Temporomandibular joint involvement by systemic inflammatory disease with reference to pain modulation and joint tissue destruction

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To my parents

Contents

Abstract

Systemic inflammatory diseases may cause progressive destruction in the temporomandibular joint (TMJ). Involvement of this joint is associated with many clinical signs and symptoms of which pain is a major problem. This thesis investigated the relationship between TMJ pain, radiographic changes of the joint, daily activities as well as the influence on TMJ pain and tissue destruction of inflammatory markers and mediators in the blood. Patients with a diagnosis of rheumatoid arthritis (RA) or psoriatic arthritis (PA) and with TMJ clinical involvement were included.

The aim of the first study was to investigate the impact of TMJ pain on daily living. A scale for the influence of TMJ pain on the activities of daily living (ADL) was used. ADL was influenced in all patients at different levels, but the impact of pain was most pronounced on the performance of jaw movements and physical exercise. The results indicate that pain from the TMJ in patients with RA has a significant negative impact on activities of daily living.

The aim of the second study was to investigate the relation between inflammatory mediators and markers versus presence of TMJ radiographic changes. The most frequent radiographic signs detected by computed tomography were sclerosis, erosions and flattening. The inflammatory origin of erosion was indicated by its correlation to the thrombocyte particle concentration, while flattening was correlated to plasma concentration of tumor necrosis factor alpha (TNFα). This study thus showed an association between systemic inflammatory activity and radiographic signs of TMJ tissue destruction in patients with clinical TMJ involvement by RA.

The aim of the third study was to investigate the longitudinal radiographic changes in the TMJ and their relation to inflammatory mediators and markers in the blood. Regression of erosions was associated with high serum concentration of serotonin (5-HT) and plasma concentration of interleukin-1 soluble receptor type II (IL-1sRII), while progression of erosions was associated with high plasma

concentration of 5-HT. Progression of flattening was associated with high C-reactive protein (CRP). This study indicates that the progression of radiographic changes that occurs in the TMJ of patients with well-controlled RA during a period of 25-46 months seems to be related to the blood levels of CRP, 5-HT and IL-1sRII, but only minor progression can be expected to occur and with considerable individual variation.

The aim of the fourth study was to investigate if the 5-HT_3 antagonist granisetron reduces TMJ pain. An intra-articular injection of granisetron (1mg) given in a randomized double-blind manner reduced the resting pain in the TMJ according to a visual analogue scale after 10 and 20 minutes. The pain during maximum mouth opening was decreased and pressure pain threshold over the TMJ was increased after 20 min. The latter finding was associated with low level of P-5-HT. Granisetron has an immediate, short-lasting and specific pain reducing effect in TMJ RA or PA and the 5-HT_3 receptor therefore seems to be involved in the mediation of TMJ pain in systemic inflammatory joint disorders.

This thesis shows that 5-HT is an important mediator of pain and inflammation of the TMJ involved by systemic inflammatory disease and that TNFα and 5-HT are significant mediators of mineralized tissue destruction. Furthermore TMJ pain in patients with RA has a significant negative impact on activities of daily living.

Key words

Acute phase proteins, Computed tomography, Cytokines, Granisetron, Inflammation, Pain, Serotonin, Temporomandibular joint, Visual Analogue Scale.

Preface

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

I. Voog Ü, Alstergren P, Leibur E, Kallikorm R and Kopp S. Impact of temporomandibular joint pain on activities of daily living in patients with rheumatoid arthritis (Acta Odontol Scand 2003; in press).

II. Voog Ü, Alstergren P, Eliasson S, Leibur E, Kallikorm R and Kopp S. Inflammatory mediators and radiographic changes in temporomandibular joints of patients with rheumatoid arthritis. Acta Odontol Scand 2003;61:57-65.

III. Voog Ü, Alstergren P, Eliasson S, Leibur E, Kallikorm R and Kopp S. The progression of radiographic changes in the temporomandibular joints of patients with rheumatoid arthritis in relation to inflammatory markers and mediators in the blood (Acta Odontol Scand, accepted).

IV. Voog Ü, Alstergren P, Leibur E, Kallikorm R and Kopp S. Immediate effects of the serotonin antagonist granisetron on temporomandibular joint pain in patients with systemic inflammatory disorders. Life Sciences 2000;68:591-602.

Abbrevations

ADL	Activities of daily living
CRP	C-reactive protein
CT	Computed tomography
CV	Coefficient of variation
DMARD	Disease-modifying antirheumatic drug
ESR	Erythrocyte sedimentation rate
5-HT	5-hydroxytryptamine, serotonin
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL-1	Interleukin-1
IL-1ß	Interleukin-1beta
IL-1sRII	Interleukin-1 soluble receptor type II
IL-6	Interleukin-6
IQR	Interquartile range: the numerical difference between the 75^{th} and 25^{th} percentile
NSAID	Non-steroidal anti-inflammatory drug
PA	Psoriatic arthritis
PGE_2	Prostaglandin E_2
P-5-HT	Plasma concentration of serotonin
P-IL-1sRII	Plasma concentration of interleukin-1 soluble receptor type II
PPT	Pressure pain threshold
P-TNFα	Plasma concentration of tumor necrosis factor alpha
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SD	Standard deviation
S-5-HT	Serum concentration of serotonin
TDP	Tenderness to digital palpation

TMJ	Temporomandibular joint
TNFα	Tumor necrosis factor alpha
TPC	Thrombocyte particle concentration
VAS	Visual analogue scale
VAS_{MVM}	TMJ pain during maximum mouth opening as assessed with a VAS
VAS_{Rest}	Current resting pain of the TMJ assessed with VAS

Introduction

Pain is a major determinant of quality of life for people with RA. Persistent pain and joint tissue destruction are clinically important aspects in autoimmune diseases such as systemic inflammatory joint diseases (Jacox 2002). Pain intensity, persistence of pain as well as the response to pain are contributing to the disability in systemic inflammatory joint diseases like RA. Gibson and Clark (1985) found that 47% of patients with RA rated pain relief as the most important treatment objective and 66% of patients with RA ranked pain as the most important problem (McKenna and Wright 1985). Pain is a common reason also for patients with TMJ involvement of systemic inflammatory joint diseases to attend treatment. TMJ arthritis may in addition induce several types of dysfunctions such as restrictions in maximum mouth opening, eating and talking. The influence by TMJ pain on daily activities is unknown so far. Cartilage and bone degradation are also important aspects of the disease that result in an impaired functional capacity of the joint and which may have negative impact on the activities of daily living.

RA is a chronic systemic inflammatory joint disease with progressive and destructive nature characterized by synovial hyperplasia and abnormal immune responses and is characterized by exacerbation and remissions (Gay et al. 1993). RA is not limited to symmetric erosive synovitis only, but may also show extra-articular manifestations. The rheumatoid process often starts as an inflammatory reaction in the synovial membrane, i.e. synovitis, which later may lead to destruction of cartilage and bone tissue in all joints of the body including the TMJ (Kopp 1994, Edwards 1998, Choy and Panayi 2001, Feldman 2001). The inflamed rheumatoid synovial membrane appears similar to an activated lymph node with a high infiltration by mononuclear cells which are predominantly lymphocytes (Miossec 1987). The events that trigger the immune system to develop a disease like RA remain unknown. There are suggestions that RA is caused by an unidentified arthritogenic anti-

gen, which could be either an exogenous antigen such as a viral protein or an endogenous protein (Gregersen et al. 1987). There might be associations between the disease and the genetic and environmental factors as well. RA affects 1 - 2 % of the world's population (Louie et al. 2003). Clinical symptoms in the TMJ have been found in 34 - 35% of patients (Syrjänen 1985, Tegelberg and Kopp 1987), while radiographic involvement of TMJ in RA has been reported to occur in 45 – 71 % (Syrjänen 1985, Larherim et al. 1988, Wenneberg et al. 1990, Çeliker et al. 1995, Gynther et al. 1996).

PA can be defined as a chronic inflammatory disorder affecting the musculoskeletal system in patients with psoriasis (Espinoza and Cuellar 1998). PA is an inflammatory, mostly seronegative and asymmetric polyarthritic disease (Helliwell and Wright 1998). The arthropathy has been found to occur in 5 - 8 % of all patients with psoriasis (Helliwell and Wright 1998, Espinoza and Cuellar 1998). TMJ clinical involvement in patients with PA occurs in 31 to 63% of the patients (Rasmussen and Bakke 1982, Könönen 1987, Könönen et al. 1991). TMJ radiographic involvement in patients with PA occurs in 31 - 41 % of the patients (Könönen 1987, Wenneberg et al. 1990, Könönen et al. 1991).

It is known that inflammation often is accompanied by pain. Evaluation and estimation of the impact of pain is a complicated matter, since pain has many different ways to interfere with everyday life. The impact of pain on the health status and quality of life in patients with chronic inflammatory joint diseases has been recognized (Jacox 2002), but there is a lack of knowledge about the specific impact of TMJ pain on daily activities in patients with clinical involvement of the TMJ RA.

5-HT probably plays an important role in the mediation of pain and hyperalgesia (Taiwo and Levine 1992, Eide and Hole 1993). Peripheral 5-HT is mainly stored in thrombocytes and several substances like substance P can induce 5-HT release from these cells (Carraway et al. 1984, Richardson and Engel 1986, Payan and Goetzl 1988). In patients with RA, thrombocytes have been found to be increased in number

and activated to release 5-HT (Zeller et al. 1983, McNicol and Israels 1999). 5-HT from platelets may contribute to inflammatory responses of RA by increasing the secretion of collagen from fibroblasts (Aalto and Kulonen 1972). 5-HT in the synovial fluid of the TMJ from patients with systemic inflammatory diseases has been associated with movement pain and decreased mandibular mobility (Alstergren and Kopp 1997, Alstergren et al. 1999).

The known 5-HT receptors comprise seven groups (5-HT_{1-7}) with a total of 14 subtypes (Zifa and Fillion 1992, Hoyer et al. 1994). The 5-HT_3 receptor is phylogenetically older than the other 5-HT receptors, all of which have developed from a single primordial 5-HT receptor and belong to the G-protein coupled receptors. Only one, the 5-HT_3 receptor is ligand-gated to fast ion (Na+/K+) channels (Gyermek 1996, Wolf 2000). Richardson and Engel (1986) showed that 5-HT participates in the mediation of spontaneous pain from inflamed peripheral tissues by sensitizing and exciting fine afferent units via the 5-HT_3 receptor. The 5-HT_3 receptor is peripherally only located on afferent neurons (Martin and Humphrey 1994).

Granisetron has been show to be a highly specific agonist for the 5-HT_3 receptor (Fake et al. 1987) and acts both peripherally and centrally (Yarker and McTavish 1994). Injection of granisetron into the human masseter muscle reduced pain induced by local administration of 5-HT (Ernberg et al. 2000). Mild side effects have been reported in the form of headache and constipation. Less common are diarrhoea, asthenia and somnolence (Tabona 1990, Yarker and McTavish 1994).

Cytokines in the RA synovium function in a network with overlapping, synergistic, antagonistic and inhibitory activities (Arend 2001). TNFα and IL-1 were the first cytokines for which a liver-stimulatory activity was reported (Darlington et al. 1986) and which move from the site of injury to the liver to trigger the acute phase reaction. The involvement of IL-1 and TNFα in the pathogenesis of RA is well known (Arend 2001), and they participate in the mediation of systemic symptoms in RA such as fever, high white blood cell count

due to increased bone marrow release, and myalgias from muscle proteolysis. TNFα is a cytokine which is important as a disease promoting mediator in rheumatoid joints (Isomäki and Punnonen 1997). TNFα is produced mainly by monocytes and macrophages at the site of inflammation (Vilček and Lee 1991) and modulates the inflammatory response. In addition, TNFα regulates the production of other pro-inflammatory cytokines such as IL-1 (Brennan et al. 1989, Haworth et al. 1991). TNFα levels are increased in the synovial fluid and membrane of patients with RA (Buchan et al. 1988, Saxne et al. 1988) and in cell cultures. TNFα also stimulates PGE_2 and collagenase production, which induces cartilage and bone destruction (Dayer et al. 1985). A detectable level of IL-1ß in the synovial fluid has been suggested to be an indicator of destructive inflammation in the TMJ involved by polyarthritis (Alstergren et al. 1998). Presence of IL-1ß in plasma has also been found to be associated with radiographic changes such as erosions of the TMJ (Nordahl et al. 1998). Inflammation in the knee joints of RA patients has also been shown to be related to the local concentration of IL-1ß (Rooney et al. 1990). There are two IL-1 receptors: type I receptors that are found in most cell types, including T-lymphocytes, endothelial cells and type II receptors that are limited primarly to blood neutrophiles, monocytes and B-lymphocytes (Spriggs et al. 1990). Interaction with the membrane type I receptor leads to signal transduction and an intracellular effect (Oldenburg et al. 1995). However, type II receptors act as inhibitory decoy receptors with antiinflammatory effects (Slack et al. 1993). Indeed, high levels of IL-1sRII in TMJ synovial fluid has been associated with no or only small degree of joint destruction in patients with TMJ involvement by chronic polyarthritides (Alstergren et al. 2003).

CRP is the most commonly used acute phase protein because it is sensitive to inflammatory stimuli (Kushner 1982, van Leeuwen et al. 1993). CRP can produce a systemic down-regulation of the innate immune system (Du Clos 2003). The radiographic progression in RA has been found to be correlated with elevated CRP values (van

Leeuwen 1993, Combe et al. 1995, Jansen et al. 2001). Associations have been found between CRP and TMJ pain as well (Tegelberg et al. 1987).

A high ESR has been shown to be associated with a poor prognosis in systemic inflammatory disease, but has no strong predictive value as a single marker (Luukkainen et al. 1983, Kaarela 1985, Möttönen 1988). In TMJ involvement by RA high ESR has been associated with more severe TMJ symptoms (Tegelberg et al. 1987).

TPC is increased in chronic inflammatory diseases (Zeller et al. 1983, Ertenli et al. 2003) and thrombocytosis in active RA has been found to be correlated with clinical and laboratory parameters of disease activity such as ESR and CRP (Kaye 1988).

RF is a well accepted predictor of disease activity in RA (van Leeuwen et al. 1995, Vittecoq et al. 2003). High serum concentration of RF has thus been found to be associated with poor prognosis (van der Heijde et al. 1992, 1995, Uhlig et al. 2000). Serum RF originates from the synovium (Randen et al. 1995). The exact mechanism by which RF is contributing to disease is unknown but probably by immunological activation of the synovial tissues. In addition, there are reports of RF isotypes that contribute to disease in different ways. The exact way how RF isotypes switch from IgM to IgG and IgA and contribute to diseases like RA is not clear yet. An early rise in serum IgA RF in RA seems to be a strong predictor of a more severe disease with appearance of erosions (Teitsson et al. 1984, Fouquet et al. 1987, Teitsson 1988, Houssien et al. 1998). IgM RF seems also to be a good predictor for progression of radiographic changes in general (van Leeuwen et al. 1995, Vittecoq et al. 2003).

Radiographic examination is commonly used for assessment of joint destruction. The first report of TMJ CT was published by Suarez et al. (1980) and this method is superior to plain transcranial or transmaxillary imaging for detecting bone changes. CT allows detailed three-dimensional examination of the TMJ and it is capable to detect even small bone changes not demonstrable by conventional tomographic procedures (Larheim and Kolbensvedt 1984, Christiansen et al. 1985, Raustia et al. 1985, Avrahami et al. 1989, Larheim and

Kolbensvedt 1990). In systemic inflammatory diseases like RA, radiographic signs of joint damage reflect the cumulative effect of the disease on bone tissue. Repeated assessments of the radiographic changes provide a measure of the rate of progression (Sharp 1989), which is important since progression of radiographic signs of joint damage can continue even despite of well-planned general treatment (Gordon et al. 2001). Radiologic progression of RA was found to develop most rapidly during the first years after disease onset and to assume a slow, nearly linear rate of increase after 10 years (Sherrer et al. 1986, Graudal et al. 1998, Uhlig et al. 2000). There are some different systems for evaluation of radiographic changes in the TMJ based on conventional tomography (Rohlin and Petersson 1989, Nordahl et al. 2001), but so far there is no special scoring system available based on CT for longitudinal investigations.

Aims

The general purpose of this thesis was to investigate TMJ pain, radiographic changes of the joint, impact of TMJ pain on daily activities and influence on pain and tissue destruction of inflammatory markers and mediators in the blood, especially 5-HT.

Specific aims

To investigate:

- The impact of pain in the TMJ on daily activities in patients with TMJ clinical involvement of the TMJ by RA.

- The relation between the inflammatory mediators TNFα and 5-HT, inflammatory markers ESR and CRP as well as RF and TPC in blood versus TMJ radiographic changes in patients with clinical involvement of the TMJ by RA.

- The progression of radiographic changes in the TMJ of patients with clinical involvement of the TMJ by RA and its relation to blood levels of inflammatory mediators and markers.

- If the 5-HT_3 receptor is involved in the modulation of TMJ pain and if the 5-HT_3 antagonist granisetron reduces TMJ pain in patients with systemic inflammatory joint disease.

Material and methods

Subjects

This investigation comprised a total of 24 patients (20 females and 4 males; Table) with clinical TMJ involvement of RA or PA.

All patients with TMJ pain were referred to the Clinic of Stomatology from the Clinic of Rheumatology at the University of Tartu, Estonia and consecutively examined for inclusion. They had their diagnosis verified and were screened for TMJ pain by one and the same rheumatologist.

The diagnosis of RA was determined according to the 1987 classification criteria of the American Rheumatism Association (Arnett et al. 1988) and the diagnosis of PA according to the European Spondylarthropathy Study Group's preliminary criteria for the classification of spondylarthropathy (Dougados et al. 1991). The patients in the *Study I, II* and *IV* had not been subjected to any treatment of the TMJ during the last 6 months. Inclusion criteria besides a diagnosis of RA or PA were pain localized to the TMJ region

Table. Age (years), number of female/male patients, duration of general disease and TMJ involvement (years) as well as diagnosis of the patients included in Study I - IV.

			Study			
			I	II	III	IV
Age and gender		Median	44	41	44	42
		IQR	23	15	20	16
		F / M	17/2	17/3	14/2	12/4
Duration	General disease	Median	9	9	11	9
		IQR	5	5	2	2
	TMJ involvement	Median	1	2	4	1
		IQR	3	4	3	3
Diagnosis	RA +/-	n	3/16	6/14	0/16	3/11
	PA	n				2

IQR = interquartile range, F = female patient, M = male patient, TMJ = temporomandibular joint, RA +/- = rheumatoid arthritis rheumatoid factor positive / negative, PA = psoriatic arthritis, n = number of patients.

at rest and at maximum mouth opening as well as at least a 35% decrease of the latter pain 5 min after an auriculotemporal nerve block with 2 mL lidocaine (Xylocain®, 20 mg/mL). Exclusion criteria were any other disease that may cause orofacial pain including previous TMJ trauma or an infection in the TMJ region. Allergy towards granisetron was also an exclusion criteria in Study *IV*.

The general treatment in the patient sample was composed of NSAID, oral glucocorticosteroid and DMARD. The general treatment of this patient category in the Clinic of Rheumatology at the University of Tartu usually starts with NSAID and DMARD or glucocorticoid and DMARD. Sixteen patients in *Study I-III* and 12 patients in *Study IV* used NSAIDs (diclofenac, meloxicam, indomethacine). Seven patients in Study I and IV and 9 patients in *Study II* as well as 10 patients in *Study III* used oral glucocorticoid (methylprednisolone, triamcinolone). DMARDs (sulfasalazine, methotrexate, azathioprine) were used by 8 patients in *Study I* and *IV* as well as 9 patients in Study *II-III*.

Study I – II and *IV* were approved by the local ethics committees at the Huddinge University Hospital, Sweden (310/97) and at the University of Tartu, Estonia (55/5, 1998). *Study III* was approved at the Huddinge University Hospital (418/02) and at the University of Tartu (94/3, 01). All individuals gave their verbal consent to participate.

Methods

Assessment of pain

In *Study I* and *IV* the VAS_{Rest} and VAS_{MVM} were measured with a 100 mm visual analogue scale (VAS, ACO, Stockholm, Sweden) with endpoints marked "No pain" (score 0) and "Worst pain ever experienced" (score 100). VAS_{MVM} was assessed after the patients opened and closed the mouth five times. In *Study I* the sum of the VAS scores for the right and left TMJ were used in the analysis. In *Study IV* VAS_{Rest} as well as VAS_{MVM} were assessed before the injection as well as after 10 and 20 minutes.

Pressure pain threshold

In *Study I* and *IV* an electronic pressure algometer (Somedic Sales AB, Sollentuna, Sweden) was used to assess the PPT to linearly increasing pressure over the lateral aspect of both TMJs. The algometer had a blunt rubber tip with an area of 1 cm^2. The algometer tip was applied perpendicularly to the skin surface over both TMJs and the pressure was increased with a pressure rate of 50 kPa/s. The patients were asked to press a button connected to the algometer to freeze the pressure pain threshold value as soon as the sensation of pressure turned to pain. The PPT was measured three times and the mean of the second and third measurements was used in the analysis (Fredriksson et al. 2000). For habituation, the procedure was performed in a standardized way before the actual recording. All measurements were done with the patients in a sitting position. In *Study I* the PPT was assessed after the patients completed the ADL scale. In *Study IV* the PPT was assessed before the injection as well as after 20 minutes. PPT was assessed by the same investigator.

Assessment of tenderness to digital palpation

In *Study I* the tenderness to digital palpation was assessed over the lateral and posterior aspects of the TMJ on each side. A three graded scale was used where 0 = no pain, 1 = tenderness without pain reflex, 2 = with pain reflex. The sum of the tenderness to digital palpation over the left and right TMJ, with a maximum of 8, was calculated and used in the analysis. Tenderness to digital palpation was performed in all patients participating in this investigation by the same investigator.

The Activity of Daily Living scale

In *Study I* the patients were asked to evaluate the influence on daily activities by pain/discomfort in the TMJ. A rating scale based on methods used in medical and behavioural science and modified by List and Helkimo (1995) for assessment of daily activities in patients

with temporomandibular disorders was used. The scale was translated into Estonian from English by the author. The patients were asked to evaluate the influence on daily activities of pain in the TMJ. A modification of the original scale was used, since one of the questions (If you feel pain/discomfort in the area of TMJ are you able to talk?) was excluded according to a study by List and Helkimo (1995). The scale ranged from 0 (activity without any pain/discomfort in the TMJ) to 10 (activity impossible due to pain/discomfort in the TMJ). The patients were asked to mark the number that best described their present ability to perform each activity considering their pain/discomfort from the TMJ. The questions in English were:

If you feel pain/discomfort in the area of TMJ are you able to:

1. socialize with family and close friends?
2. perform daily work?
3. perform daily household chores (preparing meals, cleaning, taking care of small children)?
4. sit in a company or participate in other social activities (e.g. parties)?
5. exercise (walk, bicycle, jogging, etc)?
6. perform hobbies (read, fish, knit, play an instrument)?
7. sleep at night?
8. concentrate?
9. eat (chew, swallow)?
10. yawn, open mouth wide?

as well as the question

11. how much does the pain/discomfort affect your daily activities?

Blood sampling

Blood samples were obtained at the same day as the clinical examination was performed (*Study I-IV*). Venous blood was collected in a sodium citrate tube (0.105 mol/L) for measurement of the ESR (*Study I-IV*) and in an EDTA tube that was immediately cooled, centrifuged

(1500 g for 30 minutes in 4°C), frozen (-70°C) and later examined for P-5-HT (Study II, III, IV), P-TNFα (*Study II, III*) as well as P-IL-1sRII (*Study III*). Venous blood was also collected without additives for analysis of S-5-HT (*Study II - IV*), RF, TPC (*Study II - IV*) and CRP (*Study I - IV*). These tubes were left in room temperature for 60 min to coagulate and thereafter centrifuged (1500 g for 10 minutes in 4°C). The serum was then removed and analysed for CRP, TPC and RF or frozen (-70°C) until analysis of S-5-HT. CRP values below 10 mg/L and RF levels below 20 IU/mL were considered normal. RF, CRP, ESR and TPC were analyzed in the United Laboratories of Tartu University Clinics, Tartu, Estonia and the other analyses were performed in the Department of Research, Institute of Odontology, Karolinska Institutet, Huddinge, Sweden. The time from freezing to analysis varied between 1 and 6 months (*Study I, II, IV*) and between 1 and 8 months (*Study III*) for the samples used for the inflammatory mediators.

Analysis of proinflammatory mediators

Serotonin was analyzed by a commercially available enzyme immunoassay kit (EIA-kit. No 0642. Immunotech International, Marseille, France) with a detection limit of 0.5 nmol/L and a sensitivity 0.5 nmol/L. The intra-assay coefficient of variation for this assay is less than 9.4% and the interassay coefficient of variation is less than 9.9% according to the manufacturer. The normal value to be expected for 5-HT in human serum is 300–700 nmol/L for males and 500–900 nmol/L for females, while platelet-poor plasma level is expected to be 4–15 nmol/L for both sexes according to the manufacturer.

TNFα was determined with an immunoenzymometric assay (Medgenix TNF-α EASIATM kit, BioSource Europe S.A., Zoning Industriel B-6220, Fleurus, Belgium) with a minimum detectable concentration of 3 pg/mL and sensitivity of 3 pg/mL. The intra-assay coefficient of variation is 3.7-5.2% and the interassay coefficient of variation is 8.0-9.9% according to the manufacturer. The mean (SD) of

P-TNFα in healthy individuals is 6 (4) pg/mL according to the manufacturer.

IL-1sRII was determined with an enzyme immunoassay (R&D Systems, Inc, Minneapolis, USA) with a minimum detectable level of 10 pg/mL and sensitivity of 10 pg/mL. The intra-assay coefficient of variation is 2.0-3.4% and the interassay coefficient of variation is 3.9-5.9% according to the manufacturer. The normal value to be expected for P-IL-1sRII in healthy individuals is 6000-18000 pg/mL.

CRP was analyzed with an immunoturbidimetric assay (Tina-quant® CRP, Roche, Basel, Switzerland) for the *in vitro* quantitative determination of CRP in human serum and plasma on automated clinical chemistry analyzers. Precision of the assay: intra- and interassay coefficient of variation was <7%, and the detection limit 0.3 mg/dL.

The RF concentration was analyzed with the routine procedure by HUMETEX RF (Human, Germany) as a latex agglutination slide test for the qualitative and semiquantitative determination of IgM RF in non-diluted serum and measured in international units per millilitre (IU/ml) with lower detection limit 1.25 IU/mL.

The ESR was analyzed with the routine procedure by Westergren using apparatus BD Seditainer TM (France).

The TPC was analyzed with the routine procedure by Sysmex XE-2100 (Sysmex Corporation, Kobe, Japan).

Radiographic examination

Bilateral TMJ images were obtained with CT apparatus SOMATOM AR HP Spiral (Siemens, Erlangen, Germany; *Study II* and *III*) and SOMATOM Volume Access (Siemens, Erlangen, Germany; *Study III*) within one week after clinical examination and blood sampling. All patients were examined in a supine position. Axial scans were performed with the jaw in intercuspal and open mouth position. Coronal and sagittal views were reformatted from the axial scans. The coronal sections were parallel with a line between the centres of the condyles.

The sagittal sections with the jaws in intercuspal and open position were made through the centre of each condyle.

Contiguous 1.0 mm thick axial sections with a caudiocranial table feed of 1 mm were made. Exposures started 20 mm caudally of the top of the mandibular condyles up to 5 mm cranial of the glenoid fossa of the temporal bone, and were made at 130 kV and 83 mA or 105 mA (*Study II* and *III*) and 120 kV and 100 mA (*Study III*) with an exposure time of 3 seconds. A 512 x 512 matrix and bone detail algorithm was used. Scout views were performed by using the following parameters: 256 mm, 110 kV, 83 mA or 105 mA, head lateral. The CT sections were evaluated for presence of radiographic signs of bone changes within three regions (lateral, central and medial) of the mandibular and temporal part (eminence) of the TMJ. The recording of the signs was made in the axial, coronal and sagittal views. The radiographic signs had to be visible in at least two different slices in each of the regions to be recorded. The changes were defined as follows (Rohlin et al. 1986). Erosion: a local area with decreased density of the cortical joint surface including or not including adjacent subcortical bone, score 0-6, where 1 unit was scored for presence in each of the three regions of the mandibular and temporal parts of the joint. Sclerosis: a local area with increased density of the cortical bony joint surface that may extend into the subcortical bone, score 0-6, according to the same principles as erosion. Subchondral pseudocyst: a well defined, local area of bone rarefaction underneath an intact cortical outlining of the joint surface, score 0-6, according to the same principles as erosion. Flattening: a flat bony contour deviating from the convex form, score 0-2, where 1unit was scored for presence in each of the mandibular and temporal components of the joint. Osteophyte: a marginal bony outgrowth, score 0-1, one unit was scored for presence in the mandibular component. The grade of the radiographic changes of the TMJ was also evaluated according to the scoring system developed by Rohlin and Petersson (1989). The scoring system is based on six verbally described grades illustrated by standard reference films: Grade 0 normal conditions. Well-defined convex cortical outline of the

bony joint surfaces. Grade I slight abnormality. Single, minor changes such as osteophytes, flattening, and sclerosis; this grade includes joints with findings interpreted as uncertain. Grade II definite early abnormality. Definite minor changes such as erosions and cysts. Grade III moderate destructive abnormality. Erosions and local change in form of either the mandibular or temporal joint components, such as V-shaped eminence. Grade IV severe destructive abnormality. Extensive erosions of both the condyle and the temporal joint component extending through the entire joint mediolaterally. Grade V mutilating abnormality. Total erosion of the condyle with disappearance of articular surfaces or ankylosis.

All radiographs of the 21 patients were examined independently at two occasions 9 months apart on separate forms for determination of intraobserver error (*Study II*). The error of assessment of the presence of erosion, flattening, sclerosis, subchondral pseudocyst, osteophyte and as well as Rohlin and Petersson grade was investigated.

The radiographic findings in *Study III* were first assessed independently without any information from the first examination in *Study II* and the progression of changes between the two examinations was expressed as the numerical difference in scores for the different radiographic signs. The time interval between the two independent registrations was at least 30 months. Nine months after the second independent registration of the radiographs the changes were scored dependently by pair-wise observation, and the progression of changes between the two examinations was likewise expressed as the numerical difference in scores. Radiographic changes as determined by the independent and dependent assessments were strongly and positively correlated for all variables and the deviation in score between the two assessments never exceeded 1 unit. The independent score was used in the analysis. All CT scans were examined by the same radiologist.

Administration of drugs

In *Study IV* the selective 5-HT_3 antagonist granisetron (Kytril® 1 mg/mL, F. Hoffman-La Roche Ldt, Basel, Switzerland) or saline (NaCl 9 mg/mL, Kabi Pharmacia, Uppsala, Sweden) were injected into the most painful TMJ. The injection volume was 1.0 mL and the substances were given as single injections into the posterior part of the upper TMJ compartment in a randomized double-blind order to control that neither the subject nor the investigator would know which substance was used. All injections were performed by the same investigator.

Statistics

For descriptive statistics of the variables, median and IQR were used. In order to correlate the joint related variables to the variables related to the individual, the sum of the joint related variables (right + left side) was used.

In *Study II* the intraobserver error was estimated by the observed percentage agreement and by the agreement expected by chance. The latter is calculated as the sum of the squared proportions over all categories. The CV in percent for the observed observer agreement was calculated according to the formula: CV = SD x 100/Mean.

In *Study III* the statistical significance of individual radiographic progression was tested by the Wilcoxon matched-pairs ranked sign test. In *Study IV* the variables were tested for differences within groups with the Wilcoxon matched-pairs ranked sign test and between groups with the Mann-Whitney U-test. In all studies the significance of correlations was tested by Spearman's ranked correlation test. A probability level of less than 0.05 was considered significant.

Results

Study I

Impact of temporomandibular joint pain on activities of daily living in patients with rheumatoid arthritis

Activities of daily living were influenced for all patients participating in this study, but at different levels. The interindividual variation was large for all activities, which is demonstrated by the variation of the sum of the ADL scores. The highest impact of TMJ pain on ADL was found for the performance of physical exercise and jaw movements and the lowest on the performance of hobbies and eating. On the question how much the TMJ pain/discomfort affects daily activities in general, the median score was 5, i.e. at the midpoint of the scale. The median (IQR) of VAS_{Rest} and VAS_{MVM} were 48 (36) and 72 (30), respectively. The TMJ resting pain intensity was not significantly correlated to ADL. ESR was positively correlated with difficulties to perform physical exercise ($r_s = 0.51$, $n = 17$, $p = 0.038$).

Study II

Inflammatory mediators and radiographic changes in temporomandibular joints of patients with rheumatoid arthritis

In this study the highest frequency of abnormally high levels was found for S-5-HT (65%), ESR (53%) and P-5-HT (45%). The most frequent radiographic signs were sclerosis (75%), erosion (50%), flattening (30%) as well as subchondral pseudocyst (30%).

The radiographic sign of erosion correlated positively to TPC ($r_s = 0.59$, $n = 20$, $p = 0.005$), while flattening correlated positively to P-TNFα ($r_s = 0.58$, $n = 19$, $p = 0.008$).

TPC correlated positively to S-5-HT ($r_s = 0.55$, $n = 20$, $p = 0.012$), RF ($r_s = 0.48$, $n = 19$, $p = 0.040$), ESR ($r_s = 0.74$, $n = 19$, $p < 0.001$), CRP ($r_s = 0.57$, $n = 20$, $p = 0.010$) and P-TNFα ($r_s = 0.55$, $n = 20$, $p = 0.012$).

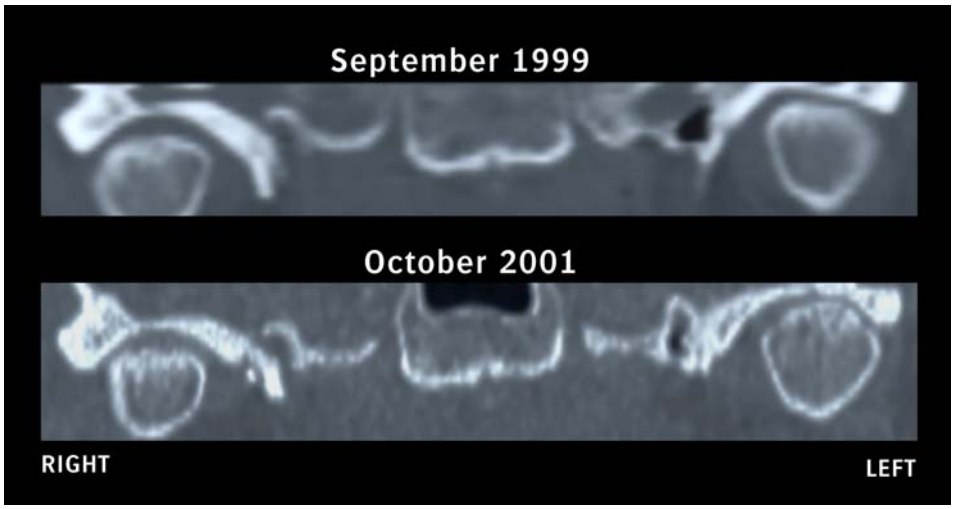

Figure. Frontal view of computed tomography. At the first examination (September 1999) sign of erosion was present in the central part of the right mandibular condyle. At the second examination 32 months later (October 2001) signs of erosion were present in the lateral, central and medial part of the right mandibular condyle as well as flattening. Sign of erosion was also present in the lateral, central and medial part of the left mandibular condyle. The blood level of S-5-HT decreased (1486.0 –> 600.0 nmol/L) and P-HT, while P-TNFα levels increased (12.9 –> 57.0 nmol/L; 15.4 –> 51.0 pg/mL, respectively) during the observation period.

P-TNFα was positively correlated to ESR ($r_s = 0.46, n = 19, p = 0.046$) and P-5-HT ($r_s = 0.66, n = 20, p < 0.001$).

Study III

The progression of radiographic changes in the temporomandibular joints of patients with rheumatoid arthritis in relation to inflammatory markers and mediators in the blood

There were no consistent or statistically significant differences in radiographic status between the two examinations, neither regarding the individual radiographic signs nor the grade. There was a considerable variation in radiographic development between individuals. Some showed progression and some regression of radiographic changes and still some no change at all (Fig).

The proportion of abnormal levels increased the most for P-TNFα (25%), P-5-HT (18%) and CRP (12%) between the examinations.

High level of CRP at the beginning of the observation period was associated with change in flattening ($r_s = 0.52, n = 16, p = 0.038$). High level of P-5-HT at the end of the observation period was associated with progression of erosions ($r_s = 0.50, n = 16, p = 0.046$), while high level of S-5-HT ($r_s = -0.56, n = 16, p = 0.024$) and P-IL-1sRII ($r_s = -0.52, n = 16, p = 0\ .034$) at the end of the observation period was associated with regression of erosions.

The change in P-5-HT during the observation period correlated negatively with change in sclerosis ($r_s = -0.52, n = 16, p = 0.038$).

At the end of the observation period P-TNFα correlated positively with P-5-HT ($r_s = 0.52, n = 16, p = 0.039$), ESR ($r_s = 0.56, n = 16, p = 0.020$) and TPC ($r_s = 0.52, n = 16, p = 0.039$). S-5-HT and P-5-HT correlated negatively at the end of observation period ($r_s = -0.51, n = 16, p = 0.044$).

Study IV

Immediate effects of the serotonin antagonist granisetron on temporomandibular joint pain in patients with systemic inflammatory disorders

VAS_{Rest} before the injections was similar in both groups. The patients in the granisetron group had significantly lower VAS_{Rest} than the patients in the saline group 10 minutes after injection ($p = 0.033$).

VAS_{Rest} was decreased 10 and 20 minutes after intraarticular injection of granisetron compared to the preinjection value ($p = 0.028$ and $p = 0.046$, respectively). VAS_{MVM} was decreased ($p = 0.002$) and PPT increased after 20 minutes ($p = 0.036$).

The change in VAS_{Rest} 20 minutes after granisetron injection correlated positively to TPC ($r_s = 0.74, n = 8, p = 0.036$), ESR ($r_s = 0.72, n = 8, p = 0.045$), CRP ($r_s = 0.71, n = 8, p = 0.047$), RF ($r_s = 0.73, n = 8, p = 0.038$). The change in PPT 20 minutes after injection of granisetron correlated negatively to P-5-HT ($r_s = -0.79, n = 8, p = 0.020$).

Discussion

The systemic inflammatory process involving the synovial tissues usually results in pain, tissue destruction and functional impairment. In *Study I* the influence of TMJ pain/discomfort on activities of daily living in patients with RA was investigated, and the daily activities in general seem to be affected to a significant extent, since the median score of this variable was 5, i.e. at the midpoint of the scale. This relatively high degree might very well contribute to a decreased quality of life. It is well known that RA affects all areas of daily life due to pain, stiffness and functional limitations (Wolfe and Cathey 1991). However, some patients with systemic inflammatory joint disease function fairly well despite pain, while others are disturbed by a small degree of pain and dysfunction (Gerecz-Simon 1989).

The TMJ pain/discomfort seems to affect daily activities in general to a significant degree, although the influence of pain intensity differs between individuals, which most probably is due to the fact that the patients respond to pain in different ways. TMJ resting pain intensity was not significantly correlated to ADL, which means that high TMJ resting pain intensity does not necessarily restrict daily activities.

The highest impact of TMJ pain/discomfort on ADL was upon the performance of physical exercise and jaw movements, where the latter easily could be explained by local TMJ pain. The smallest degree of impact was on the performance of hobbies and eating, which could be explained by the individual's ability to carry out hobbies that are possible to perform in spite of the chronic disease. The relatively small influence on eating was unexpected, although the interindividual variation was large and eating difficulties were associated with low PPT of the TMJ. The individual eating habits may be influenced by pain/discomfort leading to a selection of foods, in turn decreasing the influence of TMJ pain/discomfort.

High ESR was associated with difficulties to perform physical exercise, which probably is due to the close association between elevated levels of acute phase reactants and high general disease

activity in RA (Kaye 1988, Elkon 2000). A higher general disease activity might very well influence TMJ pain in turn (Tegelberg et al. 1987).

According to this study TMJ pain/discomfort in RA patients seems to further limit the patients' daily activities and thereby influence their well-being and quality of life. The findings also indicate that TMJ pain can cause work disability, which is a frequent problem for patients with RA (Sokka and Pincus 2001).

The main findings of *Study II* were that TNFα, as reflected by its plasma level, as well as TPC seem to be involved in the modulation of TMJ bone tissue destruction in patients with RA. The clinical and radiographic signs of TMJ involvement by RA are well known, but the role of circulating proinflammatory cytokines in the development of the disease is less known, although they have been found to be highly fundamental for the inflammatory disease process in other joints and systemically (Duff 1994). The associations found between TNFα and TPC in the blood are in agreement with previous findings, where TPC and clinical, biochemical, haematological as well as immunological parameters in RA have been found to be related (Farr et al. 1984). Thrombocyte granules contain several proinflammatory substances including 5-HT and IL-1β (McNicol and Israels 1999, Rendu and Brohard-Bohn 2001), which could explain the relations between increased TPC and bone erosion in this study. Thrombocytosis in active rheumatoid disease correlates with other laboratory parameters of disease activity like ESR and CRP (Farr et al. 1984). It is well known that TNFα is a strong inflammatory mediator, modulating the destruction of cartilage and bone (Duff 1994). The radiographic sign of erosion of the mineralized tissue of the TMJ is generally considered to be an indicator of active bone resorption (Syrjänen 1985, Åkerman et al. 1991, Gynther et al. 1996), which can be caused by either inflammation, remodeling or both. The inflammatory origin of erosion in the TMJ in this investigation is indicated by its association to TPC, which in turn was associated with S-5-HT, P-TNFα, RF, ESR and CRP.

Another important finding in this study was the association between flattening, which is interpreted as a sign of bone destruction, and high TNFα in plasma, indicating that patients with high plasma level of this mediator are more likely to develop bone destruction. The erosive process in the TMJ might result in flattening or change of the bone contour, which either could be the result of hard tissue remodeling process due to age and mechanical loading or the result of hard tissue loss due to inflammation. It has been reported that arthrotic changes in the TMJ due to age mainly appear after the age of 45 years (Öberg et al. 1971). The patients in this investigation were relatively young, median 41 years, and in addition flattening was not correlated with age but to duration of general disease, which together indicates an inflammatory origin of the sign of flattening in this study and that it is a sign of bone destruction. TNFα was also positively correlated with other markers and mediators of inflammatory activity like ESR, RF and P-5-HT, which supports the relations between TNFα, 5-HT and TMJ tissue destruction in this study.

In order to characterize the development of RA in the TMJ, a prospective longitudinal study was undertaken. *Study III* indicates that the radiographic changes that occur in the TMJ of patients with well-controlled RA during a period of 25-46 months are related to the blood levels of CRP, 5-HT and IL-1sRII. However, only minor changes of the radiographic status on a group level can be expected to occur during this observation period and with considerable individual variation.

The association found between high TNFα and 5-HT in plasma supports the view that circulating 5-HT is involved in the disease process. There is evidence of an *in vivo* secretion of 5-HT from activated thrombocytes in the synovial tissues and blood of patients with RA (Zeller et al. 1983), which is in agreement with these results. It is known that thrombocytosis occurs during the active phases in RA, which would result in increased levels of 5-HT. At the same time the TNFα levels are known to be high and capable to manipulate the

hematopoesis via other interleukins (Ertenli et al. 2003). In addition, elevated TMJ synovial fluid levels of 5-HT have been found in RA patients with TMJ pain (Alstergren and Kopp 1997, Alstergren et al. 1999), indicating that 5-HT play a role in the local inflammatory process.

It thus appears from the results that both TNFα and 5-HT are involved in the production of hard tissue changes of TMJ.

The finding that CRP at the beginning of the observation period was positively correlated to change in flattening is in agreement with the existing view that CRP is a predictor of disease activity and associated with radiographic progression (van Leeuwen et al. 1993, Jansen et al. 2001). One reason for this might be that CRP can induce release of TNFα from human peripheral blood monocytes (Ballou and Lozanski 1992). This result is also in the agreement with the study by Larsen (1988), which showed that CRP was the most accurate marker for development of radiographic changes in finger joints with RA and also in accordance with Nordahl et al. (2001), who found raised levels of CRP in association with progression of TMJ bone loss.

High P-5-HT at the end of the observation period was associated with progression of erosions and accordingly bone destruction. P-5-HT was positively correlated with P-TNFα, which indicates an interaction between these mediators in bone destruction. P-TNFα was also associated with with high number of thrombocytes, i.e. the cells that store the major part of peripheral 5-HT. The thrombocytes are activated by platelet-activating factors, including RF which could increase the 5-HT levels in the synovial tissues. It is not known whether TNFα is able to activate thrombocytes to release 5-HT or if 5-HT can induce release of TNFα.

Increase of P-5-HT during the observation period was also associated with decreased sclerosis, i.e. decreased mineral density of the bone of the TMJ. P-5-HT, which represents the unbound part of 5-HT in the blood, can reach the synovial membrane via the circulation or be released locally. In the TMJ with RA the inflammation is not only present in the synovial membrane but also in the mineralized

tissue, where several inflammatory cell types like macrophages and neutrophils may cause erosions.

A high P-IL-1sRII was found to be associated with regression of erosions. P-IL-1sRII is an endogenous regulator of IL-1 activity and reflects a systemic production of IL-1sRII in order to control activity of IL-1. Alstergren et al. (2003) found that IL-1sRII in the TMJ synovial fluid of polyarthritic patients was associated with less degree of anterior open bite, which is a clinical sign of TMJ bone tissue destruction. In a study of patients with chronic arthritis low disease activity and minor joint destruction were reported to correlate with high P-IL-1sRII (Jouvenne et al. 1998). This mechanism could be one explanation for the relatively modest radiographic progression of erosions and bone loss found in this study.

The slow progression of radiographic findings in this patient sample could also be due to the fact that most of the patients were seronegative for IgM RF. There was a tendency for the patients with abnormal RF levels at the beginning of the observation period to show increased P-TNFα and P-5-HT at the end of the observation period, which is in agreement with the view that seropositivity is an indicator of poor prognosis for RA in general (Kaarela 1985, Vittecoq et al. 2003) as well as for the TMJ (Tegelberg et al. 1987, Kopp and Alstergren 2002). The fact that a majority of the patients in the *Study III* had glucocorticoid or DMARD therapy, could be another explanation for the slow progression of the radiographic changes (Lim and Conn 2001, Bijlsma et al. 2002).

In *Study IV* granisetron was found to have an immediate, short-lasting and specific anti-nociceptive effect on TMJ pain after intra-articular administration in patients with systemic inflammatory joint disorders. This study shows that 5-HT is a mediator of pain in the TMJ with inflammation and that TMJ resting pain is modulated by the 5-HT_3 receptor on primary afferents in the synovial tissue.

5-HT has been shown to participate in the mediation of spontaneous pain from inflamed peripheral tissues by exciting or sensitizing fine afferent units by the 5-HT_3 receptor (Richardson and

Engel 1986), but it has not previously been shown that the 5-HT_3 receptor is involved in mediating joint pain, especially TMJ pain in RA or PA. It has been shown that activation of 5-HT_3 receptors causes a long-lasting sensitization of high-threshold mechanosensitive units as well as a brief excitation of chemo- and mechanosensitive units in joints (Birrell et al. 1990) of which both might be active in TMJ movement pain. However, the 5-HT_3 receptor is certainly not the only peripheral receptor involved in joint pain and besides 5-HT there are many inflammatory mediators that modulate pain.

Granisetron had an anti-nociceptive effect exceeding that of saline only on resting pain, which is in agreement with Taiwo and Levine (1992), who suggested that pain and hyperalgesia could be two different entities, spontaneous pain being mediated by the 5-HT_3 receptor and allodynia/hyperalgesia by the 5-HT_{1A} receptor. In contrast, when granisetron was injected into the healthy human masseter muscle with pain induced experimentally by 5-HT, it significantly reduced both resting pain and allodynia/hyperalgesia (Ernberg et al. 2000). 5-HT in the TMJ synovial fluid has been related to pain perceived upon movement of the joint and to decreased mandibular mobility (Alstergren and Kopp 1997), which might be due to 5-HT_{1A} receptor activation. However, 5-HT may be a mediator of both types of pain depending on its tissue concentration. In addition to a placebo effect, the reduction of the resting and movement pain found after intra-articular injection of saline might be explained by dilution of the inflammatory mediators in the synovial tissues (Gynther and Holmlund 1998).

The size of the patient sample was small, but despite that and the low frequency of IgM RF they represent the RA TMJ population with short duration of TMJ involvement. All patients participating in this investigation were selected consecutively (except *Study III*) and the ages between 18 and 70 years were represented. Both sexes were represented in a degree corresponding to the well known fact that RA affects females three times more often than males. The observation period is sufficiently long and similar to many studies investigating

other joints in RA patients (Luukkainen et al. 1983, Möttönen 1988, van der Heijde et al. 1992, van Leeuwen et al. 1993). While most patients (65%) participating in *Study III* had TMJ involvement less than or one year before the beginning of the observation period the results obtained from this study should be valid for conclusions about early RA in the TMJ. The majority of RA patients participating in this investigation were IgM RF seronegative, but it is known that RF can disappear during the disease process and after treatment. The low frequency of RF positivity in this investigation might also be due to that the Estonian population has been reported to have a higher prevalence of other RF isotypes than IgM, but this has not been confirmed yet (personal communication). A reason for the low prevalence of RF could thus be that only RF of IgM isotype was analyzed and not IgG and IgA.

Up to now there is no special scoring system available for evaluation of TMJ changes as recorded by CT. In this investigation a scoring system for conventional tomograms was used (Rohlin and Petersson 1989). The consequense of this is unknown, but this system seems to be applicable for conventional tomography as well as for CT for evaluating radiographic changes in the TMJ. The CT examination was performed within one week after the clinical examination and blood sampling, and thus reflects the current radiographic status of the TMJ.

The intraobserver agreement in the *Study II* was acceptable for all radiographic variables. The intraobserver variability of the evaluation of the radiographic progression (*Study III*) was also acceptable. The radiographic progression as determined by the independent and dependent assessments were strongly and positively correlated for all variables and the deviation in score between the two assessments never exceeded 1 unit. The independent assessment was used in the analysis in order to make *Study III* comparable with *Study II*.

Conclusions

- Pain from the TMJ in patients with RA has a significant negative impact on activities of daily living.

- High TPC and high plasma level of TNFα are associated with radiographic signs of joint tissue destruction in patients with clinical TMJ involvement by RA.

- Minor progression of radiographic changes can be expected to occur in the TMJ during a period of 25-46 months, although the individual variation is considerable. The progression of the radiographic changes that occurs in the TMJ of patients with well-controlled RA is seems to be related to the blood levels of CRP, 5-HT and IL-1sRII.

- The 5-HT_3 receptor seems to be involved in the mediation of TMJ pain in systemic inflammatory joint disorders, since the 5-HT_3 antagonist granisetron has an immediate, short-lasting and specific pain reducing effect upon intra-articular administration.

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