain threshold is modulated by systemic rather than local inflammatory mediators, which suggests that it is unrelated or only weakly related to other TMJ pain parameters in patients with RA. RF-dependent systemic modulation, in combination with local factors, seems to account for TMJ pain in patients with RA.

RA frequently affects the TMJ, and often early in the course of the disease. Aliko et al. (89) found that 65% of patients with RA have TMJ symptoms. TMJ pain, especially on movement or loading, is the most common clinical finding (93). TMJ pain due to involvement of RA modulates both via local mechanisms (such as mediators released in the synovial tissues) and systemic factors (such as circulating mediators that act on the synovial tissues or pain-associated mechanisms in the central nervous system) (94-96). For example, Alstergren et al. (2008) (52) found that TMJ pressure pain is determined by systemic rather than local mediators in RA. Pain in the jaw–face–head region correlates with an impaired state of general health, and generalized arthritis may contribute to TMD pain (97).

Clinically, determining the relative influence of systemic and local factors may affect the choice of treatment since the results of systemic treatment, with TNF blockers, for example, seem rather variable in reducing TMJ pain (55, 98).

Temporomandibular joint tissue destruction

The severity of TMJ arthritis in RA correlates strongly with the severity of general disease. TMJ involvement is common in late-stage RA, depending on the patients' diagnostic criteria (87, 88). The TMJ is often affected in patients with RA, with about 30-50% of patients experiencing TMJ pain or impaired function (99). Radiographic change, such as erosion, is more common in patients with RA (100, 101) than with other inflammatory diseases. Erosion of the TMJ correlates with decreased mandibular mobility, anterior open bite, and difficulty chewing (102). Markers of inflammation such as CRP, ESR, RF, and thrombocyte particle count (TPC) are all associated with the severity of TMJ in RA (50, 70, 87). The destructive process does not necessarily correlate with local clinical signs and symptoms because a large proportion of asymptomatic patients show radiographic signs of bone tissue resorption (79, 103, 104).

IL-1β is present in the synovial tissue and fluids of patients with RA and contributes to bone tissue and cartilage destruction in TMJ arthritis (42, 105). Patients with chronic inflammatory joint disease and detectable levels of IL-1β in TMJ synovial fluid exhibit greater extents of radiographic changes than patients with undetectable IL-1β (70, 100, 106).

Progressive articular cartilage degradation and bone tissue resorption also characterize RA, resulting in loss of function in the musculoskeletal system. If untreated, this may lead to severe disability, contributing to poor quality of life for these patients (107, 108).

Consequences of chronic pain in rheumatoid arthritis

Pain is a major determinant of quality of life for patients with RA. It is also the most common reason for patients with RA to seek treatment (109). Pain is also strongly and negatively associated with other patient-reported outcomes and quality of life (109). Voog et al. 2003 (91) found that TMJ pain was associated with difficulties in performing physical exercise and other daily activities.

Activities of daily living

Activities of daily living (ADL) refers to the basic tasks of everyday life like eating, bathing, dressing, using the toilet, and walking: the activities required for personal self-care and independent living. The ADL scale is a 10-item reliable and valid self-reported measure (110). Voog et al. 2003 (91) used the ADL to measure how TMJ pain influenced activities in daily life. The last item in their questionnaire was a summary question about TMJ pain's impact on daily activities.

Quality of life

There is some evidence suggesting the impact of pain in other chronic joint inflammatory diseases, (111) which may indicate a decrease in quality of life for patients with RA. Due to pain and functional limitation, RA affects many aspects of daily life (112). TMJ pain seems to affect daily activities in general, which may also influence quality of life. Voog et al. (91) found that TMJ pain can contribute to work disability, a frequent problem in patients with RA.

Magnetic resonance imaging

Magnetic resonance imaging (MRI), together with computerized tomography (CT) and cone-beam CT (CBCT), are the primary methods for assessing articular bone tissue changes and changes in the TMJ (113, 114). MRI has also been shown to be valuable for evaluating soft tissue changes in the TMJ in RA (105, 115, 116). Since MRI uses no ionizing radiation, use of MRI is often preferable to CT when either method could yield the same information (115).

Radiographic involvement of the TMJ occurs in 45-71% of patients with RA (70, 117, 118), while condyle resorption is found in two-thirds of the TMJs of patients with RA (114, 115). A radiographic sign of erosion is generally considered to indicate active bone resorption and ongoing inflammatory activity (50, 117). In addition, TMJ disc displacement is common and is associated with RA (115).

Aims

The overall aims of this project were to study TMJ pain and bone tissue destruction in relation to pro- and anti-inflammatory cytokines and systemic inflammatory activity, as well as the impact of TMJ pain on daily activities and quality of life.

The specific aims were to investigate, in patients with RA:

- The impact of TMJ pain and inflammation on daily activities and quality of life in relation to systemic inflammatory activity.
- The relative amounts of TNF and IL-1 compared to their respective soluble receptors in TMJ synovial fluid and blood in relation to TMJ pain.
- The relative amounts of TNF and IL-1 compared to their respective soluble receptors in TMJ synovial fluid and blood in relation to TMJ bone tissue destruction and disc displacement.

MATERIALS AND METHODS

Patients

We invited 33 consecutive outpatients with RA from the Department of Rheumatology at Dr. Bakhsh Hospital, Jeddah, Saudi Arabia, to participate in the study. Patients received the invitation at their first visit or follow-up at the rheumatology clinic without considering whether they had TMJ pain.

Inclusion criteria required patients to have a diagnosis of RA according to the 1987 criteria of the American College of Rheumatology (6). We excluded patients younger than 20 years, those with current malignancies, those who had had TMJ surgery or trauma within the past year, and those who had had an intra-articular corticosteroid injection in the TMJ in the past six months.

Seven patients declined to have blood samples taken but underwent the clinical examination. This meant that Study I included 26–33 patients (33 for the clinical measures and 26 for the blood sample measures) and Study II included 26 patients. Four more patients refused the MR examination, so Study III included only 22 patients (Table 1).

All patients received verbal and written information about the project before consenting to participate. The ethics committee of the Ministry of Health, Jeddah, Saudi Arabia (H-02-J-002) approved the study design, methods used, and patient selection and allowed this project to be conducted at Dr. Bakhsh Hospital. All subjects gave their informed consent before participation.

Clinical examination

Each patient underwent clinical examination by one calibrated operator (NA) who had no knowledge of the patient's general or rheumatologic history or status before the examination. The same clinical examination had been used in several previous studies (91, 105). In addition to general information on age, sex, duration of RA diagnosis and TMJ symptoms, smoking habits, and medication, the examination assessed the following variables.

The attending rheumatologist performed the DAS28 on the same day as the TMJ examination. A DAS28 score >5.1 indicates high disease activity, 3.2–5.1 indicates moderate disease activity, 2.6–3.2 indicates low disease activity, and <2.6 indicates remission.

The patients answered questions about ongoing pain in nine joint regions besides the TMJ (neck, shoulders, elbows, hands, upper back, lower back, hips, knees, and feet) and number of painful joint regions (score = 0–9).

To assess TMJ pain intensity during the past week, we used a 0–10 numerical rating scale (NRS) where 0 corresponded to "No pain" and 10 to "Worst imaginable pain" and assessed each TMJ at rest, at maximum voluntary mouth opening, and while chewing (Studies I and II). We then measured in mm maximum voluntary mouth opening capacity, laterotrusion to both sides, and protrusion between teeth 11 and 41 with a vertical overbite added where applicable (Studies I and II). At the same time we used an NRS (0–10) to assess pain intensity at laterotrusion to both sides, and protrusion (Studies I and II). We measured pain threshold in mm, defined as the maximum mouth opening without pain or without increase in any ongoing pain (Studies I and II). Statistical analysis calculated the sum of the pain intensities during TMJ movements for each TMJ (maximum voluntary mouth opening, lateral and contralateral laterotrusion, and protrusion) for a total score of 0–40.

Tenderness to digital palpation with a force of 10 N (score = 0–3) evaluated the lateral and posterior aspect of the TMJ on each side. Patients scored 1 if they reported tenderness upon palpation, 2 if palpation also caused a palpebral reflex, and 3 if palpation caused a defense reaction. Statistical analysis evaluated the sum of these scores for each TMJ (Studies I and II).

The patients rated the impact of TMJ pain on their ability to perform daily activities and on the quality of their life on a 0–10 NRS where 0 corresponded to "no impact of TMJ pain on daily activities/quality of life" and 10 corresponded to "maximum impact of TMJ pain on daily activities/quality of life."

Table 1

Patient characteristics and clinical and serological data. All participants had temporomandibular joint (TMJ) involvement in rheumatoid arthritis. Study I involved 33 patients; Study II, 26 patients; and Study III, 22 patients.

		STUDY I					STUDY II					STUDY III			
			Percentile					Percentile							
		Median	25th	75th	**% abn**	**n**	**Median**	25th	75th	**% abn**	**n**	**Mean**	**SD**	**% abn**	**n**
Age	*years*	47	41	54		33	47	40	54		26	47	9		22
Gender	*F/M*					29/4					24/2				20/2
Duration															
General disease	*years*	6	5	11		33	6	4	11		26	6	5		22
TMJ symptoms	*years*	2	1	4		33	2	1	4		26	3	3		22
Smoking	*Yes/No*					5/28					22/4				22/0
Systemic disease activity															
Disease activity score (28)	*0-10*	4	3.5	5		32	4.3	3.9	5.2		26	4.1	1.1		22
Number of painful regions	*0-9*	9	7.5	12		33	6	5	9		26	10	4		22
Erythrocyte sedimentation rate	*mm/hr*	40	28	70	85	33	42	28	70	80	26	42	22	82	22
C-reactive protein	*mg/L*	8	6	11	77	26	8	6	11	84	26	9	3	78	22
Rheumatoid factor	*IU/ml*	27	25	34	81	26	27	25	34	84	26	30	9	85	22
ACPA	IU/L	17	11	19	70	26	14	11	19	85	26	17	8	69	22
Medication															
NSAID					%	94				%	100			%	100
DMARD					%	100				%	100			%	100
Glucocorticoid					%	3				%	3			%	4
Anti-TNF					%	46				%	32			%	27

% abn: percentage of observations with positive or abnormal values (when applicable), n: number of observations, SD: Standard deviation, M: males, F: females, IU: international units, ACPA: anti-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 >5 mg/L, erythrocyte sedimentation rate >20 mm/h, thrombocyte particle count >300 X 10^9/L and ACPA >11 U/ml.

Temporomandibular joint synovial fluid sampling

TMJ synovial fluid sampling used the procedures of Alstergren et al. (119), a scientifically validated, routine method developed and used since 1995 that enables determination of the true synovial fluid concentration of the investigated mediators after a saline wash of the joint (Fig. 3). Briefly, we obtained TMJ synovial fluid samples by washing the joint cavity with a diluted washing solution using a push-and-pull technique. The washing solution consisted of physiological saline and 22% hydroxocobalamin, which was included to determine the amount of synovial fluid in the aspirate. This would have enabled calculation of the true synovial fluid concentration of each investigated mediator. However, due to technical and procedural difficulties in Saudi Arabia, use of the hydroxocobalamin method to determine concentrations in the samples was not possible. Thus, statistical analysis used the ratios between the synovial fluid sample concentrations of the cytokines and their endogenous control mediators. We centrifuged the samples (1500 g for 10 min at 4°C) and transferred the supernatants into other tubes, specific to each substance to be analyzed, which we stored at -80°C until analysis.

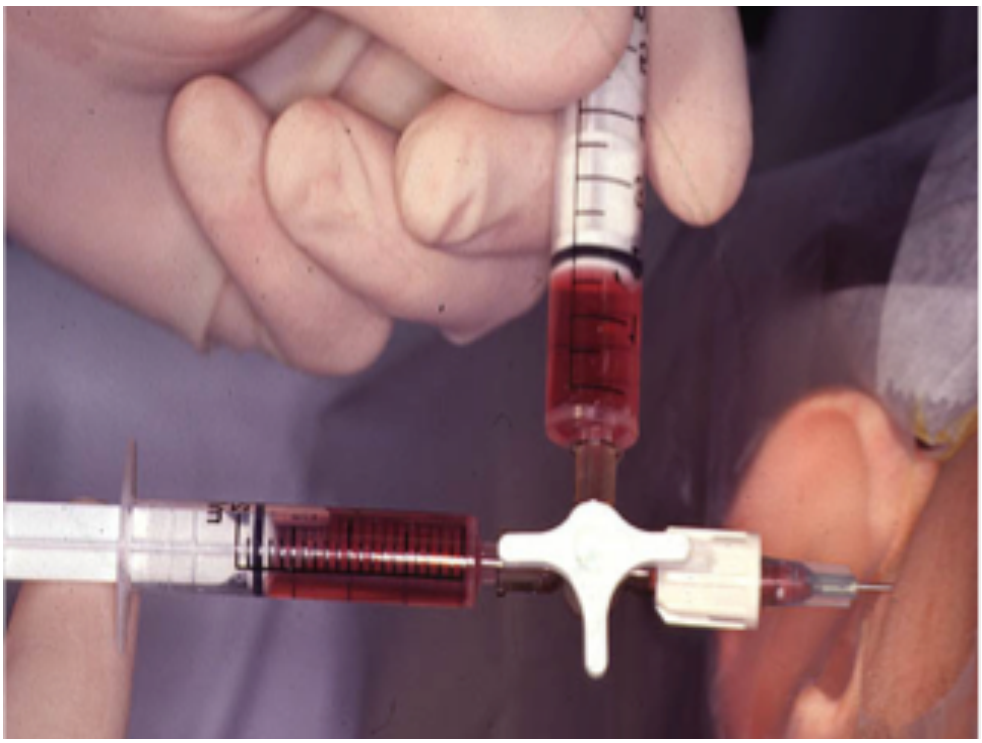

Figure 3. Using the push-and-pull technique to wash the temporomandibular joint with hydroxocobalamin (vitamin B12) as an internal standard to enable calculation of true synovial fluid concentrations. The upper syringe contains the washing solution that is injected into the joint compartment, in 1 mL increments, and the lower syringe contains the aspirate fluid (washing solution + synovial fluid). The difference in absorbance between the washing solution and the aspirate is used to calculate the true synovial fluid concentrations of the various mediators.

Analysis determined the TMJ synovial fluid levels of the cytokines TNF and IL-1ra; the soluble cytokine receptors TNFsRII and IL-1sRII; and CRP, ACPA, and RF. Since the true synovial concentration of each mediator could not be determined in the present study, we used the ratios between both TNF and IL-1 and their respective soluble receptors II (TNF/TNFsRII; IL-1ra/IL-1sRII) as well as TNF/RF, TNF/ACPA, TNF/CRP, IL-1ra/RF, IL-1ra/ACPA, and IL-1ra/CRP. These ratios are fully comparable between cases. The biological meaning of these ratios is relevant, especially

regarding the ratios between TNF and IL-1 and their soluble receptors, since the normal balance between the proinflammatory cytokines and their endogenous control systems is disturbed in inflammation, toward a relative excess of proinflammatory cytokines (45). Our studies represent some of only a few studies investigating this balance and its contribution to inflammatory activity.

Blood sampling and laboratory procedures

Immediately after the clinical examination, we collected venous blood (5 mL) in uncoated tubes and left them at room temperature to coagulate for 1 hour before centrifuging (10 min at 4°C and 1500 g). We stored the supernatant (serum) at -80°C until analysis. The accredited Saudi Laboratories at the Ministry of Health Research Center, Jeddah, Saudi Arabia then determined the ESR; the TPC; and CRP, ACPA, and RF concentrations.

Our analysis used the Westergren method to determine ESR considering levels below 20 mm/h for females and 13 mm/h for males as normal. The particle-enhanced turbidimetric test (Cobas Integra analyzer; Roche, Mannheim, Germany) analyzed CRP with levels below 5 mg/L considered normal. To analyze ACPA, we used a microparticle enzyme immunoassay for semiqualitative measurement of the IgG class of autoantibodies specific for citrullinated proteins in human serum (EL-anti-CCP/2TM; TheraTest Laboratories Inc., Lombard, IL, USA), considering levels below 11 U/ml as normal. The direct latex fixation test (Architect ci4100; Abbott Laboratories, Abbott Park, IL, USA) analyzed RF, with levels below 14 IU/mL considered normal. Analysis of TPC used the ADVIA® 2120i System with Autoslide streamlined workflow (Siemens Medical Solutions USA, Inc., Malvern, PA, USA) with the reference range for normal values at 150–400 10^9/L.

To determine the concentrations of cytokines and cytokine receptors in TMJ synovial fluid and blood serum, we used 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). The assay ranges were 20–400 ng/L for TNF, 20–800 ng/L for TNFsRII, 20–500 ng/L for IL-1ra, and 5–180 pg/ml for IL-1sRII.

We measured ACPA concentrations in the TMJ synovial fluid using an enzyme antibody immunoassay (EL-anti-CCp/2TM; TheraTest Laboratories Inc., Lombard, IL, USA) considering levels exceeding 7 IU/mL to be ACPA positive.

Magnetic resonance imaging

Study III conducted an MRI examination of the TMJ region in both closed- and open-mouth positions. For the closed-mouth position, the patients closed their mouths with their teeth in light intercuspid contact. For the open-mouth position, the patients opened their mouths as wide as possible and we placed a stepped plastic bite-block between the upper and lower incisors to support and maintain a stable mouth opening during image acquisition.

We took bilateral TMJ MR images within one week after the clinical examination. A 1.5 Tesla Siemens Magnetom Sonata Vision (Siemens, Erlangen, Germany) produced the images using a bilateral TMJ surface coil with a double-echo, turbo spin-echo sequences. We rendered images using sagittal (parallel to the sagittal plane) and coronal sections using proton density (PD) and T1-weighted algorithms for analysis.

We evaluated the MRI sections for disc position and for presence of erosions within the condylar and temporal portions of the TMJ, defining erosion as a loss of continuity of the articular margin (Fig. 4). Disc positions were classified into the five following types:

i) Normal. The disc is in the sagittal plane (relative to the superior aspect of the condyle); the border between the low signal of the disc and the high signal of the retrodiscal tissue is located between the 11:30 and 12:30 clock positions; the intermediate zone in the sagittal plane is located between the anterior-superior aspect of the condyle and the posterior-inferior aspect of the articular eminence; and, in the oblique coronal plane, the disc is centered between the condyle and the eminence in the medial, central, and lateral parts.

ii) Disc displacement with reduction. Disc location is displaced in closed-mouth images but normal in open-mouth images.

iii) Disc displacement without reduction. Disc location is displaced in closed-mouth and open-mouth images.

iv) Indeterminate. Disc location is unclear.

v) Invisible. Neither signal intensity nor outlines enable a structure to be defined as the disc in closed- or open-mouth views (120).

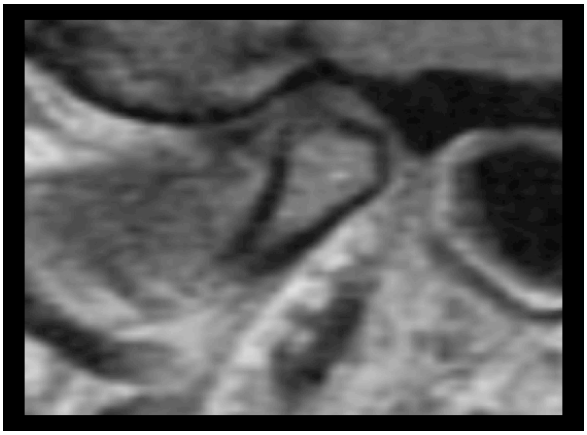

Figure 4. T1-weighted sagittal magnetic resonance image showing erosions on the anterior-superior aspect of the temporomandibular joint condyle head.

Statistics

Analysis used parametric and non-parametric methods where applicable. Descriptive statics report either the median and the 25th and 75th percentiles or the mean and standard deviation (SD). We also report the percentage of abnormal values for relevant variables.

For analytical statistics, we calculated the significance of differences between groups and correlations between variables using the Mann-

Whitney U-test and Spearman ranked correlation and partial correlation tests.

In Studies I and II, the Mann-Whitney test calculated the significance of differences between ACPA-positive and ACPA-negative patients with RA. The Spearman's ranked correlation test calculated the significance of relationships between variables. In Study III, the student's independent *t*-test calculated the significance of differences between groups and the Pearson correlation coefficient, the significance of correlations between variables. In addition, linear multiple regression calculated the significance of relationships between the dependent variable of erosion score and the various independent variables.

In Studies II and III, statistical analysis treated each TMJ in each patient as a separate entity to calculate the significance of relationships between variables related to a certain joint. On the other hand, we used the mean of both TMJs (right and left side) to calculate relationships between joint-related and individual-related variables.

In the analyses, a probability level of less than 0.05 was considered significant.

RESULTS AND DISCUSSION

Temporomandibular joint pain (Studies I and II)

Results

Table 2 reports TMJ pain, the impact of this pain on daily living and quality of life, and serologic markers.

Three patients (9%) reported no TMJ pain at all (during rest, mouth opening, or chewing) at the visit.

Ten patients (32%) reported no TMJ pain at rest; six patients (19%) had no TMJ pain at maximum mouth opening, whereas eight patients (26%) had no TMJ pain while chewing.

Table 2

Clinical findings in patients with temporomandibular joint (TMJ) involvement in rheumatoid arthritis. Study I involved 33 patients and Study II, 26 patients.

		STUDY I				STUDY II			
			Percentile				Percentile		
		Median	25th	75th	**n**	**Median**	25th	75th	**n**
TMJ pain intensity									
At rest	*0-20*	2	0	4	33	1	0	2	52
On maximum mouth opening	*0-20*	9	5	11	33	8	5	14	26
On chewing	*0-20*	4	2	8	33	2	0	4	52
Pain on movements	*0-80*	19	12	27	33	16	10	28	52
Tenderness to digital palpation	*0-8*	4	2	4	33	2	1	3	52
Impact of TMJ pain									
On daily activity	*0-10*	3	2	5	33				
Quality of life	*0-10*	3	2	5	33				
Anterior open bite	*0-9*	4	2	7	33	4	2	7	26

NRS: numerical rating scale. A 0-10 NRS assessed the impact of TMJ pain intensity on patients' ability to perform daily activities and on the quality of their life, with 0 corresponding to “no impact of TMJ pain on daily activities/quality of life” and 10 to “maximum impact by the TMJ pain on daily activities/quality of life”. For TMJ pain intensity, 0 corresponded to ”No pain” and 10 to ”worst imaginable pain”.
n: number of observations.

Patients with TMJ pain while chewing had a significantly higher DAS28 and number of painful regions than patients without TMJ pain ($p = 0.036$ and $p = 0.022$, respectively).

Patients with pain at maximum mouth opening had a significantly higher DAS28 than patients without pain at maximum mouth opening ($p = 0.037$).

Discussion

All participants had received a diagnosis of RA according to the 1987 American College of Rheumatology criteria and were all outpatients at one of the largest rheumatological clinics in Jeddah. Age, gender distribution, and prevalence of RF, ACPA, and serologic markers support the sample's representativeness of the local RA community in Saudi Arabia and in the United Arab Emirates (121-123). Patients had received their RA diagnosis at a mean age of 41 years, which corresponds well with many studies from various parts of the world (124).

RA pain and systemic inflammatory activity, as assessed by the DAS28, are related (125). A high DAS28 was associated with worse general pain and disability in early RA (125). In our studies, high systemic inflammatory activity, as assessed by the DAS28 and number of painful regions, was associated with TMJ pain on function (mouth opening and chewing), indicating that systemic inflammatory activity is one determinant for TMJ pain. Indeed, various TMJ pain constructs (at rest, movement, loading, palpation, etc.) will modulate with the combination of local and systemic factors in RA. For example, TMJ pain on movement modulates mainly via local factors whereas the TMJ pressure pain threshold over the lateral pole modulates via systemic factors to a large extent (52).

Impact of temporomandibular joint pain and systemic inflammatory activity on daily activities and quality of life (Study I)

Results

Four patients reported no restriction to activities of daily living due to TMJ pain. The TMJ pain variables – pain intensity in the TMJ at rest, at

maximum mouth opening, and while chewing – showed significant impact on daily activities (r_s = 0.74, n = 33, p < 0.001; r_s = 0.72, n = 33, p < 0.001; and r_s = 0.72, n = 33, p < 0.001, respectively; Fig. 5A and 5B) and on quality of life (r_s = 0.70, n = 33, p < 0.001; r_s = 0.73, n = 33, p < 0.001; and r_s = 0.72, n = 33, p < 0.001, respectively; Fig. 6A and 6B).

Total TMJ pain intensity during mandibular movements correlated with impact on daily activities and quality of life (r_s = 0.64, n = 33, p < 0.001 and r_s = 0.63, n = 33, p < 0.001, respectively). Pain threshold correlated negatively with impact on daily activities and quality of life (r_s = -0.44, n = 33, p < 0.001 and r_s = -0.43, n = 33, p < 0.001, respectively).

The DAS28 and number of painful regions correlated with the impact of TMJ pain on daily activities (r_s = 0.43, n = 32, p = 0.014 and r_s = 0.53, n = 33, p = 0.002, respectively) and on quality of life (r_s = 0.37, n = 32, p = 0.038 and r_s = 0.49, n = 33, p = 0.004, respectively). The DAS28, in turn, was significantly related to the number of painful regions (r_s = 0.67, n = 32, p < 0.001).

Partial correlations, controlling for the influence of systemic inflammatory activity (DAS28), showed that the number of painful movements and number of painful regions still had a significant impact on daily activities, but to a lesser degree, (r_s = 0.58, n = 29, p < 0.001 and r_s = 0.52, n = 29, p = 0.002, respectively) as did quality of life (r_s = 0.55, n = 29, p < 0.001 and r_s = 0.54, n = 29, p = 0.002, respectively).

Partial correlations, controlling for the influence of TMJ pain on movement (number of painful movements), showed that the number of painful regions, one measure of systemic inflammatory activity, had a significant impact on daily activities (r_s = 0.43, n = 29, p = 0.015) and quality of life (r_s = 0.42, n = 29, p = 0.020).

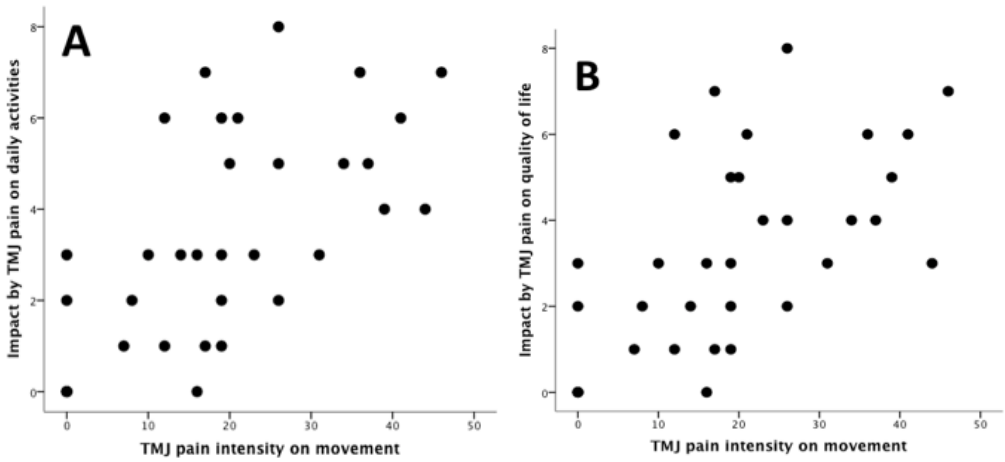

Figure 5. Scatter plots showing the relationship between temporomandibular joint (TMJ) pain intensity during movement and the impact of TMJ pain on daily activities (A: $r_s = 0.72$, n = 33, $p < 0.001$) and quality of life (B: $r_s = 0.73$, n = 33, $p < 0.001$).

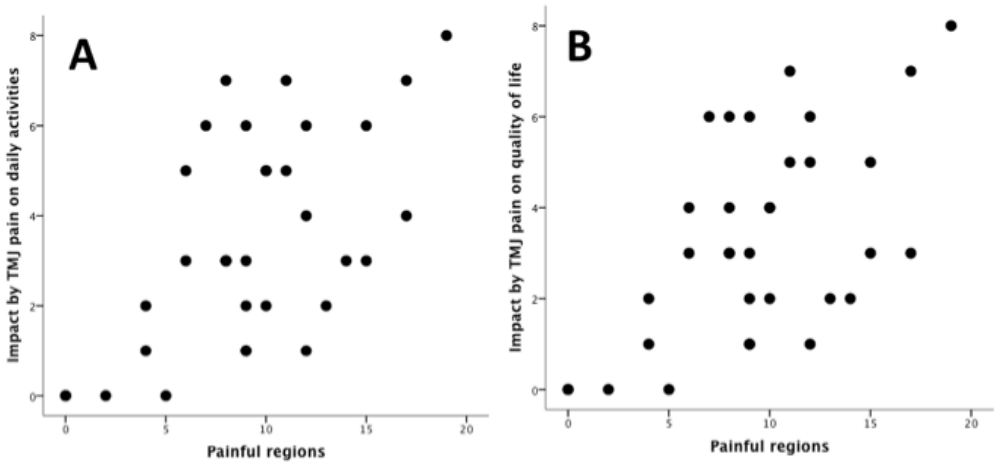

Figure 6. Scatter plots showing the relationship between number of painful regions and the impact of temporomandibular joint (TMJ) pain on daily activities (A: $r_s = 0.53$, n = 33, $p = 0.002$) and quality of life (B: $r_s = 0.49$, n = 33, $p = 0.004$).

Discussion

The main finding of Study I is that systemic inflammatory activity is an important factor behind the degree of impact of TMJ pain. The study also confirmed the substantial impact of TMJ pain on daily activities and

quality of life. This indicates that TMJ treatment planning and prognosis estimation for patients with RA should consider not only the intensity of TMJ pain but also systemic inflammatory activity.

RA impacts many aspects of daily life due to pain, stiffness, and functional restrictions. The disorder is commonly accompanied by local joint pain that increases during movement and loading, which may severely affect and limit daily activities (112). Morning joint stiffness and pain are important features in RA (126). Such morning pain has a considerable impact on the daily living and well-being of patients with RA (128). Indeed, in Study I, TMJ pain during movement and loading correlated with impact on daily activities and quality of life. These findings support previous studies in which TMJ pain seemed to have a substantial negative impact on activities of daily living in RA (91, 111, 127, 128). Voog et al. (91) showed various levels of negative influence on activities of daily living in all included patients with RA. The impact on daily living of TMJ pain/discomfort in that study was greatest for physical exercises and jaw movements. Pain during maximum mouth opening was associated with difficulties in several activities, such as yawning and opening the mouth wide (72).

TMJ movement pain is mainly related to local inflammatory activity (52). TMJ pain intensity during movement, together with the number of painful regions, was strongly associated with the degree of impact of TMJ pain on daily activities and quality of life. This indicates that both local and systemic inflammatory activity are important and interrelated determinants for the consequences of the disease.

The impact of TMJ pain on daily activities and quality of life was higher in patients with high systemic inflammatory activity. In turn, higher systemic inflammatory activity was associated with TMJ pain during mouth opening and chewing. The present study investigated TMJ pain at rest and during movement and loading (chewing), as well as palpation pain. These variables represent pain constructs which, to some extent, represent a variety of peripheral pain mechanisms that may share similar central pain mechanisms. TMJ pain during movement and chewing represents

mechanical sensitization in which normal use elicits pain, whereas palpation pain represents mechanical sensitization to externally applied pressure. In this context, pain at rest represents a mix of central and peripheral sensitization and activation of nociceptive mechanisms. However, the central mechanisms, in the trigeminal centers in the brain stem and other brain centers for affective and cognitive aspects of pain, for example, may also maintain chronic pain without a substantial sensory influx in the nociceptive system (129). This may amplify all pain aspects and may also contribute to TMJ pain. Our studies thus indicate that systemic inflammatory activity is a major factor behind the impact of TMJ pain on daily activities and quality of life.

In the arthritic synovial membrane, immunoactive cells release inflammatory mediators like cytokines (TNF, IL-1, IL-6, etc.) to bind to local target receptors. These cytokines, which may also "spill over" into the blood and eventually reach the liver, have been shown to activate afferent portions of the vagus nerve passing through the liver, causing or modulating the "illness response" when the nerve signals reach the vagus centers in the brain. The illness response consists of fever, malaise, mood changes, reduced appetite and libido, fatigue, increased or disturbed sleep, and disturbed central pain modulation (130, 131) and may therefore partly explain how TMJ inflammation influences central pain processing, in addition to peripheral sensitization of nociceptive nerve endings. Also, the cytokines found in blood increase the inflammatory markers of systemic inflammatory activity; thus, TMJ inflammation may influence systemic inflammatory activity and central pain processing via this mechanism.

Temporomandibular joint synovial fluid mediators (Studies II and III)

Results

Table 3 reports the investigated ratios between inflammatory mediators in the TMJ synovial fluid and the concentrations of TNF and IL-1ra as well as their respective soluble receptor II in blood serum. In TMJ synovial

fluid, 48% of the samples were ACPA positive. In ACPA-positive TMJ synovial fluid, the ratio of TNF to IL-1ra was significantly higher than in ACPA-negative patients ($p = 0.001$; Study III). Patients taking anti-TNF medication had a significantly lower ratio between IL-1ra and IL-1sRII levels in TMJ synovial fluid than patients who were not ($p = 0.048$).

In TMJ synovial fluid, the ACPA level correlated significantly with TNF level ($r_s = 0.47$, n = 52, $p < 0.001$), CRP level ($r_s = 0.60$, n = 52, $p < 0.001$), and RF titer ($r_s = 0.50$, n = 52, $p < 0.001$), but not with TNFsRII level. This indicates that increased inflammatory activity depends in part on an insufficient increase in anti-inflammatory mediators. The ratio between TNF and TNFsRII significantly correlated with ACPA level ($r_s = 0.36$, n = 52, $p = 0.009$), as well as CRP level ($r_s = 0.47$, n = 52, $p < 0.001$).

Table 3

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

		STUDY II				STUDY III		
			Percentile					
		Median	25th	75th	**n**	**Mean**	**SD**	**n**
Ratios between TMJ synovial fluid mediators								
TNF/TNFsRII		0.6	0.5	0.7	52	0.7	0.4	44
TNF/CRP		15	11	26	52	21	15	44
TNF/RF		3.2	2.6	5.7	52	5.4	3.8	44
TNF/ACPA		8	4.4	12	52	9.1	5.1	44
IL-1ra/IL-1sRII		1.5	1.3	2.1	52	1.9	1.2	44
IL-1ra/TNF		2.1	1.7	2.5	52	2.2	1.2	44
Blood serum levels								
TNF	*pg/mL*	100	66	135	26	149	119	22
TNFsRII	*pg/mL*	173	87	238	26	267	213	22
IL-1ra	*pg/mL*	218	162	254	26	240	122	22
IL-1sRII	*pg/mL*	108	89	158	26	136	61	22

n: number of observations, SD: standard deviation, TNF: tumor necrosis factor, TNFsRII: soluble TNF receptor II, CRP: C-reactive protein , RF: rheumatoid factor, ACPA: anti-citrullinated protein antibodies, IL-1ra: interleukin-1 receptor antagonist, IL-1sRII: interleukin 1 soluble receptor type II.

Discussion

Studies II and III show that excess levels of TNF in TMJ synovial fluid relative to its endogenous control, as assessed by TNFsRII, are associated with ongoing inflammatory activity. In Study II, high TMJ synovial fluid levels of ACPA, CRP, and RF correlated with excess levels of TNF, but not with the TNFsRII level. This means that insufficient cytokine control is probably an important factor behind increased inflammatory activity.

Patients with ACPA-positive TMJ synovial fluid also had higher TNF levels in their synovial fluid relative to IL-1ra levels than did ACPA-negative patients. In addition, high ACPA concentrations were associated with high TNF levels in TMJ synovial fluid. ACPA, the autoantibody for citrullinated peptides that is found, for example, in the synovial tissues, activates the immune system and would therefore be expected to contribute to TNF and IL-1 release. However, ACPA in synovial tissues seems to a larger extent to affect TNF production and release.

Levels of ACPA in TMJ synovial fluid have never been reported before. In this study, 48% of the TMJ synovial fluid samples were positive for ACPA. In the synovial fluid, ACPA levels were strongly related to levels of CRP and RF, supporting ACPA's association with local inflammatory activity, as expected.

In TMJ synovial fluid, high TNF was associated with a high level of TNFsRII. This indicates that inflammatory activity increases proinflammatory cytokines as well as their endogenous controls. However, since the soluble receptor level was not related to ACPA, CRP or RF in TMJ synovial fluid, the increase in the endogenous control is probably not always sufficient to control or inhibit the inflammatory process (132).

Systemic inflammatory activity (Studies I–III)

Results

The percentage of patients who tested ACPA-positive in serum was 85% (Study II) and 86% (Study III). In ACPA-positive patients, significant

correlations occurred between the concentrations of ACPA and TNF (r_s = 0.56, n = 26, p = 0.007; Study II) and TNFsRII (r_s = 0.51, n = 26, p = 0.016; Study III) in serum. In serum, TNF concentrations correlated with TNFsRII concentrations (r_s = 0.84, n = 26, p < 0.001; Study II). Also, ACPA-positive patients had higher concentrations of IL-1sRII in serum (p = 0.004; Study II).

Discussion

Presence of ACPA in blood correlates with higher systemic inflammatory activity and worse RA prognosis, in part perhaps due to a consistent stimulation of TNF production and release (133, 134). In our studies, 84–85% of the patients had ACPA in their blood, compared to approximately 72% in samples from Western European countries (135). However, in a study on Egyptian patients with RA, the proportion of ACPA-positive patients was found to be 84% (136), which is similar to what we found in this study of a similar RA population.

High ACPA levels were associated with high TNF levels in TMJ synovial fluid. ACPA, that is, the autoantibody towards citrullinated peptides found, for example, in the synovial tissues, activates the immune system and can therefore be expected to contribute to TNF release. ACPA levels in TMJ synovial fluid have never been reported before. Presence of ACPA in blood indicates higher inflammatory activity and a worse prognosis, in part possibly due to elevated TNF levels (133, 134).

Modulation of temporomandibular joint pain (Study II)

Results

There was a positive correlation between high levels of TNF compared to TNFsRII in TMJ synovial fluid and pain during posterior palpation of the TMJ at maximum mouth opening (r_s = 0.32, n = 52, p = 0.022).

High levels of IL-1ra compared to IL-1sRII in TMJ synovial fluid positively correlated with palpation pain of the lateral TMJ pole, as well as with total tenderness to TMJ palpation (r_s = 0.31, n = 52, p = 0.025 and r_s = 0.31, n = 52, p = 0.024, respectively; Fig. 7).

Discussion

Study II shows that TMJ palpation pain in RA is related to high TNF and IL-1ra levels relative to their soluble anti-inflammatory receptors TNFsRII and IL-1sRII in TMJ synovial fluid. High levels of ACPA, CRP, and RF in TMJ synovial fluid correlate with increased concentrations of TNF, but not of TNFsRII. A deficiency in local cytokine control thus seems to contribute to inflammatory activity, including decreased mechanical pain thresholds in the TMJ.

A relative excess of the proinflammatory cytokines TNF and IL-1 in the TMJ synovial fluid relative to their endogenous control, as assessed by TNFsRII and IL-1sRII, thus seems to sensitize the articular and/or adjacent tissues to mechanical stimulation. However, from the results of this study it is unclear if this sensitization is local/peripheral or systemic/central in origin, or if it is a combination. TMJ pain to palpation has shown to be due to either local/peripheral sensitization to mechanical stimuli of the articular tissues or the tissues overlying the TMJ, systemic/central sensitization, or both (47). There is at least 15 mm from the surface of the skin to the most lateral part of the TMJ capsule and lateral pole (Holmlund, personal communication). Palpation over the lateral pole of the TMJ thus also affects tissues other than the joint, such as muscles, skin, subcutaneous tissue, and connective tissue. These tissues may well be systemically or centrally sensitized and pain on palpation may therefore reflect more of a systemically mediated sensitization. Indeed, Alstergren et al. found that the pressure pain threshold over the TMJ in systemic joint diseases involving the TMJ, that is, mechanical stimulation in the same manner as digital palpation, is related only to systemic factors and not to local (intra-articular) inflammatory mediators (52). The correlation found in the present study between pain on palpation and a disturbed intra-articular ratio between TNF and one of its soluble receptors might therefore include the influence of central sensitization to a substantial degree.

A deficiency in cytokine control mechanisms (soluble receptors, decoy receptors, anti-inflammatory cytokines, etc.) seems to associate with increased articular pain as well as tissue degradation (137). Low plasma

levels of TNFsRII, indicating compromised endogenous cytokine control, seem strongly related to both TMJ pain and tissue destruction (55).

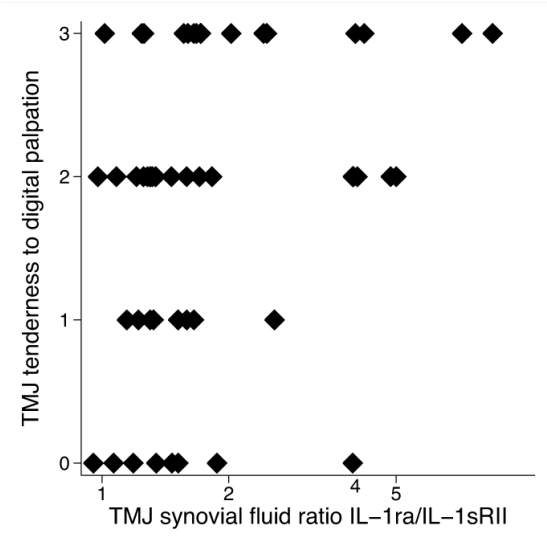

Figure 7. Scatter plot showing the relation of interleukin I receptor antagonist (IL-1ra) to soluble interleukin I receptor type II (IL-1sRII) levels in the temporomandibular joint (TMJ) synovial fluid of 26 patients with rheumatoid arthritis compared to TMJ pain on palpation (r_s = 0.31, n = 52, p = 0.025).

Temporomandibular joint erosions (Study III)

Results

The majority of TMJ erosions occurred on the condyle. Of the 132 TMJ condyle regions examined, 38% had erosions, compared to only 3% in the temporal areas (p = 0.001). Of these erosions, 24% occurred in the medial regions of the condyle, 29% in the lateral regions, and the majority, 53%, in the central regions of the condyle.

The total erosion scores of the condyle and of the temporal portion correlated with each other (r_s = 0.65, n = 44, p < 0.001).

Discussion

Erosions were only occasionally observed in the temporal portion of the TMJ, but these correlated with erosive changes on the condyle. Several previous studies that used MRI and CT to assess erosive changes support these findings (50, 71, 138). A previous study shows that most radiographic changes occurred in the condylar region with far fewer in the temporal part (118). The study concluded that radiographic changes were primarily located on the condyle.

Another study showed (139) that systemic inflammatory activity, as assessed by DAS28 and CRP, was strongly related to MR bone tissue erosion in wrist/metacarpophalangeal joints. Also, that study confirmed that changes in CRP are related to changes in MR measures of inflammation, like synovitis and edema. Changes in the DAS28 score did not relate strongly with changes in the MR scores, probably because of the composite nature of the DAS28, which includes a tender joint count and pain intensity not assessed by MR.

Temporomandibular joint erosions in relation to synovial fluid mediators (Study III)

Results

High levels of TNF relative to TNFsRII in the TMJ synovial fluid correlated with the TMJ condylar erosion score (r_s = 0.32, n = 44, p = 0.036; Fig. 2 in Study III).

The erosion scores of the medial condylar region and the posterior temporal area each correlated with TNF/TNFsRII ratios in the TMJ synovial fluid (r_s = 0.31, n = 44, p = 0.042 and r_s = 0.40, n = 44, p = 0.007). Multiple regression revealed no significant contribution of the independent relations TNF/TNFsRII or IL-1ra/IL-1sRII versus the dependent variable erosion score.

Discussion

Study III shows that a relative excess levels of TNF in the TMJ synovial fluid compared to its endogenous control, as assessed by TNFsRII, are

associated with ongoing inflammatory activity, resulting in TMJ bone tissue resorption. Our findings further indicate that changes in the temporal portion occur in TMJs with more severe inflammatory activity involving bone tissue changes.

High TMJ synovial fluid levels of TNF relative to TNFsRII were associated with erosive changes of the TMJ cartilage and bone tissue. TNF plays a major role in RA, not least by promoting cartilage and bone tissue destruction (50). The cytokine stimulates the release of matrix metalloproteinases and other proteolytic enzymes that degrade proteoglycans. TNF also has potent effects on bone metabolism by stimulating osteoclast formation and activity while inhibiting osteoblast formation of new bone tissue. Our findings also indicate that the relationship between these pro- and anti-inflammatory factors to some extent determines local inflammatory activity, including TMJ bone tissue resorption. Insufficient endogenous control of TNF, as represented by low TMJ synovial fluid levels of TNFsRII relative to TNF, may therefore be a risk factor for developing structural TMJ changes. This has been reported before in cases where insufficient systemic endogenous control of TNF was found to contribute to TMJ pain and tissue destruction in RA (140). Study II found that deficient TNF control by TNFsRII was related to TMJ pain in RA. Insufficient formation of soluble TNF receptors may thus contribute to the development or maintenance of inflammation (141). It was, however, not possible in the present studies to determine which factor, a high TNF or a low TNFsRII level, was the most important for TMJ bone tissue resorption.

TNF and ACPA have been separately associated with structural joint damage (142). Patients who were positive for ACPA in the TMJ synovial fluid had higher TNF synovial fluid levels in the TMJ relative to IL-1ra levels than did ACPA-negative patients. This suggests that presence of ACPA in synovial tissues has a strong affect on TNF production and release.

Temporomandibular joint erosions in relation to systemic inflammatory activity (Study III)

Results

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

Patients taking anti-TNF medication had significantly lower IL-1ra relative to IL-1sRII levels in TMJ synovial fluid than patients who were not (p = 0.048).

Discussion

ACPA positivity in the blood may provide an early means of differentiating between patients with erosive and non-erosive RA (134). ACPA positivity in the blood is associated with progressive radiographic joint destruction in patients with recent-onset RA (143). Presence of ACPA in the blood also indicates higher inflammatory activity, in part perhaps due to elevated TNF levels (133, 134).

ACPA can induce differentiation of bone-resorbing osteoclasts from monocytic precursors and activate osteoclasts, thereby contributing to bone tissue loss (144). Bone tissue damage in early and even recent-onset RA, which occurs years before arthritis starts and clinical symptoms begin to emerge, has been attributed to ACPA (145). ACPA is associated with bone tissue loss and alterations in bone tissue metabolism before the clinical onset of arthritis, suggesting that these antibodies are linked to structural bone damage in RA (144).

Patients on anti-TNF medication had lower IL-1ra levels relative to IL-1sRII in TMJ synovial fluid. Although this study detected no significant relationship between IL-1ra or IL-1sRII and bone tissue changes in the TMJ, this finding indicates that anti-TNF medication influences the cytokine balance for cytokines other than TNF. This was expected, however, and has been shown before (146).

CONCLUSIONS

TMJ pain intensity and systemic inflammatory activity in patients with RA are involved in activities of daily living and quality of life impairment.

TMJ pain in RA seems to be related to a deficiency in local cytokine control that contributes to increased inflammatory activity, including lowered mechanical pain thresholds over the TMJ.

TNF in TMJ synovial fluid seems to be one factor mediating TMJ bone tissue resorption in RA. The degree of endogenous TNF control seems to contribute to TMJ bone tissue destruction.

In summary, TNF, including its endogenous control system, seems to be involved in TMJ inflammation, which results in TMJ pain and tissue destruction. In turn, TMJ pain has a negative impact on daily living and quality of life in patients with RA.

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