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# ORAL AND TEMPOROMANDIBULAR JOINT FINDINGS IN RHEUMATIC DISEASES

By

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Academic dissertation

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“We are born for co-operation as are the feet, the hands,

the eyelids and the upper and lower jaws.”

*Marcus Aurelius*

To Ilkka, Mikaela and Oliver

## ABSTRACT

The aim of this study was to investigate oral health characteristics and findings, clinical and radiographic findings of the TMJ, and the association between HLA antigens in patients with different rheumatic diseases.

**Study design**: A cross-sectional study was carried out between 1996 and 1998. Eighty six patients (25 with rheumatoid arthritis (RA), 19 with mixed connective tissue disease (MCTD), 20 with ankylosing spondylitis (AS), 22 with spondyloarthropathy (SPA) and 86 age- and sex -matched controls participated in the study. They were clinically examined and all filled in a questionnaire for oral- and temporomandibular disorders (TMD). Unstimulated and stimulated salivary flow rates were measured. Selection of salivary proteins and immunoglobulins were analysed. In addition patients underwent minor salivary gland biopsy, panoramic- and lateral panoramic radiographs and MRI of TMJ were obtained. HLA alleles (A, B, C and DRB1*) analysis was performed.

**Results:** Focal sialadenitis was observed in 68% (57/84) of all patients. It affected 80% (20/25) of the RA, 94% (17/18) of the MCTD, 58% (11/19) of the AS, and 41% (9/22) of the SPA patients (p=0.0013). Secondary Sjögren's syndrome (SS) was diagnosed in 31% of the patients. It was most frequent (73%) in MCTD and least frequent (15%) in SPA patients. Salivary secretion correlated negatively with the focus scores, i.e. severity of focal sialadenitis. In all patients salivary albumin, total protein, IgG, and IgM concentrations were higher than in controls. Oral yeast counts were significantly higher in the patients than in controls (p<0.001). Severe periodontitis (CPI 3-4) existed more often in the patient groups than in control subjects. Patients with rheumatic diseases reported severe TMJ symptoms significantly more often than control subjects (p<0.001).

Mean maximum opening of the (SD) was significantly less in patients with rheumatic disease (46.3 [8.6] mm than in control subjects (55.0 mm [7.4] mm; $p<0.001$) mouth.

Marked erosions in TMJ by panoramic tomography were observed in all rheumatic groups, but most often in SPA (38%) and AS patients (37%). The existence of erosion was associated with evidence of restricted movement of condyle in panoramic radiographs ($p<0.001$). There was correlation between radiographic findings relating to the TMJ and subjective and clinical symptoms of temporomandibular disorders (TMD) in patients with rheumatic diseases.

MRI showed many changes in TMJ ie. condylar changes including erosion, osteophytes and abnormal shape, and disc alterations including perforation, abnormal anterior position, as well as decreased movement. These abnormalities were most frequent in RA patients, and least frequent in MCTD and SPA patients. Reduced maximum opening of the mouth correlated with abnormalities of the disc and articular cartilage in MRI. Severe condylar erosion in panoramic tomography was significantly associated with MRI findings. In the whole patient population, HLA-DRB1*01 allele was significantly associated with erosions 16/36 (44%) vs. 6/46 (13%) ($p = 0.0014$).

**Conclusions:** Focal sialadenitis affected two-thirds and secondary SS one-thirds of the different rheumatic patients. The patients, irrespective of specific diagnosis, had various alterations in salivary flow and composition. The TMJ is commonly affected in patients with RA, and in patients with other forms of rheumatic diseases. There was a good association between radiographic findings and subjective symptoms, and between radiographic findings and restricted condylar movement. However, to obtain a more detailed anatomic picture, MRI is suitable for patients with acute unexplained pain or as part of preoperative work-up. Genetic factors seem to contribute to destructive lesions in the TMJ as well as composition of saliva in patients with various rheumatic diseases.

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ORIGINAL PUBLICATIONS

## LIST OF ORIGINAL PUBLICATIONS

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

**I** Helenius LM, Hietanen JH, Helenius I, Kautiainen H, Piirainen H, Paimela L, Lappalainen M, Suuronen R, Lindqvist C, Leirisalo-Repo M. Focal sialadenitis in patients with ankylosing spondylitis and spondyloarthropathy: a comparison with patients with rheumatoid arthritis or mixed connective tissue disease. Ann Rheum Dis 2001;60:744-49.

**II** Helenius LM, Meurman J, Helenius I, Kari K, Hietanen J, Suuronen R, Kautiainen H, Leirisalo-Repo M, Lindqvist C. Oral and salivary parameters in patients with rheumatic diseases. Acta Odontol Scand 2005;63:1-10.

**III** Helenius LM, Hallikainen D, Helenius I, Meurman JH, Könönen M, Leirisalo-Repo M, Lindqvist C. Clinical and radiographic findings of the temporomandibular joint in patients with various rheumatic diseases. A case-control study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005;99:455-63.

**IV** Helenius LM, Hallikainen D, Helenius I, Meurman JH, Koskimies S, Tervahartiala P, Kivisaari L, Hietanen J, Suuronen R, Lindqvist C, Leirisalo-Repo M. HLA-DRB1* alleles and temporomandibular joint erosion in patients with various rheumatic diseases. Scand J Rheumatol 2004;33:3324-9.

**V** Helenius LM, Tervahartiala P, Helenius I, Al-Sukhun J, Hallikainen D, Kivisaari L, Suuronen R, Kautiainen H, Lindqvist C, Leirisalo-Repo M. Clinical, radiographic and MRI findings of temporomandibular joint in patients with different rheumatic diseases. Int J Oral Maxillofac Surg (submitted).

## ABBREVIATIONS

ANA= antinuclear antibody

AS= ankylosing spondylitis

CFU= colony forming unit

C3= complement factor 3

C4= complement factor 4

CPI= Community Index of Periodontal (Treatment Needs)

CRP= C-reactive protein

DMARDS= disease modified anti-rheumatic drugs

ENA= extractable nuclear antigen

ESR= erythrocyte sedimentation rate

Gd-DTPA= gadolium contrast medium

HLA= human leucocyte antigen

IgA= immunoglobulin A

IgG= immunoglobulin G

IgM= immunoglobulin M

IQR= interquartile ranges

JIA= juvenile idiopathic arthritis

JLA= lateral panoramic tomography, special program of TM joint

MCTD= mixed connective tissue disease

MRI= magnetic resonance images

RA= rheumatoid arthritis

RF= rheumatoid factor

RNP-AB= ribonuclear protein antibody

SD= standard deviation

Sm-AB= anti-Sm antibody

SPA= spondyloarthropathy

SS= Sjögren's syndrome

SSA-AB= SSA antibody

SSB-AB= SSB antibody

TMD= temporomandibular disorders

TMJ= temporomandibular joint

# INTRODUCTION

Sjögren's Syndrome (SS) is a chronic inflammatory autoimmune disorder characterized by the triad of xerostomia, keratoconjunctivitis sicca, and another autoimmune disease (1). The disease was described first in 1888. Four years later, Mikulicz published a case report. In the 1920´s, the disease was described in France and was the first to note the association between lacrimal gland abnormalities and athrophy of the mucous glands. In 1933, Henrik Sjögren, a Swedish ophthalmologist, published classical monograph, which resulted in keratoconjunctivitis sicca, xerostomia and rhinopharyngeal laryngitis (2). Several sets of diagnostic criteria for SS have been proposed, of which five are currently in general use.

Secondary SS is known to occur with a variety of autoimmune diseases, such as RA (3), systemic lupus erythematosus (4), and primary biliary cirrhosis (5). The classification criteria for SS vary between study groups. According to Fox et al. (6), the verification should consider all three components of diagnostic relevance: focal sialadenitis in minor salivary gland biopsy, keratoconjunctivitis sicca and in the case of secondary SS, also an associated disease. The European classification criteria suggest that at least four out of six items (subjective oral and ocular symptoms, decreased tear secretion, decreased unstimulated salivary flow, focal sialadenitis by biopsy, and the presence of autoantibodies) correctly classify patients with primary SS (7). The classification of secondary SS accepts the presence of one of the two subjective symptoms with at least two objective items of glandular dysfunction (7). According to the new SS criterias, there have to be either focal sialadenitis or positive serology, while other criterias are the same (at least two objective items of glandular dysfunction) (8).

Oral infections have been associated with systemic diseases such as RA (9). Risk for periodontal disease has been substantially increased in patients with long-standing RA (10, 11). However, data are sparse on periodontal condition in seronegative arthritides or MCTD and no studies have been conducted on periodontal disease in patients with SPA. Saliva secretion, which is the principal defensive factor in the oral cavity is affected by the rheumatic diseases with subsequent detrimental effects on teeth and mouth mucosa. Reduced salivary flow enhances oral microbial colonization, in particular yeasts which, in turn, are an infectious burden to the patient and may worsen the systemic condition (12,13).

For a long time, it has been known that the temporomandibular joint (TMJ) can be involved in patients with rheumatic diseases (14). Examination of a 50-year old Egyptian male mummy, from the period of the Fifth Dynasty (2750-2625 B.C.), revealed typical changes of rheumatoid arthritis (RA) in the joints of the hand and the temporomandibular joint (15). The prevalence of TMJ involvement in rheumatic diseases has been found to vary greatly, depending on the diagnostic criteria, the population studied and means of assessment of the TMJ.

In previous studies, prevalences of clinically evident TMJ involvement have been reported to vary between 2%-98% in rheumatic patients, more often in RA patients. Use of conventional radiographic methods has allowed demonstration of frequent TMJ abnormalities in patients with RA, ankylosing spondylitis (AS), mixed connective tissue disease (MCTD), juvenile idiopathic arthritis (JIA) and psoriatic arthropathy (16-20). Typical findings are joint-space narrowing, and condylar erosion, flattening and sclerosis (16-19, 21). Inflammation of TMJ may frequently cause micrognathia in patients with juvenile idiopathic rheumatoid arthritis (20).

Genetic factors play a role in the development of rheumatic diseases. AS and spondyloarthropathy (SPA) are closely associated with human leucocyte antigen (HLA) B27 (22, 23). The association of RA with HLA-DR4 (25-26), and in some of the populations with HLA-DR1 (27), is well established. However, results concerning the influence of HLA-DR4 on disease severity have been conflicting. Many (28-31), but not all, studies (32-34) have described a more severe disease course in HLA-DR4-positive patients. The correlations between TMJ erosion and HLA antigens is not known yet.

Magnetic resonance imaging (MRI) is being increasingly recognised as a useful method for early detection of destructive as well as inflammatory lesions. MRI shows mild arthritis and synovitis better than other radiographic methods (35, 36). MRI has also been applied in examination of the TMJ, where it can show abnormalities of the glenoid fossa, disc, articular cartilage, condylar shape and bone marrow (37). TMJ symptoms are frequent even in normal subjects, but more frequent in patients with inflammatory arthritis.

# 2 REVIEW OF THE LITERATURE

## 2.1 Common rheumatic conditions

The major groups of synovial joint disorders are inflammatory and non-inflammatory arthropathies (*Table 1*).

### 2.1.1 Non-inflammatory arthropathies

Non-inflammatory disorders refer to disorders in which joint dysfunction occurs in the absence of overt inflammation (*Table 1*). Osteoarthritis is the most common degenerative disease of synovial joints. It primarily affects the articular cartilage, probably due to its limited adaptive capacity compared with other connective tissues, and the subchondral bone. Primary osteoarthritis develops in the absence of any known underlying predisposing factor; in secondary osteoarthritis, an underlying local or systemic pathogenetic factor, e.g., trauma, surgery, recurrent dislocation, crystal deposition disorders, avascular necrosis, or post-inflammation cartilage damage, can be identified (38).

Osteoarthritis affects not only the articular cartilage but also the subchondral bone, the synovial lining cells, the synovial fluid and capsular ligaments. Osteoarthritis includes an inflammatory component caused by waste products and inflammatory mediators (i.e. osteoarthritis with synovitis). Throughout life, the articular cartilage and underlying bone display shifting equilibria between changes in form and function by tissue remodeling. The tissues adapt to applied stresses. When loading is beyond the limits of the system, compensatory responses may lead to new steady states.

*Table 1. Classification of arthropathies*

| Inflammatory arthropaties (arthritis) | Non-inflammatory arthropathies |
|---|---|
| Primary arthritis | Osteoarthrosis (osteoarthritis) |
| -Rheumatoid arthritis | -primary |
| -Juvenile idiopathic arthritis | -secondary |
| -Spondyloarthropathy | |
| -Ankylosing spondylitis | Internal joint derangement |
| -Psoriatic arthritis | Aseptic necrosis |
| -Reiter´s syndrome | Synovial chondromatosis |
| Arthritis following external insult | |
| Infective and infection-associated arthritis | |
| Traumatic arthritis | |
| Crystal-induced arthritis | |
| Systemic collagen vascular diseases | |
| -Systemic lupus erythematosus | |
| -Mixed connective tissue disease | |
| -Systemic slerosis (scleroderma) | |

Cartilage breakdown in osteoarthrosis affects the sliding properties of the joint surfaces. Deterioration of the synovial fluid in osteoarthrosis gives rise to friction and adhesive wear. Osteoarthrosis can be secondary as a result of other joint disorders, e.g., RA, avascular necrosis, and osteochondritis dissecans.

In TMJ impairment the movement of the disc may cause disc degeneration. This may induce joint stiffness and repetitive stretching of the disc attachments. The attachments may gradually elongate to an extent that permits disc displacement. Although disc displacement in the TMJ is a real clinical entity, the position and form of a physiologically functioning disc have certain variations. Large percentage of patients have a different basis for their intracapsular symptoms than only disc displacement (38).

### 2.1.2 Inflammatory diseases

The common term for inflammatory joint disorders is arthritis (*Table 1*).

## 2.2 Inflammatory rheumatic diseases

### 2.2.1 Rheumatoid arthritis

Rheumatoid arthritis (RA) is a systemic chronic disease, characterized by an acute inflammatory response, with symmetric polyarticular joint pain and swelling, morning stiffness, malaise, and fatigue. The inflammation may be reversible over months, and patients may experience spontaneous remission. However, most patients whose symptoms have persisted for longer than 90 days experience a progressive disease, in which the reversible inflammatory activity leads to irreversible joint damage. RA is found in approximately 0,5% to 1% of the population in many cultures (39). The prevalence of RA in the Finnish population is 0.8% (40). About 70% of the patients are female.

The disease can affect individuals at any age, including infants and aged individuals; however, the most common onset is in women aged 50 to 60 years (41). In Finland, the mean age is 59 year (41).

While the disease course is highly variable in individual cases, many patients experience joint damage within the first 2 years of disease. Joint damage in RA ultimately has resulted in work disability in at least 50% of patients within 10 years, and the patients are prone to premature death.

The clinical history of a patient with RA generally includes pain and symmetric swelling involving multiple joints. Any joint may be affected, but those most commonly involved are the metacarpophalangeal joints of the hand, proximal interphalangeal joints of the hand, metatarsophalangeal joints, wrists, knees, elbows, and, less commonly, shoulder, hip, and distal interphalangeal joints (42,43).

A characteristic finding is morning stiffness, which may last for several hours after rising. Although RA is manifested primarily by joint involvement, it is a systemic inflammatory disease. Extra-articular involvement may be seen, including secondary SS with dry eyes and dry mouth, vasculitis, episcleritis, neuropathy, rheumatoid nodules and more rarely, Felty´s syndrome with splenomegaly and leukopenia.

The etiology of RA remains unknown. Genetic factors in the presence of favorable environmental conditions are considered to play a role in the development of RA (44). Historically, RA was called chronic infectious arthritis, because the clinical and pathologic features of disease resemble those seen in chronic infectious diseases such as tuberculosis.

One important host variable is the major histocompatibility locus. Human leukocyte antigen (HLA) –genes located within the major histocompatibility complex on chromosome 6p have been found to have a strong association with RA (13). Individuals carrying HLA-DR4 and HLA-DR1 alleles in particular have been shown to posses a higher risk of the disease. It has been suggested that the susceptibility alleles all share a single epitope that is responsible for the predisposition of individuals to RA (42). It has also been suggested that the relationship of HLA and RA may be related more to the severity of the disease, rather than to the tendency to acquire RA (42).

The diagnosis of RA may be made in the absence of any laboratory tests, and all laboratory tests may be normal in a proportion of patients (*Table 2*) (45). Nonetheless, four types of laboratory data may contribute to the diagnosis assessment of the severity of RA in an individual patient. Rheumatoid Factor (RF) is found approximately 70% to 90% of people with RA. People with a specific haplotype at the HLA-DR4 locus (*0401 or *0101) have a five-fold higher likelihood of developing RA than an individual in the general population (43). In a population based stydy in Finland, occurense of HLA-DR4 was 54% in patients with RA and in 30% with control patients (46). HLA-DR4 is not a diagnostic test for RA for several reasons. Firstly, most people who have the *0401 or *0101 haplotype do not have RA. Secondly, only about 70% of people who have a diagnosis of RA have these haplotypes. Finally, although the *0401 and *0101 haplotypes are associated with a somewhat higher likelihood of radiographic damage and the presence of RF they are not associated with greater severity of disease other than as a predictor some subtypes of RA. Therefore, a HLA typing test is not useful clinically in the diagnosis or management of patients with RA (43).

The treatment of RA based on combination of a non-steroidal anti-inflammatory drugs and disease modified anti-rheumatic drugs (DMARDS). Nowadays there are also biological medication available (i.e TNF-alfa-blockers).

***Table 2. Classification criteria of RA.***

At least four of following criteria.

- Morning stiffness of joints (≥1 hour)
- Arthritis of three or more joint areas
- Arthritis of hand joints
- Symmetric arthritis
- Rheumatoid nodules
- Serum rheumatoid factor
- Radiographic changes

### 2.2.2 Connective tissue diseases

Connective tissue diseases are a group of closely related conditions, with many overlapping clinical features. While uncommon, they cannot be considered rare. Systemic lupus erythematosus incidence in Finland is 8/1 milj. / year (47). Many of the features of connective tissue diseases involve the skin, joints, muscles or blood vessels. Serological examination reveals that connective tissue diseases are associated with a variety of antinuclear antigens (ANA), and other related antibodies (i.e. antibodies to Sm, RNP antigens etc).

Mixed connective tissue disease (MCTD) is a rare connective tissue disease, with typical features such as oedema or pale fingers, inflammatory arthritis and skin rashes. The dryness of mucosal surfaces may also be present.

Connective tissue diseases are associated with considerable morbidity even with increaced mortality. The treatment of MCTD based on anti-inflammatory- and DMARDS.

### 2.2.3 Spondylarthritides

The concept of spondyloarthropathy is based on mainly clinical findings. Several inflammatory arthritides have common features which include familial clustering, association with HLA-B27 (Table 3), predominant axial and peripheral asymmetrical joint involvement, enthesitis, extra-articular signs and negative RF. The incidence of the seronegative spondylarthritides (SPA) in Finland is 13/100 000 (47,48).

SPA (*Table 3*) form a group of disorders which share a number of characteristic overlapping clinical features (*Table 4*) and an association with HLA-B27. The most typical and common spondylarthritides is ankylosing spondylitis (AS). One therefore needs to be aware of these conditions as features of sacroilitis or spondylitis may occur later in, for example, patients with reactive arthritis or psoriatic arthritis.

*Table 3. Spondyloarthritis: grouped together with following clinical characteristics:*

1. Peripheral arthritis – lower limb, asymmetrical
2. Radiological sacro-iliitis
3. Negative for rheumatoid factor
4. Absence of nodules and other extra-articular features of rheumatoid arthritis
5. Overlapping extra-articular features characteristic of the group
6. Significant familial aggregation
7. Association with HLA-B27

*Table 4. Spondyloarthritis*

- Ankylosing spondylitis
- Reactive arthritis (Reiter´s syndrome)
- A) sexually acquired reactive arthritis
- B) post dysenteric
- Arthropathy of inflammatory bowel disease
- Psoriatic arthritis
- ´Forme fruste´ and ´undifferentiated´presentations
- Certain forms of juvenile idiopathic arthritis

Infection is the triggering factor in reactive arthritis. Infection can cause also other rheumatic conditions (*Table 5*).

*Table 5. Differential diagnosis of Reactive Arthritis*

- Disseminated gonogoccal infection
- Rheumatic fever
- Still´s disease
- Psoriatic arthritis
- Inflammatory bowel disease-associated inflammatory joint disease
- Rheumatoid arthritis
- Lyme arthritis

Acute reactive arthritis is by no means always a benign self-limiting condition; there is progression to a chronic SPA in approximately 15-30% of cases (48). Recurrent attacks are more common in patients with chlamydia-triggered RA.

Enthesitis – inflammation at the insertion of tendon or ligament into bone – is a frequent feature in many forms of SPA and may involve synovial joints, cartilaginous joints and syndesomes as well as extra-articular entheses. In psoriatic arthritis, fatsuppressed T2-weighted MRI show peri-entheseal inflammation and bone marrow oedema at entheseal insertions (49). These findings have led to the hypothesis that synovitis in psoriatic arthritis (and perhaps SPA in general) is secondary to entheseal inflammation, in contrast to the primary synovitis of RA (49).

Enthesitis in the SPA most frequently involves the lower limbs, perhaps related to the greater bulk or physical stress on entheses at these sites. Eye inflammation, especially uveitis, is a prominent extra-articular feature in SPA (*Table 6*).

*Table 6. Classification criteria for SPA (43)*

| Inflammatory spinal pain | OR | Synovitis: Asymmetrical or predominantly in lower limbs |
|---|---|---|

AND one or more of the following:

- Alternate buttock pain
- Sacroilitis
- Enthesopathy
- Positive family history
- Psoriasis
- Inflammatory bowel disease

Urethritis, cervicitis or acute diarrhoea within 1 month

Many patients with SPA and mild disease respond well to treatment with non-steroidal anti-inflammatory drugs and physical therapy including physiotherapy, regular exercises and hydrotherapy. Persistent oligoarthritis is often improved by intra-articular steroids. SPA patients with severe peripheral joint disease commonly require treatment with a combination of a non-steroidal anti-inflammatory drugs and DMARDS. Biologically active agents, such as Infliximabe TNF alfa-blockers are increasingly used in patients with SPA (50). The DMARDS are used in the treatment of SPA largely overlap with those used in RA.

### 2.2.4 Ankylosing spondylitis

Ankylosing spondylitis (AS) is a chronic inflammatory disorder affecting predominantly, the axial skeleton although peripheral joint involvement may also be a significant feature. The disease affects synovial and cartilaginous articulations, and the sites of tendon and ligament attachment to bone (enthesopathy). The current diagnostic criteria included axial symptoms, limitation spinal movement, and radiological evidence of sacroiliitis (51). In the primary care setting it is a clinical diagnosis supported by radiological evidence of sacro-iliitis. The Prevalence of AS in Finland is 0.15% (52).

The association with HLA B27 is greatest with AS (over 95%) (53) and weaker with psoriatic and enteropathic arthritis (*Table 7*). The typical presentation of AS is a young adult with insidious onset of back-pain and stiffness. Diagnosis of AS, which is frequently delayed for several years after presentation of symptoms, usually involves the finding of inflammatory back pain and limitation of spinal movement in multiple planes together with radiological evidence of sacroilitis. A misdiagnosis of mechanical pain with symptoms present for a few years is not unusual. In chronic progressive disease there is loss of lumbar lordosis with

increased thoracic and cervical kyphosis which becomes fixed as a result of fibriosis and bony ankylosis at which stage pain is generally less prominent.

*Table 7. HLA-B27-associated spondyloarthritides*

| Disease | HLA-B27 frequency % |
|---|---|
| Ankylosing spondylitis | 96% |
| Undifferentiated spondyloarthropathy | 70% |
| Reactive arthritis | 30-70% |
| Colitis-associated spondyloarthritis | 33-75% |
| Psoriatic arthritis | 40-50% |
| Juvenile enthesitis-related arthritis | 70% |
| Iritis | 50% |
| Cardiac conduction defects with aortic incompetence | Up to 88% |

## 2.3 Sjögren's Syndrome

Dryness of the eyes or mouth are common subjective symptoms in general population. The menopause, diabetes mellitus and drugs such as anti-depressants are all associated with such symptoms.

Sjögren's Syndrome (SS) is characterized by an immune-mediated inflammatory process of the exocrine glands (1). It is generally divided into primary and secondary forms (53) based on whether or not another rheumatic disorder is present, such as RA or any of the other connective tissue diseases. Originally, sicca syndrome was defined as a trial of RA or another autoimmune disease, xerostomia and dry eyes (*Table 8*). The prevalence of primary SS has been estimated to range from <0.1% up to 0.4% in among Caucasian women in general practices (54). It has been described in 13.3% of patients in ambulatory patients attending a tertiary care centre (54). Signs of focal sialadenitis in labial submandibular and lacrimal glands were identified in 18.6% of 102 medicolegal post-mortem subjects in Finland (55).

In Northern lands there has been reported keratoconjuntivitis sicca syndrome in 14.9% and primary SS in 2.7% of patients (56).

In most patients, the presenting complaint is dryness, typically of the eyes (xerophthalmia) or mouth (xerostomia). Tenderness or swelling of the parotid glands may also be seen.

Evaluation of patients with suspected SS may include biopsy of the minor salivary glands of the lip, imaging of the enlarged salivary glands etc. by scintigraphy or MRI, investigation of damaged ductal structures by sialography, functional tests of ocular or oral glands, and testing for autoantibodies. SS must be differentiated from other disorders that affect the salivary glands. Minor salivary gland biopsy is the only reliable method to diagnose the disease with certainty.

Typical pathology consists of local aggreates of lymphocytes, plasma cells, and macrophages adjacent to and replacing the normal acini. Larger foci often exhibit formation of germinal centers.

SS is more prevalent in women (female to male ratio 9:1). Although it usually appears in the fourth and fifth decades of life, it has also been described in children. In paediatric presentations, the youngest reported patient has been 3 years old. (57). Familiar aggregation in SS is common as up to 12% of patients have a similary affected relative (58).

The aetiology of SS is still poorly understood. It appears that the autoreactivity observed (autoantibodies, lymphocytic infitrates of the exocrine glands) is probably due to the triggering of autoreactive clones by environmental factor(s) in genetically predisposed individuals.

*Table 8. Adapted summary of the Greek, the European classification and the European criteria proposed by the American-European Consensus group criteria for secondary Sjögren's syndrome.*

| Criteria | Skopouli et al 1986 | Vitali et al 1993 | Vitali et al 1996 | Vitali et al 2002 |
|---|---|---|---|---|
| Ocular component:<br>1. Subjective<br><br><br>2. Objective | <br>Xeropthal-mia<br><br>And<br>Sch≤ 5mm/ 5min or<br>RB + | <br>Xeropthalmia (specif. Quest.)<br><br>Sch I≤ 5mm/5min or<br>RB: van Bijsterveld score ≥4 | <br>Xeropthalmia or Xerostomia<br>And<br>Sch I≤ 5mm/5min or<br>RB: van Bijsterveld score ≥4 | <br>Xeropthalmia or Xerostomia<br>And<br>Sch I≤ 5mm/5min or<br>RB: van Bijsterveld score ≥4 |
| Oral component:<br>1. Subjective<br><br><br>2. Objective<br>-saliva<br><br><br><br>-biopsy | <br>Xerostomia<br><br>And<br>Parotid flow≤ 1 cc/ 5min or<br>RSGS<br><br>And<br>LSG≥ 2+ | <br>Xerostomia/ RSGS (specif. Quest.)<br>Unstimulated SRF ≤ 1.5ml/15min or<br>Scintigraphy + or Sialography +<br><br>LSG≥ 1 focus | <br>Xerostomia or Xeropthalmia<br>And<br>Unstimulated SRF ≤ 1.5ml/15min or<br>Scintigraphy + or Sialography +<br>or<br>LSG≥ 1 focus | <br>Xerostomia or Xeropthalmia<br>And<br>Unstimulated SRF ≤ 1.5ml/15min or<br>Scintigraphy + or Sialography +<br>or<br>LSG≥ 1 focus |
| Laboratory | - | RF+ or<br>ANA+ or<br>SSA/SSB-ab + | | RF+ or<br>ANA+ or<br>SSA/SSB-ab + |
| Exclusions | - | Lymphoma, GVHD, AIDS, Sarcoidosis | | Lymphoma, GVHD, AIDS, Sarcoidosis, PHNRT, Hepatitis C infection, use of anticholinergic drugs |
| Diagnosis of SSS | Definite: > 2/3 and LSG≥ 2+<br>Possible: ≥1/3 and LSG≥ 0 | ≥ 4/6 criteria, no exclusions | One or two subj. symptoms and at least two obj. items of glandular dysfunction | Posit. serology or focal sialad. And one or two subj. symptoms and at least two obj. items of glandular dysfunction |

Sch= Shirmer test, RB= Rose-Bengal test, BUT= break-up time, RSGS= recurrent salivary gland swelling, SRF= salivary flow rate, LSG= labial salivary gland biopsy, KCS= keratoconjunctivitis sicca,
SSS= secundary Sjögren's syndrome, RF=rheumatoid factor, ANA= antinuclear antibodies, GVHD= graft-versus-host disease, AIDS= acquired autoimmune deficiency syndrome, PHNRT=Past head and neck radiation treatment.

The most typical clinical features of SS are symptoms of dryness in various glandular tissues: eyes, mouth, nose, posterior pharynx, larynx, respiratory epithelium, skin and vagina (59).

Decreased tear secretion causes a sandy sensation in the eyes, burning, redness, photosensitivity, eye fatique, itching and disturbance of vision (60). Eye involvement in SS is diagnosed on the basis of decrease or qualitative abnormalities in tear secretion, and lesions on the surface of the eye (52). The Schirmer´s tear test is used to assess tear secretion by the lacrimal glands. Keratoconjunctivitis sicca, the sequela of decreased tear secretion, is diagnosed using an aniline dye (Rose Bengal) that stains the damaged epithelium of both the cornea and conjunctiva.

The diagnosis of salivary gland involvement is based on the detection of functional impairment or anatomical changes resulting from an autoimmune inflammatory proccess in which the salivary glands are the main target. Decreased salivary flow may cause difficulty in chewing, swallowing and phonation, abnormalities of taste and smelling, fissures on the tonque, buccal membranes and lips, worsening of dental caries etc (1). Candida albicans is also detected more often in patients with SS than in healthy controls (61). Diminished salivary flow may also predispose SS patients to ascending sialadenitis (62). Parotid gland enlargement, often recurrent and symmetric, occurs in about half of secondary SS patients (63). The inflammatory infiltrates in the glands may be so large and numerals that swelling of the parotid glands or, more rarely, of the submandibular or sublingual glands may occur repeatedly during the course of the disease.

A reduction in saliva production can be documented simply by collecting, in calibrated tube, the saliva produced by the patient in a certain amount of time. This test can be performed without or with stimulation (gustatory or masticatory), although conflicting results have been

obtained and it is not yet clear which is preferable. The current diagnostic criteria of SS (8) include unstimulated secretion of saliva as one of the variables for the diagnosis.

Sialometry allows a rough assessment of the functional status of the glands, although it is far from specific for SS. Salivary scintigraphy is an alternative method of assessing the functional status of the major salivary glands. The rate of tracer uptake in the glands and the rate of tracer secretion into the mouth are considered good indicators of the functional and anatomical integrity of the major salivary glands. The obvious disadvantage of this method is its high cost. Parotid sialography has frequently been used in the diagnosis of SS, sialectases being the most typical finding. MR imaging and MR sialography are noninvasive methods that provide definitive information of morphologic changes in parotid glands and can be used as diagnostic indicators of SS. MR sialography is more sensitive, but conventional MRI gives complementary information on the progressive pathologic changes of glandular parenchyma (64). Minor salivary gland biopsy is the most widely used method of assessing oral involvement in SS.

Autoantibodies are commonly detected in patients with SS, in particular RF, antinuclear antibodies, and antibodies to extractable nuclear antigens, termed Ro (SSA) and La (SSB). These autoantibodies are not specific for SS and may be found in other autoimmune diseases, especially in SLE.

The treatments of SS is largely symptomatic with the goal of keeping the conjunctiva and mucosal surfaces moist. Artificial tears should be used regularly. Soft contact lenses may help to protect the cornea, especially in the presence of filimentary keratitis.

Cigarette smoking and drugs with anticholinergic side effects should be avoided whenever possible. Treatment of xerostomia is difficult. Most patients learn on their own the importance of taking small sips of water frequently and carrying bottles of water with them at all times. Stimulation of salivary flow by chewing sugar-free gum or using lozenges is often helpful. Periodontal disease and tooth decay are serious problems in patients with xerostomia; thus, patients should be reminded of the importance of brushing their teeth after meals. Topical treatment of the teeth with stannous fluoride enhances dental mineralization and retards damage. Corticosteroids and immunosuppressive drugs such as oral or intravenous cyclophosphamide are used for patients with severe, progressive extraglandular disease. SS patients are at increased risk for the development of lymphoma.

### 2.3.1 Minor salivary gland biopsy

Minor salivary gland biopsy is the most widely used method of assessing oral involvement in SS. A sufficient amount of glandular tissue should be taken from the lower lip after a local incision midway between the midline and the corner of mouth. Harvestin of minor salivary glands can be done using single or more preferrably by small multiple incision. Focal sialoadenitis is a characteristic histopathological feature of SS. Daniels and Whitcher (65) reported a correlation between reduction of parotid salivary flow rate and inflammatory-focus score in lip biopsy specimens from patients with primary SS.

There is as yet no consensus on the threshold focus score to be used for diagnosis. Some authors suggest a focus score >1 per 4 $mm^2$ (66), while others accept a focus score of 1 as virtually diagnostic of SS (67). Although the presence of focal sialoadenitis is considered the most specific diagnostic test for SS, a similar histopathological picture has been demonstrated in conditions other than SS, e.g., primary biliary cirrhosis, bone marrow transplants,

HIV infections, and myastenia gravis. An inflammatory focus is defined as an aggregate containing 50 or more mononuclear cells. The focus score os the number of such aggregates in a 4 $mm^2$ area.

Only two studies on repeat labial salivary gland biopsies in secondary SS patients have been carried out (68,69). The lesions were mainly progressive with time. They observed for their part morphological progression of sialadenitis in 14 out of 21 patients (67%) with primary SS, and in 14 out of 18 (78%) with secondary SS after a mean follow-up time of three years.

## 2.4. Saliva and oral microbial flora

### 2.4.1 Salivary flow

The formation of saliva consists of formation of secretory fluid, made up of water and electrolytes and secretion of preformed proteins and enzymes, mainly originating from acinar cells. Salivary composition mainly depends on the source of the saliva and type of stimulation. Many causes can affect decreased salivary secretion (*Table* 9). The main organic components in saliva are proteins and glycoproteins, which are different in different secretions. Parotid saliva contains large amounts of glycoproteins, such as amylase, salivary peroxidase and IgA. More glycosylated glycoproteins, mucins, are typical of submandibular and sublingual secretions, making them viscous.

Bacterial plaque is the major etiological factor of dental caries and periodontal disease. Saliva contains many substances, both innate and acquired, which can protect the oral tissues against bacteria (70).

Many studies have been published about salivary flow in RA patients (13), but only a few reports have been published on sialochemistry in patients with AS and SPA, diseases that may also be associated with focal sialadenitis and SS (71).

*Table 9. Main causes of decreased salivary production.*

| ACUTE AND TRANSIENT | CHRONIC AND USUALLY STABLE |
|---|---|
| Short-term drug use (x) | Chronically adminstered drugs (x) |
| Viral and bacterial infections (mumps, cytomegalovirus, coxsackle A) | Sjögren´s syndrome |
| Dehydration | Granulomatous diseases (sacroidosis,tuberculosis, leprosy) |
| Psychogenic (depression, anxiety, panic attacks) | Amyloidosis |
| | Human immunodeficiency virus infection |
| | Graft-versus-host disease |
| | Cystic fibrosis |
| | Diabetes mellitus, hyperlipoproteinaemia |
| | Ageing |
| | Hepatitis C |
| | Radiotherapy of the neck and head |

(x) antihistamines, antidepressants, anticholinergics, neuroleptics, anti-parkinsonians, anti-hypertensive agents (especially clonidine).

### 2.4.2 Salivary biochemistry

Amylase is the most important digestive enzyme in saliva, and a major component of parotid saliva. Amylase concentration is a marker of protein synthesis in the acinar cell (72). Van der Reijden et al. (73) have reported that concentrations of salivary amylase in cases of secondary SS were similar to those in controls.

Secretory IgA is the main immunoglobulin isotype of saliva (74). The main function of secretory IgA is to inhibit microbial colonization by aggregating bacteria and preventing their adhesion (74). Elkon et al.(75) found that salivary IgA concentrations were higher in RA patients with dry eyes than in control subjects and that even RA patients without dry eyes exhibited high concentrations of salivary IgG. Mandel and Baurmash (76) found higher salivary IgA concentrations in patients with primary SS than in control subjects. High levels of IgA, IgG, and IgM have also been reported in whole saliva from patients with secondary SS (75, 77-79). In a normal population, concentration of IgA in saliva is inversely related to salivary flow rate. Stimulating flow results in dilution of IgA both in the parotid and whole saliva (78). Ben-Aryeh et al. (79) have suggested a positive correlation between focus score and salivary IgA concentration. The increases in salivary IgA and IgG concentrations detected in primary and secondary cases of SS could result from massive infiltration of salivary glands by B cells, or leakage from serum into the damaged glands (80). High numbers of IgG-producing plasma cells have been observed in lymphocytic infiltrates of minor salivary gland biopsy specimens in patients with secondary SS (81).

High serum IgA concentrations are characteristic in active AS (82). It has been suggested that it results from stimulation of the gut immune system by Gram-negative bacteria in the gut (83). Use of sulfasalazine by patients with active AS has been shown to restore the levels to normal of IgA in serum (81) and of secretory IgA in the gut (84).

The high levels of salivary albumin may indicate decreased mucosal integrity in the oral cavity, like what is seen in the gut of AS patients (77). High salivary albumin concentrations have previously been reported in RA, SS and control subjects (75) and, for example, in patients treated for lymphoma (78).

Increased concentrations of salivary albumin, cystatin C and S, IgA and total protein, but not amylase, have been reported in relation to both primary SS and in RA patients with secondary SS (65). Information on the composition of saliva in patients with MCTD, an autoimmune disease in which SS is also often seen (19) is sparse, however.

### 2.4.3 Oral microbial flora

The normal oropharyngeal flora is made up of more than 400 bacterial species. Thirty per cent of the bacteria are aerobic, 70% anaerobic (79). Concentrations of bacteria in saliva vary between 10(8) and 10(9) CFU/ml. In the gingival sulcus and pockets, especially in periodontitis, anaerobic Gram-negative rods are present (80). In healthy individuals, Gram-negative bacteria (2-18%) are rarely isolated from the oropharynx (81).

## 2.5. Oral health

Systemic health is often closely linked to the state of the oral cavity: many systemic diseases and conditions have oral manifestations. Population-based studies now suggest the periodontal diseases may be linked with systemic diseases and conditions including cardiovascular diseases, diabetes, respitatory diseases, adverse pregnancy outcomes, and osteoporosis (82,84).

There is good evidence to suggest that individuals with moderate to severe periodontal disease are at higher risk of suffering from RA and vice versa (10, 11).

SS is known to occur in association with various rheumatic diseases (19, 3, 85). In Primary SS incidences of caries and changes in the oral mucosa are relatively high (78, 86, 73, 87). Oral infections have been associated with systemic diseases such as RA (9). Risk for periodontal disease has been substantially increased in patients with long-standing RA (10, 11). However, data are sparse on periodontal condition in seronegative arthritides or MCTD

and no studies have been conducted on periodontal disease in patients with SPA. Saliva secretion, which is the principal defensive factor in the oral cavity is affected by the rheumatic diseases with subsequent detrimental effects on teeth and mouth mucosa. Reduced salivary flow enhances oral microbial colonization, in particular yeasts which, in turn, are an infectious burden to the patient and may worsen the systemic condition (13).

Salivary secretion depends on the general state of hydration but is mostly affected by systemic diseases and drugs (13, 19).

A close correlation between minor salivary gland inflammation and whole salivary secretion has been observed (88). Similar to the situation in other organs, the salivary glands can compensate functionally for modest loss of parenchyma. In the early stages of disease, stimulated flow rates may therefore be normal or only slightly reduced. In later stages, however, there is a much greater loss of tissue and stimulated flow rates may be significantly reduced.

## 2.6. Temporomandibular joint

### 2.6.1 Anatomy

The temporomandibular joint (TMJ) obeys the same biologic laws as do other synovial joints in the body, except that this joint has fibrocartilage on articular surfaces, while most other joints have hyaline cartilage (38). The thin, loose fibrous capsule surrounds the articular surface of the condyle and blends with the periosteum of the mandibular neck. On the temporal bone the articular capsule completely surrounds the articular surfaces of the eminence and fossa. Attachments of the capsule adhere firmly to bone. Anteriorly, the capsule is attached in front of the crest of the articular eminence; laterally, it adheres to the edge of the eminence and fossa; and posteriorly, it extends medially along the anterior lip of the

squamotympanic and petrotympanic fissures. The medial attachment runs along the sphenosquamosal suture. The articular capsule is strongly reinforced laterally by the temporomandibular (lateral) ligament, composed of a superficial fan-shaped layer of obliquely oriented connective tissue fibers and a deeper, narrow band of fibers that run more horizontally. The ligament attaches broadly to the outer surface of the root of the zygomatic arch and converges downward and backward to attach to the back of the condyle below and behind its lateral pole.

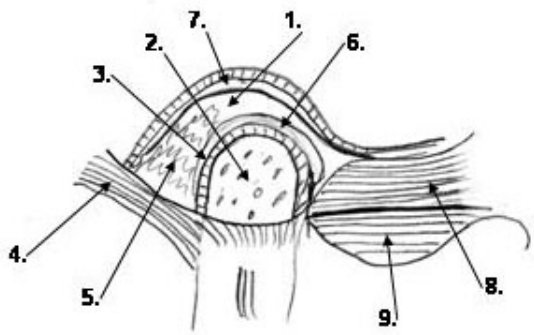
The articular disc is a firm but flexible structure with a biconcave shape. The disc is divided into three regions: posterior band, intermediate zone, and anterior band. The central intermediate zone is considerably thinner than the posterior and anterior bands. The upper surface of the disc adapts to the contours of the fossa and eminence of the temporal bone, and the lower surface of the disc adapts to the contour of the mandibular condyle.

Posteriorly, the disc and the loosely organized posterior attachment tissues (bilaminar zone, retrodiscal tissue) are contiguous. The retrodiscal tissue is a soft, areolar connective tissue with large vascular spaces. The posterior attachment tissues are attached to the tympanic plate of the temporal bone posterosuperiorly and to the neck of the condyle posteroinferiorly. Anteriorly, the disc and the capsule and fascia of the superior head of the lateral pterygoid muscle are contiguous. The superior head of the lateral pterygoid muscle may have some fibers inserting directly into the disc anteromedially (*Figure 1*).

The articular disc of the TMJ is a hypovascular intra-articular structure that separates the condylar head from the glenoid fossa. It is firmly attached to the condyle at its lateral pole while it is not directly attached to the temporal bone. The articular disc and its posterior

attachment tissues merge with the capsule around their periphery. The disc and its attachments divide the joint space into separate superior and inferior spaces. In the sagittal plane, the upper joint space is contiguous with the glenoid fossa and the articular eminence. The upper joint space always extends farther anteriorly than the lower joint space. The lower joint space is contiguous with the condyle and extends only slightly anterior to the condyle along the superior aspect of superior belly of the lateral pterygoid muscle. In frontal plane, the upper joint space overlaps the lower joint space. Therefore, entrance through the lateral capsule starts in the superior compartment (89).

*Figure 1. Temporomandibular joint (with permission modified after Okeson 2003 (89))*




1. Disc
2. Condyle
3. Fibrocartilage
4. Capsular ligament
5. Retrodiscal tissue
6. Inferior joint cavity
7. Superior joint cavity
8. Superior belly of lateral pterygoid muscle
9. Inferior belly of lateral pterygoid muscle

### 2.6.2 Imaging

#### 2.6.2.1 Panoramic tomography

Plain radiography of TMJ, panoramic tomography and lateral panoramic tomography can be valuable for initial screening for osseus abnormalities, such as fractures and advanced degenerative joint disease. In addition, these methods can be applied in the examination of inflammatory changes of TMJ (90). The panoramic radiograph is suitable (91, 92) and is also

justified by its small dose of radiation (65) and for providing sufficient information on TMJ pathology (91).

#### 2.6.2.2 Lateral panoramic tomography

The joint lateral (JLA) program is designed for obtaining lateral views of the TMJ's. Both TMJ's are imaged on the same film. The image layer is nearly straight, vertically located, with a slight angulation ventrally toward the midline. The JLA program is used for examination of various disorders of the TMJ's as well as the mastoid area. The TMJ's can be imaged with the mouth closed or open (94).

#### 2.6.2.3. Magnetic resonance imaging

The overall advantage of magnetic resonance imaging (MRI) as a diagnostic tool is its ability to visualize soft tissue as well as bony structures (95). MRI has been used in RA to characterice both bone damage and synovitis. Periarticular bone erosion as shown by conventional radiography is the most characteristic feature of RA.

Conventional radiographs detect cortical bone decalcification, but MRI demonstrates marrow changes and, therefore, has a different pathological significance. Radiographic erosions are uncommon in early RA, and several studies have shown that MRI is superior for showing bone damage in disease of less than 12 months duration (96).

Most patients with RA have MRI-detectable bone changes. In addition, studies of the wrist, finger and shoulder joints have confirmed the greater sensitivity of MRI for bone changes in more long-standing discease. The longitudinal use of MRI as a surrogate marker for disease activity has also been assessed. MRI may be more sensitive than clinical assessment for diagnosing early synovitis. This has important implications for the early diagnosis of RA and a preliminary study has shown that MRI criterion had high sensitivity and specificity for

subsequent clinical diagnosis of RA. The earliest MRI bone change in RA is bone oedema which is secondary to synovitis. Bone oedema seems to be the forerunner of frank bone erosion (97).

MRI and ultrasonography are superior to computer tomography in detecting small erosions. Ultrasonography, MRI and computer tomography detect large erosions quite similarly. Plain radiography misses small erosions (98).

MRI without contrast has been widely used in diagnosing internal derangement of TMJ without relation to an arthritic disease, such as disc displacements (99-106). There seem to be a general acceptance of using the method by Drace and Enzmann (107) in defining the correct disc position in the TMJ verified by MRI. Although the disc is a rather small structure it is very easy to see on non-enhanced MRI. Also the disc morphology can easily be described on MRI (108). In addition, MRI has proven to be very effective in diagnosing bony changes in the TMJ (108-111) in patients with functional TMD. There is general agreement, that MRI is superior to conventional radiographic examination or tomographs (37, 112-113). The presence of synovitis in TMJ is best determined with MRI using Gadolinium contrast medium (Gd-DTPA).

MRI in relation to diagnosing TMJ involvement in patients with an arthritic disease is only sparcely described. Larheim et al.1990 (37) compared MRI findings of the TMJ in patients with RA with tomographies of the same joints, and found that there was good agreement between the two imaging modalities regarding surface irregularities and that MR imaging even demonstrated more extensive bone abnormalities than did tomography in some of the TMJs. The potential of MR imaging for depicting bone and soft-tissue abnormalities associated with rheumatic TMJ involvement was clearly demonstrated.

Only one study describes contrast-enhanced MRI of the TMJ (114). Smith et al have performed MRI enhanced with Gd-DTPA of the TMJ in adults with RA and in patients without a rheumatic disease and a few asymptomatic adults (114, 115).

They found, that the synovium in the TMJ in the non-rheumatic patients with signs of TMJ disorder and in the healthy adults did not enchance whereas the synovium in the patients with rheumatic disease enhanced clearly.

When imaging of TMJ by MRI, there are sagittal and coronal projections. While coronal sections give more information about disc dislocation and thickening of joint capsule, the sagittal projections are more useful in showing the disc and its position in relation to condylar head (16).

### 2.6.3 Pathology

In the ”temporomandibular joint osteoarthrosis concept”, different conditions of the articular cartilage are described, i.e., from normal variation to initial degenerative changes, from initial degenerative changes to advanced changes, and finally to destroyed cartilage.

Based on these assumptions, when classifying temporomandibular arthopathies, osteoarthritis with and without disc displacement should be distinguished. A twelve o´clock position of the posterior band of the disc is no longer a standard of normal, since asymptomatic normal subjects show disc malposition and deformity in a significant portion of the studied population (38).

Synovitis refers to inflammation of the synovial membrane. It results in an escape of fluid into the joint cavity (effusion), and alterations in the composition of the synovial fluid. When

severe, necrosis and fibrin deposition on the synovial surfaces may cause adhesions, which reduce the joint space and eventually may lead to fibrous ankylosis.

Capsulitis describes inflammation of the outer layer of the capsule. It is characterized by pain with capsular stretching. Clinically, capsulitis is indistinguishable from synovitis. Most commonly, capsulitis results from stretching the capsule beyond its physiological range, e.g., due to habits (e.g. brukxism) or local trauma. During the healing process, the capsule may adhere to adjacent tissue (adhesive capsulitis) or heal in a shortened state (capsular fibrosis).

#### 2.6.3.1 Temporomandibular disorders

Temporomandibular disorders (TMD) are defined as a collective term embraging number a clinical problem that involve the masticatory muscles, the TMJ and associated structures (89). TMD has several possible causes:

- Muscle tension. Muscle tightness in the TMJ usually results from overuse of muscles. This overuse in turn is often associated with psychological stress and clenching or grinding of the teeth (bruxism).
- Injury. A direct blow to the jaw or the side of the head can result in bone fracture, soft tissue bruising, or a dislocation of the temporomandibular joint itself.
- Arthritis. Both osteoarthritis and rheumatoid arthritis can cause TMD.
- Internal derangement. Internal derangement is a condition in which the cartilage disk lies in front of its proper position. In most cases of internal derangement, the disc moves in and out of its correct location, making a clicking or popping noise as it moves. In a few cases, the disc is permanently out of position, and the patient's range of motion in the jaw is limited.
- Hypermobility. Hypermobility is a condition in which the ligaments that hold the jaw in place are too loose and the jaw tends to slip out of its socket.
- Birth abnormalities. These are the least frequent cause of TMD but do occur in a minority of patients. In some cases, the top of the jawbone is too small; in others, the top of the jawbone outgrows the lower part.

The symptoms of TMD depend in part on its cause. The most common symptoms are facial pain in front of the ears; headaches; sore jaw muscles; a clicking sound when chewing; a grating sensation when opening and closing the mouth; and temporary locking of the jaw. Some patients also report a sensation of buzzing or ringing in the ears.

Usually, the temporomandibular joint itself is not painful. Most cases of TMD are seen in women between 20-50 years of age. The symptoms are usually aggravated by function, wide opening for prolonged periods of time such as during dental treatment, and with the chewing of hard and chewy food (18, 89). Pain is frequent in the preauricular area and is often experienced as ear pain (90). Compression of the retrodiscal tissue (bilaminar zone) has been proposed and is one possibility as the source of the pain. Others are the inflammatory changes secondary to internal derangement, stretching of the joint capsule, and synovitis. Another important source of pain is the masticatory muscles. With an abnormally functioning joint, the patient frequently develops tender muscles that can be experienced as facial pain (116). Although it frequently is difficult to distinguish muscle and joint pain on physical examination (90), the tenderness in masticatory muscles in a patient with rheumatic disease is a good indicator of TMJ inflammation. Also, it might refer to the presence of permanent TMJ destruction. Bruxism and direct facial trauma all have been proposed as possible aetiologies of TMD.

#### 2.6.3.2 Rheumatoid arthritis and temporomandibular joint

The reported frequency of clinical TMJ involvement in patients with RA has varied from 2% to 98% (86), and most studies indicate that more than 50% of patients with RA exhibit clinical involvement of the TMJ (16, 117-120), but even then TMJ symptoms are usually minor (119-121). Wenneberg et al. (17) studied 61 patients with RA, 61 with psoriatic arthritis, 61 with AS, and 77 non-matched control subjects.

TMJ changes were observed radiologically in 66% of the RA patients, 38% of the psoriatic-arthritis patients and 30% of the AS patients but in only 12% of the control subjects. The changes seen radiologically, especially cortical erosions and the presence of subcortical cysts, were more severe in the RA patients than in the AS or psoriatic arthritis patients. Subjective TMJ symptoms and clinical findings relating to the TMJ were more common in the RA and AS patients than in the control subjects. Erosions and cysts of the mandibular condyle are typical radiological findings in patients with RA (119). In early RA, synovial proliferation and joint effusion can be observed in MRI of the TMJ (35, 120, 121).

#### 2.6.3.3 Mixed connective tissue disease and temporomandibular joint

MCTD is a heterogeneous disease, in which the clinical features of the patients vary considerable between the patients and also with time. Some of the patients end up with an erosive peripheral arthritis (122). There is only one study report of MCTD and radiographic TMJ changes (19) TMJ erosion was found in 7 out of 10 MCTD patients. Erosion of the condyle resembling changes seen in RA was detected in 4 of 10 MCTD patients (19). In one patient limited function of TMJ was observed (19).

#### 2.6.3.4 Ankylosing spondylitis and temporomandibular joint

The frequency of TMJ involvement in patients with AS has varied from 4% to 35% depending on the diagnostic criteria, the population studied, and the tools used to assess TMJ involvement (123, 129). Crum and Loiselle (1971) reported that 16% of patients with AS had complaints of pain and tenderness in the region of the TMJ's, with limited jaw opening. Davidson et al reported that 10% of patients with AS had restricted jaw opening (125).

Ramos-Remus and Major et al (126) studied 65 AS patients and 22 control subjects and found that TMJ involvement is frequent in AS patients and is associated with variables that suggest more severe disease. Könönen et al (123) reported that TMJ involvement was found in 32% of the patients with AS.

#### 2.6.3.5 Spondyloarhropathy and temporomandibular joint

There are only a few studies relating to SPA patients other than those with psoriatic arthropathy. In a recent study, it was found that patients with Reiter's disease frequently exhibited TMJ symptoms and that 33% had radiographic evidence of erosions (126).

# 3. AIMS OF THE STUDY

The present series of studies were undertaken to investigate the oral health and TMJ in various rheumatic diseases (RA, MCTD, AS and SPA).

The specific aims were:

1. To study the prevalence of focal sialadenitis in patients with various rheumatic diseases. To correlate focal sialadenitis with possible xerostomia or decreased tear secretion in these patients.

2. To investigate oral health status, prevalence of dental pathogens and yeasts, as well as salivary flow rates and composition in patients with various rheumatic diseases.

3. To investigate the associations between clinical and radiographic findingsof the TMJ in patients with various rheumatic diseases.

4. To investigate whether certain HLA alleles are associated with TMJ erosions, salivary composition and signs of focal sialadenitis in patients with a wide spectrum of rheumatic diseases.

5. To investigate MRI findings of the TMJ in various rheumatic diseases and compare them to clinical and radiographic tomographic findings.

# 4 MATERIALS AND METHODS

## 4.1 Study design

The whole study was carried out from September 1996 to August 1998. All consecutive patients with MCTD, AS, and SPA treated at the Outpatient Department of Rheumatology of the Meilahti Hospital, Helsinki University Central Hospital, were asked to participate in the study. During the same period, patients belonging in to a prospective cohort of early RA started in 1986-1989 were asked to participate. Participation was requested irrespective of the presence of oral or ocular symptoms. All patients initially gave their informed consent, but three patients (one with MCTD, one with AS, and one with SPA) later withdrew it (Study I, N=85).

The controls were randomly selected volunteers, patients and staff of the Institute of Dentistry of the University of Helsinki. Each control was matched for sex and age ($\pm$2) with a patient. No control had any history of diabetes, rheumatic disease or any other disease affecting the masticatory system.

The HLA-antigen frequencies for the Finnish population were derived from 100 healthy Finnish blood donors, which were randomly picked up from 3000 blood donors. The controls were not clinically or radiologically examined.

In study IV, one RA patient was excluded from the original study group, since determination of HLA alleles was not available. In study III, one RA, three MCTD, and one SPA patient were excluded, due to missing recent panoramic tomography (N=2) or answers on TMD questionnaire (N=3). In study II, one RA, four MCTD, one AS, and two SPA patients were

excluded, due to missing recent panoramic tomograms (N=2) or saliva samples (N=6). Sixty-seven patients with rheumatic diseases participated in study V. Of the 85 patients originally studed, 67 (79%) had a complete set of MRI available. Seventeen patients did not undergo a complete MRI examination for a variety of reasons, including acute panic disorder (four), severe kyphotic spinal deformity (two), incomplete MRI examination (six), and refusal by the patient (five).

### 4.2 Study population

The study population consisted of 25 patients with RA, 19 with MCTD, 19 with AS, and 22 with SPA (Study I) (*Table 10*). Of these patients, 77 participated in Study II (24 with RA, 15 with MCTD, 18 with AS and 20 with SPA), 80 in study III (24 with RA, 16 with MCTD, 19 with AS, and 21 with SPA), 84 in study IV (24 patients with RA, 19 with MCTD, 19 with AS, 22 with SPA), and 67 in study V (16 patients with RA, 15 with MCTD, 17 with AS, 19 with SPA). In studies II and III, an age and sex matched controls were also evaluated. In study IV, 100 healthy blood donors served as control subjects.

All RA patients fulfilled the American Rheumatism Association 1987 classification criteria for RA (45), MCTD patients met the criteria for the diagnosis by Alarcon-Segovia (127), and AS patients fulfilled the modified New York criteria for definite ankylosing spondylitis (128). Other patients with seronegative oligoarthritis or spondylitis not fulfilling the diagnostic criteria for AS were grouped into SPA patients and fulfilled the European Spondylarthropathy Study Group criteria (129). No patient was suffering from psoriatic arthropathy.

*Table 10. Characteristics of the study groups.*

| | RA (N = 25) | MCTD (N = 19) | AS (N = 19) | SPA (N = 22) | Controls ( N = 85) |
|---|---|---|---|---|---|
| Sex (M/F) | 2/23 | 1/18 | 13/6 | 13/9 | 29/56 |
| Mean (SD) age, years | 49.3 (11.2) | 46.3 (15.5) | 42.1 (11.4) | 38.3 (9.8) | 44.0 (12.6) |
| Mean (SD) duration of disease, years | 10.5 (2.6) | 10.6 (11.9) | 13.3 (8.9) | 13.0 (9.2) | 0 (0%) |
| Peripheral arthritis | 25 (100 %) | 16 (84 %) | 14 (74 %) | 21 (95 %) | 0 (0%) |
| History of use of | | | | | |
| Sulfasalazine | 18 (72 %) | 0 (0 %) | 17 (89 %) | 17 (77 %) | 0 (0%) |
| Prednisolone | 11 (44 %) | 17 (89 %) | 11 (58 %) | 14 (64 %) | 0 (0%) |
| Current use of | | | | | |
| Sulfasalazine | 3 (12%) | 0 (0%) | 11 (58%) | 8 (36%) | 0 (0%) |
| Prednisolone | 7 (28%) | 15 (79%) | 8 (42%) | 9 (41%) | 0 (0%) |
| Laboratory tests | | | | | |
| Rheumatoid factor + | 17 (68 %) | 12 (63 %) | 3 (16 %) | 2 (9 %) | nd |
| Positive SSA-AB or SSB-AB | 0 (0 %) | 11 (58 %) | 1 (5 %) | 0 (0 %) | nd |
| Positive ANA | 11 (44 %) | 19 (100 %) | 5 (26 %) | 6 (27 %) | nd |
| Low C3 | 0 (0 %) | 3 (16 %) | 0 (0 %) | 0 (0 %) | nd |
| Low C4 | 2 (8 %) | 5 (26 %) | 2 (11 %) | 1 (5 %) | nd |
| Positive RNP-AB | 0 (0 %) | 11 (58 %) | 0 (0 %) | 1 (5 %) | nd |
| Positive Sm-AB | 0 (0 %) | 3 (16 %) | 0 (0 %) | 0 (0 %) | nd |
| Present use of other medications: | | | | | |
| Antibiotics and antimicrobial drugs | 0 | 0 | 0 | 1 | 0 |
| Cardiovascular drugs | 5 | 0 | 1 | 3 | 9 |
| Respiratory drugs | 0 | 0 | 0 | 1 | 5 |
| Gastrointestinal drugs | 0 | 2 | 1 | 0 | 2 |
| Sex hormones and gynecological drugs | 1 | 1 | 0 | 0 | 9 |
| Psychiatric drugs | 2 | 1 | 1 | 0 | 3 |
| Neurological drugs | 1 | 0 | 0 | 0 | 1 |
| Drugs for allergy | 1 | 0 | 0 | 0 | 4 |
| Endocrinological drugs | 0 | 2 | 0 | 2 | 7 |
| Dermatological drugs | 0 | 0 | 0 | 0 | 1 |
| Analgesics | 9 | 5 | 12 | 14 | 1 |
| Hematological drugs | 0 | 0 | 0 | 0 | 1 |
| Vitamins | 1 | 0 | 0 | 0 | 1 |
| Ophthalmological drugs | 0 | 0 | 0 | 0 | 2 |
| Otorhinological drugs | 1 | 0 | 0 | 0 | 1 |
| Current use of drugs known to decrease salivary flow | 5 (20%) | 1 (5%) | 1 (5%) | 1 (5%) | 8 (9%) |

### 4.3 Questionnaire

All patients filled out a questionnaire on eye and oral symptoms according to the European Community Study Group Diagnostic Criteria for SS (128) with the following modifications (Appendix). For the ocular symptoms, the question about persistent or recurrent tear gland involvement was omitted, and a question about drugs with potential to cause decreased salivary flow was added. The questionnaire includes also questions on ear and TMD (Appendix).

Answers were checked during personal interviews (LMJH). At the time of the examination, the examiner was unaware of the clinical diagnosis of the subjects. In addition, questions concerning facial trauma, headache and chewing habits were also included.

The severity of TMJ symptoms in the patients was assessed on the basis of responses to the question:"How would you describe your TMJ symptoms?" Responses were graded as 1 (no discomfort or very minimal discomfort), 2 (mild discomfort), 3 (moderate discomfort), 4 (severe discomfort) or 5 (very severe discomfort). During data analysis grades 3 to 5 were combined and described as "severe symptoms" (Appendix).

Use of medication over the whole disease period and the use of DMARDS, other drugs for chronic diseases, and antidepressants –for example, antihypertensive, sedative, anticholinergic- were recorded. All patients were allowed to continue with their routine medication. Because sulfasalazine can induce autoimmune effects (129), duration of use of this drug was separately classified (0 to less than three months, three to 11 months, 12 months or more).Use of sulfasalazine at the time of examination was also recorded. Patients were further divided into three groups with respect to the use of glucocorticosteroids (current users, ex- users, and non- users of glucocorticosteroids).

### 4.4 Clinical examination

The patients and controls were examined in a normally equipped dental office using World Health Organization recommendations for clinical recording. Dental status, including signs of dental infection foci, caries lesions, periodontal status and oral mucosal diseases were recorded for each subject. “Periodontitis” was recorded if the CPI was of score 3 or more (130). To assess dryness of the eyes, Schirmer’s test was performed using standardised tear strips (Clement Clarke, Edinburgh, UK), placed for five minutes on the conjunction at the most lateral part of the inferior lid, without previous use of anaesthetic eye drops. The patients sat with eyes closed, but not shut tight.

All patients were subjected to a routine stomatognathic examination (17,131) to detect signs or symptoms of TMD, and to allow the occlusion to be recorded. The examination included palpation of the masticatory muscles and the TMJ. Tenderness was recorded whenever palpation resulted in reflex or the patient reported subjective discomfort. TMJ sounds i.e. clicking and crepitation were recorded from each side separately. Maximum ranges of mouth opening movement and lateral movements of the mandible were measured to the nearest millimetre, using a ruler (21) and pain during these movements was recorded. Deviations of more than 2 mm during opening and closure were also recorded. The occlusion was examined and use of removable dentures and any loss of molar support were recorded. During examination of the occlusion unilateral contacts in the retruded contact position, laterotrusion-, mediotrusion- and protrusion interferences,
in accordance with the method of Wenneberg and Kopp (17) were also recorded.

### 4.5 Laboratory examinations

Venous blood samples were collected from the patients and serum concentrations of serum IgA, IgG, IgM concentrations were determined by means of immunoturbidometry. The standard laboratory tests included whole blood cell count and erythrocyte sedimentation rate (ESR). C-reactive protein (CRP), creatinine and rheumatoid factor (RF) were determined. Serum C3 and C4 concentrations, and antibodies to SSA, SSB, RNP and Sm, as well as antinuclear antibodies and antibodies to hepatitis C were determined. All analyses were carried out in the hospital laboratory using routine clinical chemical procedures. Due to ethical reasons, no blood samples were taken from the controls.

### 4.6 Saliva

The patients and controls provided resting and stimulated saliva samples according to routine procedure of our hospital (132). Values for resting flow rates of less than 0.1 ml/min and for stimulated flow rates of less than 0.7 ml/min were taken to indicate reduced flow rates. Values for pH and buffering capacity (regarded as normal if the final pH was 4.0 or more) were determined immediately after collection by means of the Dentobuff-Strip® method (Orion Diagnostica, Espoo, Finland). Salivary pH was measured using a pH indicator paper and the values were classified as normal if 6.5 or more. Rest of salivas was centrifuged and deep frozen (-70 $^{o}$C) until further analyses.

#### 4.6.1 Salivary microbes

Cotton swab samples from the tongue were taken to inoculate Oricult-N® dip-slides (Orion Diagnostica, Espoo, Finland) for the assessment of yeasts. Counts of mutans streptococci (SM) and lactobacilli (LB) were assessed by the Dentocult -SM Strip Mutans® and Dentocult-LB® dip-slides, respectively (Orion Diagnostica, Espoo, Finland). *Actinobacillus actinomycetemcomitans* (A.a.), *Porphyromonas gingivalis* (P.g.),

*Bacteroides forsythus* (i.e. *Tannerella forsythensis*) (B.f.) and *Prevotella intermedia* (P.i.) were analyzed from saliva samples using PCR methods according to Wahlfors et al. (133) and Meurman et al. (134).

### 4.6.2 Salivary biochemical analyses

Amylase was determined immediately after thawing the saliva samples, using an enzymatic colorimetric test (MPR 3 EPS method, Boehringer Mannheim GmbH, Mannheim, Germany), total protein by means of the colorimetric Lowry method and albumin according to Webster (132) using human serum albumin standards. Salivary IgA, IgG and IgM levels were determined by means of the enzyme immunoassay (135). Results were based on at least duplicate assays and standards and controls were used in all the analyses.

## 4.7 HLA-alleles (tissue typing)

HLA typing for A, B, C antigens was performed in all patients according to the standard microlymphocytotoxicity test and for DRB1* alleles at the low resolution level using the commercial PCR / reverse dot-blot hybridization kit (INNO-Lipa, Innogenetics, Belgium) covering all common alleles DRB1*01-DRB1*14 at the Finnish Red Cross Blood Transfusion Service, Helsinki, Finland. The control population for HLA was typed at the same laboratory.

## 4.8 Minor salivary glands

Rheumatic patients underwent minor salivary gland biopsy. Minor salivary gland biopsies were performed according to the procedure suggested by Daniels (136). After local anaesthesia, a 1.5 cm incision was made parallel to the vermilion border in the lower lip, between the midline and the corner of the mouth.

Between 5 and 10 lobes of labial glands were obtained by blunt dissection. After removal, the mucosa was reapposed by 2 to 3 interrupted sutures.

**Technique**

All glands were embedded in paraffine along the same plane, to provide midplane sections through all glands. Sections 5 μm thick were stained with haematoxylin and eosin and were evaluated under the microscope at 4 × magnification, using a graticule to measure the number of foci per $mm^2$. The focus score was defined as the number of agglomerations of at least 50 mononuclear cells per 4 $mm^2$ of glandular tissue. The lymphoplasmacytic foci occurred adjacent to normal appearing acini. Focal sialadenitis was defined as focus score ≥1 (137) (*Figure 2 and 3*). If agglomerations of at least 50 mononuclear cells were observed, but their amount was below one per 4 $mm^2$ of glandular tissue, the focus score is expressed as <1. The histopathology and ranking procedures were performed blind by one investigator (JHH), who was not aware of the diagnosis or symptoms of the patients.

*Figure 2. Focal sialadenitis in small salivary gland biopsy in patient with MCTD*

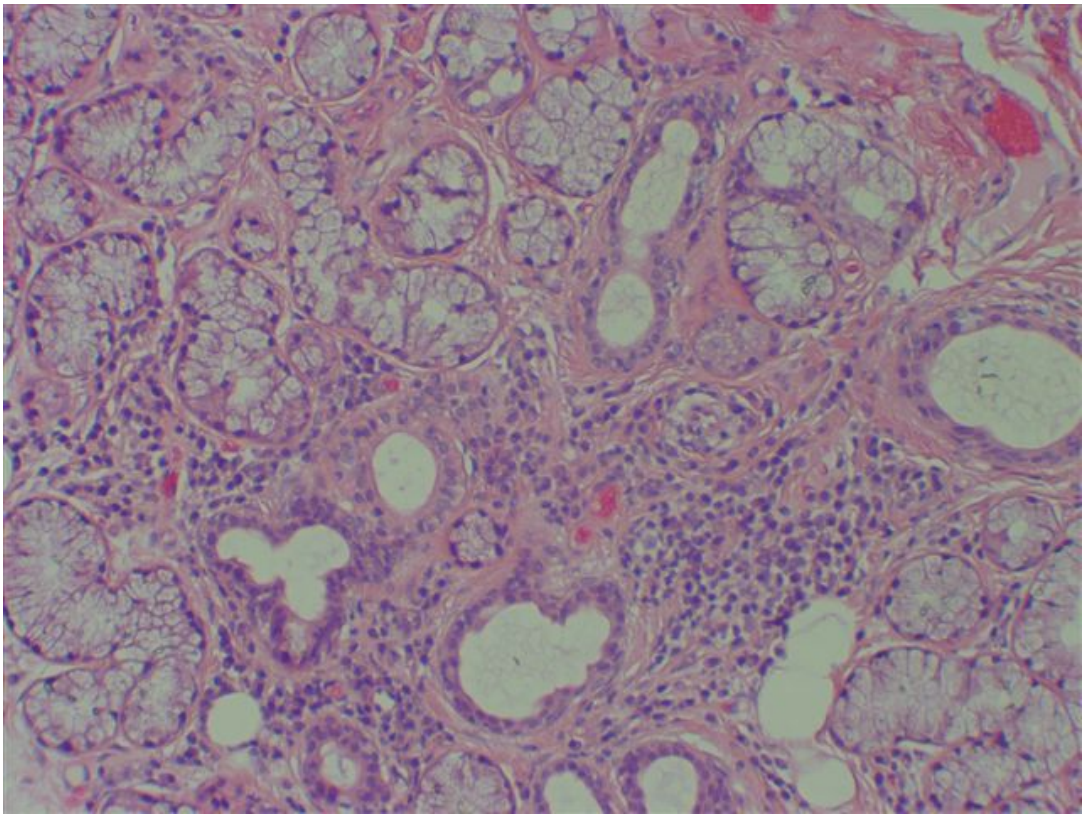
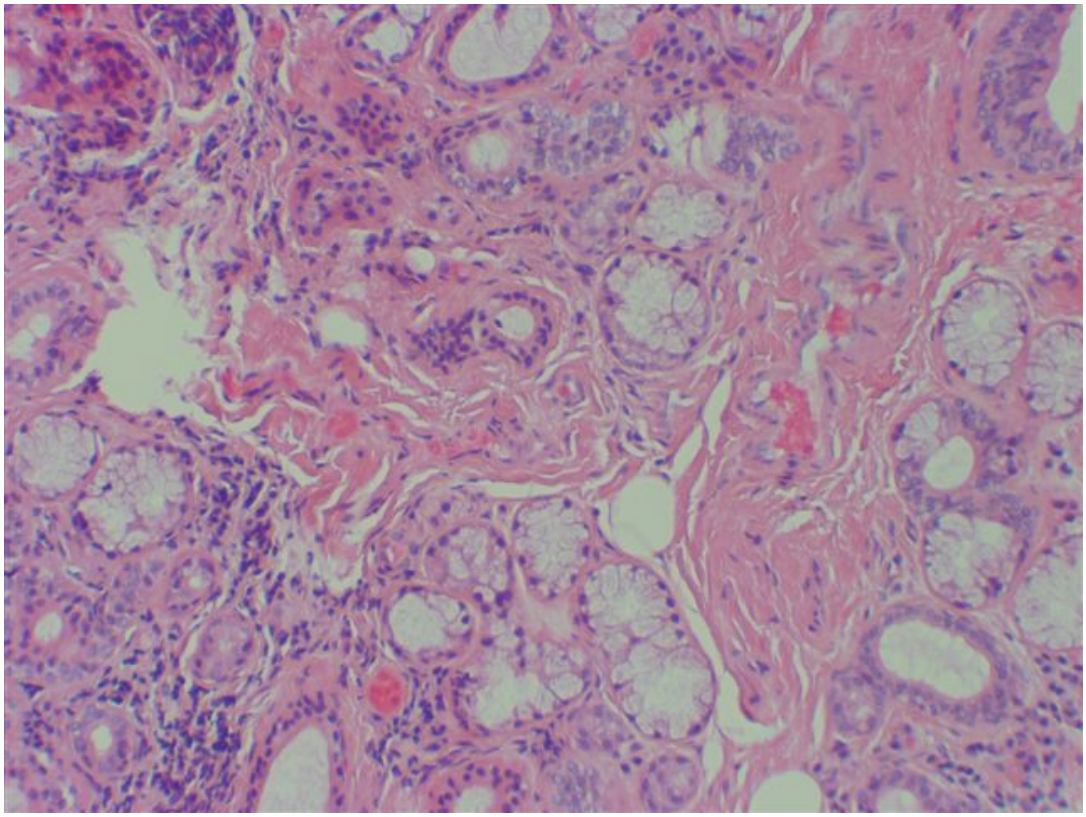


*Figure 3. Focal sialadenitis in small salivary gland biopsy in patient with RA*

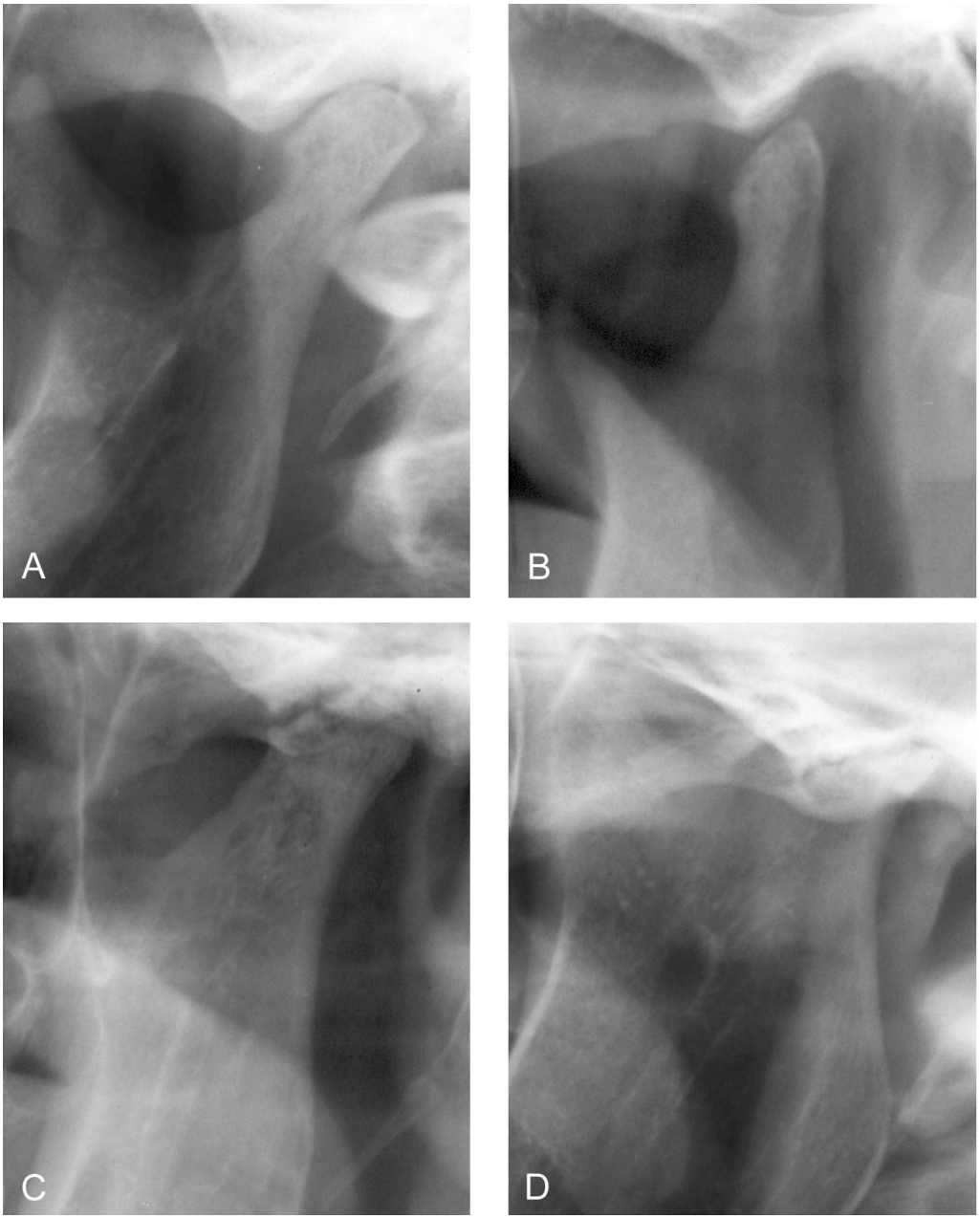


### 4.9 Radiology

TMJs were examined by means of the Scanora Soredex® X-ray equipment by using standard orthopanthomography, and the lateral view program. The radiographs were analysed independently by two observers (LMJH and DH) blinded to the clinical characteristics of the patients and controls. In borderline cases the more conservative option was chosen.

Panoramic tomography of the jaws was taken and lateral panoramic images of both joints (94) were examined in patients. Lateral panoramic tomographs were taken only the rheumatic patients. Erosion in condyles in the radiographs was scored by using an arbitrary scale with five grades from 0 (no erosion), 1 (only very slightly eroded), 2 (erosion in top of the condyle), 3 (half of condyle eroded) to 4 (condyles completely eroded) (*Figure 4*). During analysis scores from 0 to 2 were classed as normal or reflecting mild changes and scores from 3 to 4 as reflecting marked erosion.

*Figure 4a-4d. Examples of TMJ erosions for the 4 grades. A, very slight erosion in condyle (1). B, erosion of top of condyle (2). C, half of condyle eroded (3). D, condyle completely eroded (4).*

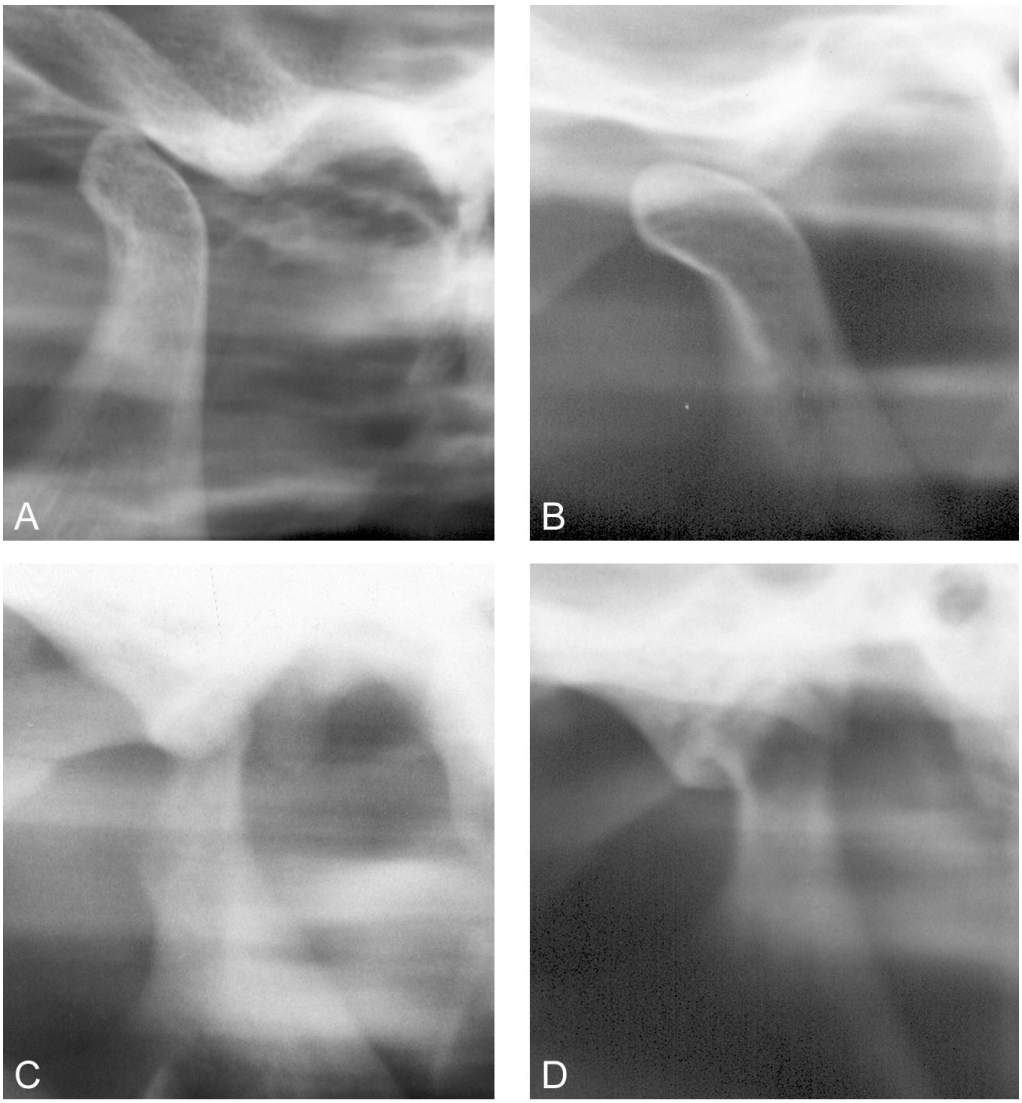


Analysis of the tomograms focused particularly on signs of dental infection foci. Radiolucent cystic lesions, dental furcation lesions, residual roots, retained teeth with enlarged follicles, pericoronitis, horizontal alveolar bone loss, deep vertical periodontal pockets, radiologically visible dental caries, and apical periodontitis lesions were recorded (134).

Condylar movements were recorded by means of JLA and graded from 0 (normal movements) to 3 (no movements). During analyses scores from 0 to 1 were classed as normal or mild and scores from 2 to 3 as marked. The JLA projections are one lateral image of the TMJ with the mouth in closed position and one image with the mouth in maximally open position.

Examples of restricted movements of condyle in lateral panoramic tomographs for the three grades are given in *Figures 5a – 5d*.

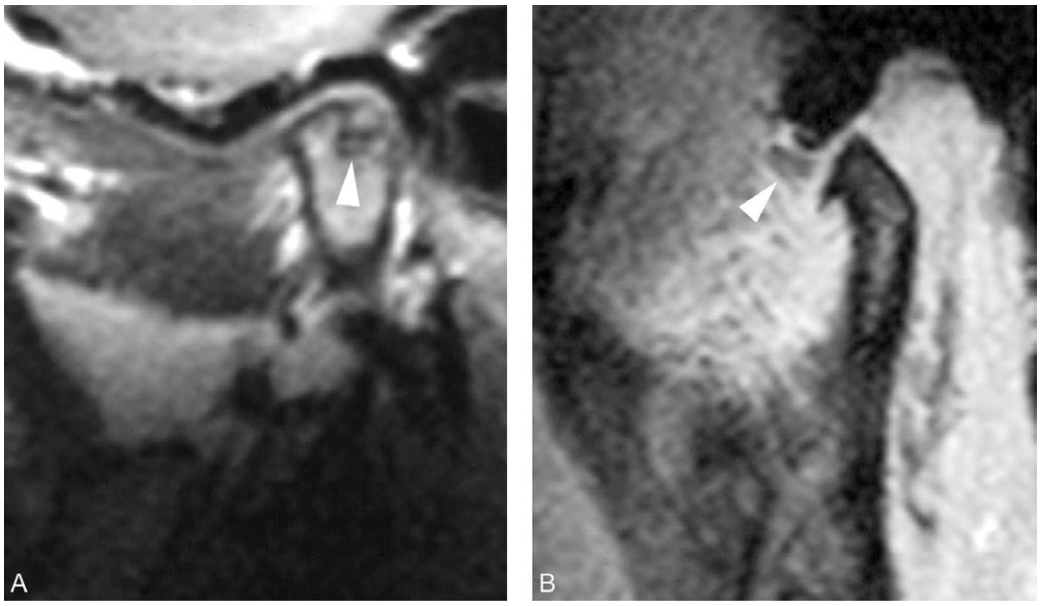
*Figure 5a-5d. Examples of the position of the condyle in the lateral panoramic radiograph view (mouth open). A, over or B, normal joint movement (1) C, light movement (2). D, only light or no movement at all (3).*



MRI of the TMJ was performed with a 1.5T scanner (Siemens Magnetom Vision, Siemens AG, Erlangen, Germany). A dedicated bilateral TMJ coil was used. Proton Density-weighted turbo spin echo, were used in sagittal and coronal cross-sections. T1-weighted slices with were 1.5 mm, thick, with a 2 mm interslices gap. T2-weighted slices with were 1.5 mm, thick, with a 3 mm interslices gap. The protocol for MRI interpretation included description of condyles and articular eminence morphology, translocation, assessment of disc position and bone marrow changes. Two radiologists (LK, PT) interpreted the images independently without knowing the clinical data or panoramic tomography findings and scored the erosions in condyles from 0 (no erosion or mild changes) to 1 (clear erosion). The MR images were evaluated for disc morphology. Perforations were identified when there was abnormal disc structure where the disc was severely destroyed that only remnance or no disc structure at all could be seen (*Figure 6*).

*Figure 6. a. A 50-year-old man with AS. Occasional subjective TMJ symptoms, maximal mouth opening 38 mm, pain and crepitation on palpation in right TMJ. MR image of TMJ in mouth closed position. The discus is totally destroyed and no disc material is visible There is well delineated erosion of the condyle (arrow head).*

*Figure 6. b. A 42-year-old woman with RA. Very sore TMJ muscles on palpation on both sides, maximal mouth opening 44 mm and crepitation on right side on palpation. MR image of TMJ in maximally opened position. The remnants of the disc are anteriorly luxated (arrow head) and translocation of the condyle is decreased. Note also the eroded and flattened condyle with an anterior hook formation.*




**4.10 Statistics**

Data are given as means with standard deviations (SD) or as medians and interquartile ranges (IQR) when appropriate. Statistical significance was determined using the Mann-Whitney test, analysis of variance (ANOVA), the Kruskal-Wallis test, and the $\chi^2$-test when applicable. Odds ratios (OR) for the presence of focal sialadenitis and severe erosion in TMJ in panoramic radiograph and their 95% confidence intervals (95% CI) for different patient groups were analysed with a logistic regression model (NCSS 6.0, Statistical software, Kayswille, UT).

Significances of correlations were calculated using Spearman's rank correlation test. A two-tailed p value below 0.05 was considered to indicate statistical significance. In the HLA frequencies, the corrected probablity (p) value (pc) was obtained by multiplying the p value by the number of HLA alleles tested (n=34) (Bonferroni correction).

### 4.11 Ethics

All subjects had given written informed consent to their participation in the study, and the Ethics Committee of Helsinki University Central Hospital had approved the study protocol.

A panoramic radiograph that had been taken within the previous year had to be available for each control, because the Ethics Committee did not approve studies in which controls are subjected to X-ray. Control group did not undergo minor salivary gland biopsy for ethical reason.

# 5 RESULTS

## 5.1 Symptoms

Information concerning smoking and dental care is shown in Table 11.

Thirty-six patients had subjective oral symptoms (p=0.002). The symptoms were most frequent in MCTD (*Table 12*). Forty-five patients had ocular symptoms (13/25 patients with RA, 12/19 patients with MCTD, 10/19 patients with AS and 10/22 patients with SPA, p=0.73).

The number of patients exhibiting severe TMJ symptoms was significantly higher than the number of the control subjects with such symptoms (p<0.001). The AS patients reported TMJ symptoms most often (7/19, 37%). TMJ clicking and crepitation were reported by the patients with rheumatic disease significantly more often than by the control subjects (data not shown). Decreased subjective mouth opening was reported by 40% of the patients, most frequently by those with AS.

*Table 11. Smoking and dental care habits.*

| | Rheumatoid arthritis (N=15) | Mixed connective tissue disease (N=10) | Ankylosing spondylitis (N=13) | Spondylo-arthropathy (N=12) | Control subjects (N=67) |
|---|---|---|---|---|---|
| No of smoking patients | 1 (7%) | 2 (20%) | 6 (46%) | 3 (25%) | 8 (12%) |
| Use of sugar with tea/coffee | 7 (47%) | 3 (30%) | 7 (54%) | 6 (50%) | 22 (33%) |
| Dentist visits/ year, mean (SD) | 1.2 (0.4) | 1.5 (0.9) | 1.5 (0.9) | 1.5 (0.9) | 1.2 (0.5) |
| Brushig the teeth/day, mean (SD) | 1.9 (0.3) | 1.9 (0.3) | 1.9 (0.3) | 2.0 (0.4) | 2.0 (0.3) |
| Use of the dental floss | 4 (27%) | 4 (40%) | 4 (31%) | 4 (33%) | 13 (20%) |
| Use of the dental sticks | 12 (80%) | 5 (50%) | 8 (62%) | 7 (58%) | 36 (54%) |
| Use of dental intermediate brushs | 2 (13%) | 2 (20%) | 2 (15%) | 0 (0%) | 0 (0%) |

*Table 12. Number of patients reporting subjective symptoms via questionnaire. (TMJ = temporomandibular joint.)*

| | Rheumatoid arthritis (N = 24) | Mixed connective tissue disease (N = 16) | Ankylosing spondylitis (N = 19) | Spondyloarthropathy (N = 21) | Controls (N = 80) |
|---|---|---|---|---|---|
| Oral symptoms | 11 (46%) | 14 (88%) | 8 (42%) | 3 (14%) | 2 (3%) |
| Sounds from TMJ | 14/24 (58%) | 5/16 (31%) | 10/19 (53%) | 10/21 (48%) | 20/80 (25%)Ψ |
| Morning stiffness/tiredness in jaw | 8/24 (33%) | 6/16 (38%) | 5/19 (26%) | 11/21 (52%) | 7/80 (9%)Φ |
| Unable to open mouth sufficiently | 11/24 (46%) | 3/16 (19%) | 10/19 (53%) | 8/21 (38%) | 7/80 (9%)Φ |
| Pain in TMJ area | 12/24 (50%) | 4/16 (25%) | 8/19 (42%) | 9/21 (43%) | 5/80 (6%)Φ |
| Pain in TMJ on chewing | 10/24 (42%) | 5/16 (31%) | 11/19 (58%) | 14/21 (67%) | 17/80 (21%)Φ |
| Facial trauma | 6/24 (25%) | 2/16 (13%) | 7/19 (37%) | 3/21 (14%) | 21/80 (26%) |
| Pain in cheeks | 8/24 (33%) | 7/16 (44%) | 8/19 (42%) | 4/21 (19%) | 17/80 (21%) |
| Ocular symptoms | 13/24 (54%) | 9/16 (56%) | 10/19 (53%) | 8/21 (38%) | 16/80 (19%) |
| Aural symptoms | 6/24 (25%) | 3/16 (19%) | 5/19 (26%) | 3/21 (14%) | 5/80 (6%)# |
| Frequent headache | 9/24 (38%) | 8/16 (50%) | 6/19 (32%) | 6/21 (29%) | 6/80 (7%)Φ |
| Habits (biting nails, chewing pencils, cheeks etc.) | 11/24 (46%) | 10/16 (63%) | 11/19 (58%) | 15/21 (71%) | 37/80 (46%) |
| Number of patients with moderate to severe subjective TMJ symptoms* | 7/24 (28%) | 5/16 (31%) | 7/19 (37%) | 4/21 (19%) | 0/80 (0%)Φ |

*Grades 3 to 5 included.

ΦStatistically significant difference between patient and control groups, $p < 0.001$
ΨStatistically significant difference between patient and control groups, $p = 0.003$
# Statistically significant difference between patient and control groups, $p = 0.01$

### 5.2 Clinical findings

Masticatory-muscle tenderness occurred significantly more often in the patients with rheumatic disease than in the control subjects (73% vs 30%, $p<0.001$). Tenderness of the masticatory muscles was observed frequently in all patient groups, with the lowest frequency (43%) in SPA patients ($p=0.004$ between patient groups) (Paper IV, *Table 3*, page 460).

Values for maximum opening of the mouth (46.46mm (8.59) vs 55.0mm (7.4)) and maximum protrusion (5.23mm (2.78) vs 6.0 mm (2.0)) were significantly lower in the patients with rheumatic disease than in the control subjects ($p<0.001$ in each case). Decreased maximum mouth opening (≤ 33 mm) was found in 6% (1/16) of RA, 0% (0/15) of MCTD, 17% (3/18) of AS and 11% (2/18) of SPA patients (NS). TMJ crepitation on clinical examination was common in all patient groups. Prevalences of laterotrusion, mediotrusion, protrusion and retrusion interferences did not differ between the groups of patients, or between the patient and control groups (NS).

Decreased tear secretion occurred most often in patients with MCTD, and least often in SPA patients ($\chi^2$-test, $p=0.021$) (*Table 13*).

There were no statistically significant differences in the number of patients with missing one or several teeth or clinically or radiographically detected caries lesions between the rheumatic patients and control subjects (Paper II, *Table 2*, page 5). The number of patients with CPI score 3 or 4 was significantly higher in rheumatic patients than in controls ($p<0.0001$) Severe periodontal disease was common in all patient groups being most prevalent in the RA group. In addition, abnormalities in oral mucosa were significantly more common in the rheumatic patients than controls ($p=0.0002$). Positive yeast count was significantly more common in the rheumatic patients than in the control subjects ($p<0.001$).

## 5.3 Saliva

### Salivary flow

A statistically significant difference was observed in the number of patients with low resting salivary secretion rates (p=0.007) and stimulated salivary secretion rates (p<0.001) between the different patient groups and controls (*Table 13*). Decreased salivary secretion (either unstimulated or stimulated) was most frequently observed in patients with MCTD and least often in SPA patients ($\chi^2$-test, p<0.0001).

The AS patients exhibited low resting salivary secretion rates significantly more often than the respective controls (22% [4/18] vs. 0% [0/18], respectively (p = 0.03). The MCTD patients had significantly more often reduced salivary flow both in the stimulated (40% [6/15] vs. 0% [0/15], p = 0.0062) and resting values (60% [9/15] vs. 0% [0/15], p = 0.003) than the respective controls. Only eight patients and five controls used drugs known to affect salivary flow. However, all the patients who had taken such medication also exhibited other features of SS, such as focal sialadenitis and/or a positive result in Schirmer's test. Salivary buffering capacities and pH values were similar in the patients and controls.

### Salivary composition

The patients as a group had significantly lower salivary amylase concentrations (p<0.001), while albumin (p=0.0065), total protein (p<0.001), IgG (p<0.001) and IgM (p<0.001) concentrations were significantly higher than in controls (*Table 14*). Within the patient groups, concentrations of IgG and IgA were highest in the MCTD patients, the RA patients were characterized by significantly (p=0.005) lower salivary amylase concentrations. The MCTD patients had significantly higher salivary concentrations of total protein (p=0.0061), IgA (p=0.018), IgG (p=0.010), and IgM (p=0.0014). The AS patients had significantly higher salivary concentrations of total protein (p<0.001) and IgA (p=0.017) (*Table 14*).

*Table 13. Clinical and laboratory findings*

| | Rheumatoid arthritis (N=25) | Mixed connective tissue disease (N=19) | Ankylosing spondylitis (N=19) | Spondyloarthropathies (N=22) | Controls (N=85) |
|---|---|---|---|---|---|
| Focal sialadenitis | 20 (80%) | 17 (94%) † | 11 (58%) | 9 (41%) | n.d. |
| Decreased salivary secretion* | 3 (12%) | 11 (73%) | 4 (22%) | 0 (0%) | 2 (2%) |
| Decreased tear excretion # | 11 (44%) | 13 (87%) | 6 (32%) | 3 (15%) | 6 (7%) |
| Patients with Sjögren's syndrome** | 7 (28%) | 11(73%) | 5 (26%) | 3 (15%) | n.d. |
| Laboratory tests: | | | | | |
| Positive SSA-ab or SSB-ab | 0 (0%) | 11 (58%) | 1 (5%) | 0 (0%) | n.d. |
| Positive RF | 17 (68%) | 12 (63%) | 3 (16%) | 2 (9%) | n.d. |
| Low C3 or C4 | 2 (8%) | 8 (42%) | 2 (11%) | 1 (5%) | n.d. |
| Positive RNP | 0 (0%) | 11 (58%) | 0 (0%) | 1 (5%) | n.d. |
| Positive Sm | 0 (0%) | 3 (16%) | 0 (0%) | 0 (0%) | n.d. |

* Either unstimulated or stimulated salivary excretion abnormal. Not studied in 4 patients with MCTD and 2 patients with SPA, and 1 patient with AS.

† One minor salivary gland biopsy sample was not representative and was therefore excluded.

• $\chi^2$ – test between the groups.

** Fullfilling the European criteria for secondary Sjögren's syndrome (8).

# Not studied in 4 patients with MCTD and in 2 patients with SPA.

n.d. Not done

*Table 14. Salivary and serum biochemistry (median [IQR]) in patients and controls*

| | Rheumatoid arthritis (N=24) | | Mixed connective tissue disease (N=15) | | Ankylosing spondylitis (N=18) | | Spondyloarthropathy (N=20) | |
|---|---|---|---|---|---|---|---|---|
| | Patients | Controls | Patients | Controls | Patients | Controls | Patients | Controls |
| Salivary: | | | | | | | | |
| Amylase; U/ml | 63.0 (48.0-104.0) | 113.0 (72.0-208.0) # | 67.0 (45.0-122.0) | 111.0 (76.0-158.0) | 97.5 (51.5-154.0) | 137.5 (51.0-162.5) | 62.0 (31.0-87.0) | 83.0 (47.0-103.0) |
| Albumin: mg/l | 152.9 (107.7-177.7) | 118.0 (90.3-153.8) | 154.3 (101.9-204.3) | 129.0(73.0-163.0) | 156.7 (92.4-205.5) | 109.0 (87.0-128.5) | 137.6 (113.7-187.5) | 125.0 (108.0-179.0) |
| Total protein: mg/ml | 1.0 (0.7-1.3) | 0.79 (0.6-1.1) | 0.97 (0.8-1.2) | 0.5 (0.3-0.9) # | 1.3 (0.9-2.1) | 0.7 (0.5-0.9) ♣ | 0.9 (0.6-1.5) | 0.7 (0.5-1.0) |
| Saliva: | | | | | | | | |
| IgA mg/l | 33.0 (19.9-48.9) | 26.0 (17.0-45.3) | 53.0 (43.0-90.0) | 22.5 (14.5-46.3) ξ | 35.8 (26.0-54.6) | 23.0 (16.0-34.0) ξ | 27.0 (18.8-67.0) Φ | 50.0 (23.0-84.0) |
| IgG mg/l | 8.3 (5.1-15.8) | 5.9 (4.3-12.5) | 27.3 (14.0-37.4) | 5.5 (2.4-11.4) # | 8.1 (5.7-20.6) | 6.2 (2.1-8.8) | 10.9 (5.9-17.9) Φ | 7.4 (3.2-11.0) |
| IgM mg/l | 3.1 (1.7-5.4) | 1.7 (0.9-3.3) ξ | 6.6 (3.0-7.2) | 1.8 (0.9-2.9) ♣ | 2.1 (0.8-6.3) | 1.5 (1.0-2.1) | 2.5 (1.4) | 2.1 (1.1-3.1) |
| Serum:IgA g/l | 1.7 (1.4-2.4) | - | 3.6 (2.5-4.5) | | 2.5 (2.1-3.7) | - | 3.0 (2.2-3.6) | - |
| IgG g/l | 10.3 (9.0-11.3) | - | 18.1 (13.2-23.4) | - | 12.9 (10.6-14.6) | - | Ψ 14.7 (11.0-17.9) Ψ | - |
| IgM g/l | 1.2 (0.9-1.4) | - | 1.4 (1.1-1.9) | - | 1.4 (0.8-1.6) | - | 1.2 (0.9-2.0) | - |

ΦStatistically significant difference between patient groups, $p<0.05$
ΨStatistically significant difference between patient groups, $p<0.001$
ξStatistically significant difference between the patient and matched control group, $p\leq0.05$
#Statistically significant difference between the patient and matched control group, $p\leq0.01$
♣Statistically significant difference between the patient and matched control group, $p\leq0.001$

**Relationship between serum and salivary immunoglobulin concentrations**

Serum IgA and IgG concentrations were significantly higher in the MCTD patients than in the other patients ($p<0.001$), while IgM concentrations did not differ significantly between the patient groups. Concentrations of serum IgG correlated significantly with salivary IgG concentrations ($r_s = 0.31$, CI 0.10 to 0.50) and serum IgM levels with salivary IgM levels ($r_s = 0.36$, Cl 0.16 to 0.55). However, no significant correlation was observed between serum and salivary IgA concentrations. There was no statistically significant difference in the levels of serum IgA between the AS patients who had and who had not taken sulfasalazine medication (data not shown).

**5.4 Focal sialadenitis and secondary Sjögren's Syndrome**

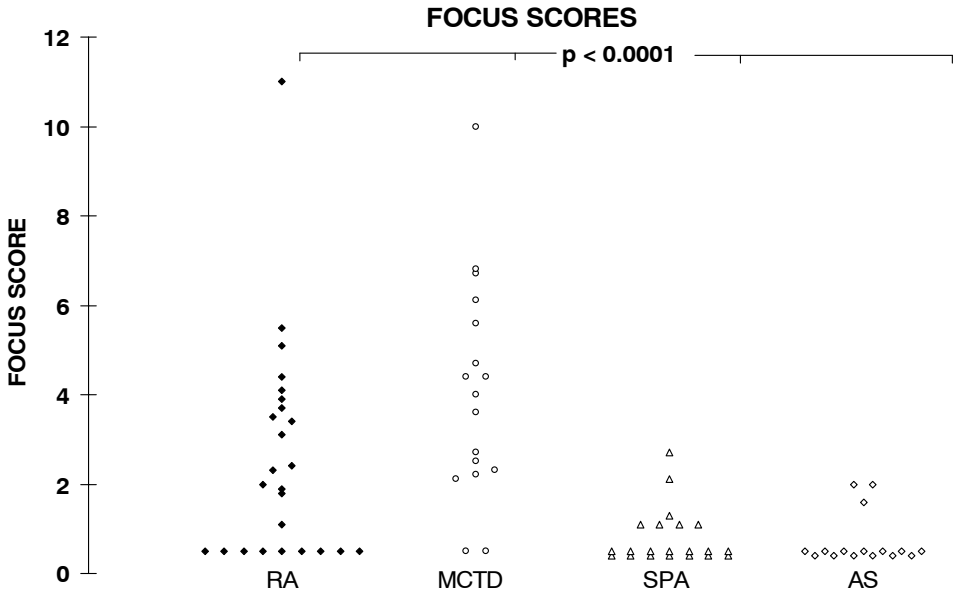
One biopsy sample (MCTD patient) was not representative and was therefore excluded from further analysis. Focal sialadenitis was observed in 68% (57/84) of all patients. It was most frequent in MCTD and least frequent in SPA patients ($\chi^2$-test, $p = 0.0013$). The median focus scores differed also significantly among the study groups, being highest (4.1) in the MCTD group and lowest (<1) in the SPA group (Kruskall-Wallis, $p < 0.0001$) (*Figure 7*). Compared to patients by whom salivary gland biopsy findings were normal, the patients with focal sialadenitis had more often reduced resting salivary flow rates (11/53 versus 1/24, $p = 0.063$) and stimulated salivary flow rates (12/53 vs. 1/24, $p=0.045$).

Patients with focal sialadenitis had more often both decreased salivary secretion (30 % vs. 4%; $\chi^2$-test, $p = 0.0074$) and decreased tear secretion (58 % vs. 35%; $\chi^2$-test, $p = 0.048$) than had patients without it. Focus scores correlated negatively with the amount of both unstimulated and stimulated saliva secretion (Spearman rank correlation test, $r_s = -0.46$, 95% CI -0.27 to -0.61; and $r_s = -0.51$, 95% CI -0.33 to -0.65, respectively).

Focal sialadenitis tended to occur more often in women (41/55) than in men (16/29) ($\chi^2$-test, p = 0.071). In the multiple logistic regression model, increasing age and the MCTD group were independent risk factors for focal sialadenitis (Paper I, *Table 4*, page 747). No associations were observed between focal sialadenitis and the disease duration, the use of corticosteroids or sulfasalazine (data not shown). Significant correlations were found between focus scores and salivary concentrations of IgA ($r_s$ = 0.28, 95% CI 0.06 to 0.47), IgG ($r_{s=}$ 0.34, CI 0.13 to 0.52) and IgM ($r_s$ = 0.40, CI 0.19 to 0.67), and between focus scores and resting ($r_s$ = -0.45, 95% CI -0.61 to -0.25) and stimulated salivary flow rates ($r_s$ = -0.49, 95% CI 0.64 to 0.30).

According to the 1996 European diagnostic classification criteria of secondary SS (37) 28% (7/25) of RA, 73% (11/19) of MCTD, 26% (5/19) of AS and 15% (3/22) of SPA patients had a secondary SS (*Table 13*).

*Figure 7. The variation of focus score in various rheumatic diseases*




**Association between focal sialadenitis and laboratory parameters**

Patients with RF had significantly more often focal sialadenitis than had patients without it ($\chi^2$-test, p=0.002). Patients with focal sialadenitis had higher RF titers than those without it (Mann-Whitney, p<0.001). Similarly, patients with ANA, SSA-AB, or SSB-AB had more often sialadenitis than had patients without these antibodies ($\chi^2$-test, p=0.0041, 0.013, and 0.077, respectively). No associations were observed between focal sialadenitis and low complement levels or the presence of RNP or Sm antibodies. HCV antibodies were negative in all the patients tested.

The subgroup of patients with AS or SPA was further analyzed for risk factors for sialadenitis. The presence of focal sialadenitis was not associated with decreased salivary or tear secretion, the clinical type of disease (axial or peripheral arthritis), age, the use of medication (corticosteroids or

sulfasalazine), the disease duration, presence of ANA, ENA, SSA-AB, SSB-AB, RNP-AB, Sm-AB, positive RF or low complement levels (data not shown).

### 5.5 Radiology

Distinct erosions were observed in four RA patients (17%), three MCTD patients (19%), seven AS patients (37%), eight SPA patients (38%) (*Table 15*) and one control subject (1%) ($p<0.001$). Patients with SPA had the most severe changes. The mean (range) erosion scores were 1.7 (0-4) for RA, 1.3 (0-3) for MCTD, 2.5 (0-4) for SPA, and 1.6 (0-4) for AS patients ($p=0.04$).

Age and sex adjusted ORs (95%CI) for the presence of severe erosion in panoramic radiographs were 19.8 (1.95 to 2.01) for RA, 27.6 (2.45 to 311) for MCTD, 40.7 (4.41 to 375) for AS, and 42.5 (4.79 to 377) for SPA patients as compared with control subjects. Restricted condylar movement was found in lateral panoramic radiographs relating to six RA patients (25%), five MCTD patients (31%), six AS patients (32%) and seven SPA patients (33%) (NS) (*Table 15*). Evidence of distinct erosion in a panoramic tomogram was significantly associated with evidence of restricted condylar movement in a lateral panoramic radiograph ($p < 0.001$). In the lateral panoramic radiographs restricted condylar movement was found in 25% (4/16) of RA, 13% (2/15) of MCTD, 33% (6/18) of AS and 28% (5/18) of SPA patients (NS).

In MRI joint effusion was observed in one (6%) SPA patient. Erosions occurred in all groups, but were most frequent in RA patients, of whom 31% (5/16) showed these changes. Condylar osteophytes affected more than 60% of the patient groups studied (NS). Abnormal shape of the condyles was found in 27% of the patients. Osteophytes were observed in all groups, most frequently in RA patients and least often in SPA patients (NS). Joint space narrowing tended to be less frequent in SPA patients than in the other patient groups ($p=0.093$).

*Table 15. Radiologic and MRI findings in various rheumatic diseases, number of patients (%).*

| | Rheumatoid arthritis | Mixed connective tissue disease | Ankylosing spondylitis | Spondyloarthropathy |
|---|---|---|---|---|
| Severe erosion of TMJ in panoramic image | 4/24 (17%) | 3/16 (19%) | 7/19 (37%) | 8/21 (38%) |
| Restricted condyle movement of TMJ in lateral panoramic images | 7/24 (29%) | 5/16 (31%) | 6/19 (32%) | 7/21 (33%) |
| Decreased movement of disc in MRI | 2/16 (13%) | 2/15 (13%) | 4/18 (22%) | 5/18 (28%) |
| Dislocation of the disc in MRI | 4/16 (25%) | 1/15 (7%) | 2/18 (11%) | 4/18 (22%) |
| Perforation of disc in MRI | 8/16 (50%) | 5/15 (33%) | 8/18 (44%) | 7/18 (39%) |
| Osteoarthrosis in MRI | 7/16 (44%) | 3/15 (20%) | 5/18 (28%) | 3/18 (17%) |
| Joint effusion in MRI | 0 (0%) | 0 (0%) | 0 (0%) | 1/18 (6%) |
| Joint space narrowing in MRI | 13/16 (81%) | 14/15 (93%) | 17/18 (94%) | 12/18 (67%) |
| Thin cartilage of condyle in MRI | 4/16 (25%) | 0 (0%) | 3/18 (17%) | 3/18 (17%) |
| Erosion or cyst of condyle in MRI | 5/16 (31%) | 2/15 (13%) | 5/18 (28%) | 2/18 (11%) |
| Osteophytes of condyle in MRI | 12/16 (75%) | 9/15 (60%) | 12/18 (67%) | 11/18 (61%) |
| Abnormal shape of condyle in MRI | 5/16 (31%) | 2/15 (13%) | 6/18 (33%) | 5/18 (28%) |
| Abnormal shape of glenoid fossa in MRI | 3/16 (19%) | 1/15 (7%) | 5/18 (28%) | 5/18 (28%) |

Disc alterations were common in all patient groups and included perforation, anteriorly dislocated disc, and decreased movement (*Table 15*). Abnormal position of the discs occurred most often in RA patients and decreased movements most often in SPA patients.

**Correlations between clinical findings and MRI**

Reduced maximum mouth opening correlated significantly with the occurrence of disc perforation (normal, either side, both sides; $r_s$ = -0.51, 95% CI –0.67 to –0.30), decreased movement of the disc (-0.38, -0.48 to –0.02), osteoarthrosis (-0.47, -0.64 to –0.26), abnormal shape of the glenoid fossa (-0.42, -0.60 to –0.20), abnormal shape of the condyle (-0.46, -0.63 to –0.24), and erosion of the condyle (-0.36, -0.56 to –0.13). The occurrence of TMJ crepitation on clinical examination was significantly associated with perforation of the disc ($p<0.05$ in the right side only),
decreased movement of the disc ($p<0.05$ in the right side only), joint space narrowing of the temporal surface of the TMJ ($p<0.05$ in the right side only), abnormal shape of the condyle ($p<0.05$ both sides) and condylar osteophytes ($p<0.05$ both sides) in MRI. Tenderness of the masticatory muscles was significantly associated with condylar osteophytes ($p<0.05$ both sides).

Pain in the TMJ during maximum mouth opening was associated with a flattened condyle ($p=0.001$ for left side only). Pain in lateral movements was significantly associated with abnormal shape of the condyles ($p<0.05$ for both sides) and diminished thickness of the condylar cartilage ($p<0.05$ for both sides). No correlations were observed between deviated mouth opening and MRI findings.

**Panoramic tomography and MRI**

Severe condylar erosion (scale 3-4) in the panoramic radiographs was significantly associated with condylar erosion ($p<0.01$ for both sides), diminished thickness of the condylar cartilage ($p\leq0.001$ for both sides), abnormal condylar shape ($p<0.001$ for both sides), and abnormal shape of the temporal surface of the TMJ ($p<0.001$ for both sides) in MRI.

In the lateral panoramic radiographs decreased movement was significantly associated with perforation of the disc seen in MRI ($p<0.01$ for both sides), abnormal anterior placement of the disc ($p<0.005$ for both sides), osteoarthritis of the condyles ($p<0.05$ for both sides), abnormal temporal surface of the TMJ ($p<0.005$ for both sides), abnormal shape of the condyle ($p<0.005$ for both sides) and diminished thickness of the condylar cartilage ($p<0.05$ for both sides).

**Association between clinical and radiographic findings**

In the patients with rheumatic diseases, subjective TMJ symptoms were commoner in patients with evidence of restricted movement in a lateral panoramic radiograph than in patients in whom lateral panoramic radiographs were normal ($p<0.001$). A similar association was also observed in the RA patients ($p=0.043$), MCTD patients ($p<0.001$) and AS patients ($p=0.006$) but not in the SPA patients. Among the more specific signs, clicking of a TMJ was associated with radiographic evidence of distinct erosion in the MCTD patients ($p=0.007$). TMJ crepitation was associated with radiographic evidence of distinct erosion in the AS patients ($p=0.003$). There was a significant inverse correlation between the movement of the condyle in the radiographs (graded as 0 to 3) and maximum clinical mouth opening in the patient groups ($r_s$=-0.27, 95%CI –0.48 to –0.02, $p = 0.034$). Similarly, maximum mouth opening correlated inversely with the severity of erosion in panoramic radiographs ($r_s$=-0.47, -0.64 to –0.25, $p<0.001$).

Laterotrusion movement was significantly associated with radiographic evidence of distinct erosion in the entire group of patients ($p < 0.001$). Interferences were not associated with radiographic evidence of distinct erosion or with evidence of restricted movement in panoramic radiographs.

In panoramic tomography the number of periapical lesions was significantly higher in the total rheumatic patient group than in controls ($p=0.0015$).

## 5.6 HLA-associations

### HLA and diagnosis

AS and SPA patients had a higher frequency of HLA-B27, and RA patients had a higher frequency of HLA-DRB1*04 than did control subjects. The frequencies of the other alleles which were typed did not deviate between any of the patient groups and controls (*Table 16*).

*Table 16. Frequencies of selected HLA alleles in the patient groups and control subjects. Results given as number of patients (percentage).*

| | RA (n = 24) | MCTD (n = 19) | AS (n = 19) | SPA (n = 22) | Controls (n=100) |
|---|---|---|---|---|---|
| HLA-B27 | 6 (25%) | 2 (10%) | 18 (95%)* | 20 (91%)* | 14 (14%) |
| HLA-DRB1*01 | 9 (38%) | 8 (42%) | 9 (47%) | 11 (50%) | 35 (35%) |
| HLA-DRB1*04 | 15 (63%)** | 2 (10%) | 7 (21%) | 4 (18%) | 29 (29%) |
| HLA-DRB1*06 | 3 (13%) | 8 (42%) | 5 (26%) | 8 (8%) | 23 (23%) |
| HLA-DRB1*08 | 1 (13%) | 5 (26%) | 6 (32%) | 9 (41%) | 22 (22%) |

*Pc = 0.0006 **Pc = 0.06 compared with control subjects

### HLA and TMJ erosion

In the whole patient population, HLA-DRB1*01 was significantly associated with erosions in panoramic image: 16/36 (44%) of patients with HLA-DRB1*01 *vs*. 6/46 (13%) of patients without HLA-DRB1*01 had TMJ erosions ($p = 0.0014$; $p_c = 0.048$). In the subgroup of patients with disease duration 10 year or lower, HLA-DRB1*01 was significantly associated with TMJ erosions (5/17 vs. 2/22, p=0.031), when as in those patients with disease duration over 10 years this association tended to be statistically significant (11/19 vs. 4/15, p=0.069). This effect was mainly due to a high association in the SPA subgroup, where HLA-DRB1*01 carried a significant risk for erosions: 8/10 (80%) of HLA-DRB1*01 positive patients vs. 0/11 (0%) of HLA-DRB1*01 negative patients had

erosions (p=0.0002; $p_c$=0.0068). DRB1*06 was protective against erosion: 0/8 (0%) of SPA patients with this allele showed erosive findings *vs*. 8/13 (62%) of patients without this allele (p=0.018; $p_c$=0.061).

**HLA and oral and salivary findings**

When all patients were analysed as a group, the presence of focal sialadenitis was significantly associated with HLA-DRB1*03 (presence of sialadenitis in 12/12 [100%] in HLA-DRB1*03 positive patients *vs*. 45/70 [64%] in HLA-DRB1*03 negative patients, p = 0.013), while HLA-DRB1*08 was slightly protective (10/20 [50%] *vs*. 47/62 [76%], p = 0.029).

RA patients with HLA-DRB1*04 had more often increased salivary IgG (8/16, 50%) compared with HLA-DRB1*04 negative patients (1/8, 13%) (p = 0.074). A reverse trend with respect to IgA was observed in AS patients: 1/7 (14%) of patients with HLA-DRB1*04 had elevated salivary IgA compared with 6/11 (55%) of patients without HLA-DRB1*04 (p=0.088).

No associations were observed between HLA alleles and salivary total protein, amylase, IgM, or albumin concentrations (data not shown). Neither were associations found between the presence of periapical infection foci and the HLA alleles (data not shown).

# 6. DISCUSSION

## 6.1 Validity of the data

In the study reported here routine examination protocols and methods were used generally accepted in stomatognathic physiology.

The rheumatic patients, with or without TMJ problems, were consecutive patients from the Outpatient Department of Rheumatology. All patients were examined at the same time by only one person using the same material and methods. It is possible that medication may have influenced the results of salivary or tear secretion, but this was carefully recorded. The use of sulfasalazine and corticosteroids had no effect on the occurrence of focal sialadenitis within each of the study groups.

Salivary gland biopsies of the lower lip were taken in a standardized way. All of the biopsies were representative except one, which was excluded. The labial salivary gland biopsy procedure described here is safe and effective, provided that the biopsy is performed through clinically normal mucosa. The specimen should contain enough separate glands for interpretation, and the histopathologic examination includes determining a focus score. Focal sialadenitis in an adequate labial salivary gland specimen is said to have a good specificity and sensitivity for SS when the focus score is at least one (128). However, patients with SS can have normal focus score with advanced disease (136) or focal sialadenitis with normal salivary flow disease (136) indicating a low specificity and sensitivity of the histology in the diagnosis of SS.

Conventional radiographic methods have been used to demonstrate TMJ abnormalities in series of patients with RA (37, 138-140), AS (37, 140, 141) and psoriatic arthropathy (37, 139-142). The panoramic radiographs were examined by two investigators blinded to the clinical characteristics of the patients. In borderline cases the more conservative option was chosen. We used an arbitrary scale with five grades.

MRI has proved valuable in the assessment of the TMJ in patients with rheumatic diseases (37, 120, 121). In addition to joint effusion and bony abnormalities, various stages of disc destruction have

been shown to be indirect signs of synovial membrane proliferation and pannus formation (37, 120, 121). It has, however, been difficult to identify the thickened synovium itself, indicating that conventional MRI without gadolinium enhancement is limited in depicting early changes of rheumatic TMJ disease (114). Our results on chronic patients are in agreement with this.

### 6.2 Focal sialadenitis

Focal sialadenitis was common in patients with various rheumatic diseases, being most common in the MCTD patients But surprisingly it was also common in the AS and SPA patients. The presence of secondary SS was also high in all study groups. Focal sialadenitis was significantly associated with decreased salivary and tear secretion. Significant associations were observed between focal sialadenitis and RF and its titer; and the presence of ANA, and SSA and SSB antibodies. This observation was confined to the RA and MCTD patient group. Increasing age and MCTD were independent factors for focal sialadenitis. There was also a correlation between the HLA allele and focal sialadenitis.

Our results confirm previous findings on the high prevalence of focal sialadenitis and decreased salivary excretion in MCTD patients (19, 142) (Paper I, *Table 2*, page 746). Konttinen et al. (19) observed focal sialadenitis in nine and decreased salivary excretion in seven out of ten MCTD patients. These are comparable with the 94 % and 61% prevalence rates, respectively, that was observed in our 18 MCTD patients. In the present study, 80 % of the RA patients had focal sialadenitis, and 40% had sialadenitis combined with decreased salivary or tear secretion. These figures are higher than those by Andonopoulos et al. (3) who found focal sialadenitis in 31% and sialadenitis combined with clinical manifestations of SS in 24% of RA patients. The difference can be explained by the scoring systems.

Andonopoulos et al (3) used Tarpley's classification (143) from 1974, which accepts higher number of inflammatory cell aggregates as pathological compared with the presently widely used

scoring system applied by us. In agreement with previous literature (3,19,143), the focus scores in our patients with focal sialadenitis in association with MCTD or RA were distinctly abnormal. This contrasts with the minor increase in the scores in patients with AS or SPA. Thus, while abnormal scores occurred in all the patient groups, patients with MCTD or RA differed distinctly from those with AS or SPA.

A few studies have investigated the occurrence of focal sialadenitis in patients with AS or SPA (144,145). In the present study, 58% of the AS and 41% of the SPA patients had focal sialadenitis (Paper I, *Table 2*, page 746). Whaley et al. (146) observed a distinct (grade III) focal sialadenitis in two out of twelve AS patients, of which neither had decreased salivary or tear secretion. Brandt et al. (71) found also a definite focal sialadenitis (focus scores from 2 to 13) in seven (7%) out of 105 SPA or AS patients. However, Brandt et al. (71) collected biopsies only from patients, who had a combination of both symptoms of dry mouth and/or eyes and positive ANA antibodies. The differences in the higher frequencies of focal sialadenitis between the present study compared with the low figures by Whaley et al. (146) and Brandt et al. (71) can be explained by the different criteria for the definition of abnormal focus score. We have accepted all patients with the focus score of $\geq$1, as suggested by the European classification criteria 1996 (7). Despite the high occurrence of focal sialadenitis in the SPA group, none showed decreased salivary secretion, and the median focus score was quite low, suggesting that the severity of sialadenitis was mild in this group. However, 23 % of the SPA patients had decreased tear secretion. The moderately increased focus scores observed in AS and SPA may be an indicator of mild sialadenitis. They can be also interpreted as reflecting poor specificity of focus scores, because of the low association with clinical findings (146, 147).

On the other hand, the focus score can be increased prior to the development of oral symptoms (148), indicating a need for follow-up of the patients with abnormal focus score in the present study.

In the normal population, both tear secretion and salivary secretion are physiologically reduced in the elderly (149). Vitali et al. (128) found that the presence of inflammatory foci in lip biopsies of patients without Sjögren's syndrome did not correlate with age, whereas Syrjänen (146) observed that foci of inflammatory cells increased with ageing, as well as with acinar atrophy, ductal dilatation, and degree of fibrosis, among 78 healthy individuals. Disease duration did not correlate with focal sialadenitis in the present study, which is in accordance of the findings of Gerli et al. (147).

In patients with RA, the presence of ANA was observed in 44%, a figure comparable to that in the literature (150), while SSA/SSB antibodies were not present in RA. SSA/SSB antibodies are most common in patients with primary SS and SLE (151, 145) but occur infequently in patients with RA (57) (Paper I, *Table 1*, page 745). In accordance with previous reports (152), we observed SSA/SSB antibodies in 58% of the patients with MCTD. We used immunodiffusion to measure these antibodies. Immunodiffusion is less sensitive than ELISA to detect SSA and SSB antibodies (152). Immunodiffusion detected these antibodies only in 0-2 % of RA patients, while the frequency was 22-28 % when measured by ELISA (152, 155). The antibody levels have been shown to change in association with changes in the disease activity of patients with SS and SLE (154). The absence of SSA and SSB antibodies is a further evidence in favour of poor agreement between histology and autoantibodies as discussed previously (155).

In accordance with the findings of Saito et al. (155), we observed an association between the presence of RF, ANA, SSA-ab or SSB-ab and focal sialadenitis in labial salivary gland biopsies. Patients with focal sialadenitis also had higher titers of RF than had patients without sialadenitis. Shah et al. (152) and Gerli et al. (147) also found significant associations between focal sialadenitis in labial salivary gland biopsies and the presence of ANA, SSA, and SSB antibodies. An autoimmune focal sialadenitis, as confirmed by high focus scores in labial salivary gland biopsies

in the present study, seems to be the most likely reason for decreased salivary secretion in patients with MCTD or RA.

### 6.3 Oral health and saliva

In primary SS incidences of caries and changes in the oral mucosa are relatively high (80, 87, 146). There is an increasing risk for oral and dental infections, when salivary flow is decreased. However, in most studies SS does not appear to increase the risk of periodontal disease (87, 88). But there is a good evidence to suggest that individuals with moderate to severe periodontal disease are at higher risk of suffering from RA and vice versa (10, 11).

In the present study periodontal disease commonly affected all rheumatic diseases, also patients with seronegative arthritides (Paper II, *Table 2*, page 5). Fifty-six per cent of AS and 45% of SPA patients showed a CPI score of 3-4 indicating serious periodontal condition. The presence of secondary SS was not a risk for periodontal disease in our study (Paper II, *Table 6*, page 7). Konttinen et al. (19) studied 10 patients with MCTD: All dentulous patients (8/10) had pathological gingival pockets (CPI score 3 or 4), two patients showed fungal growth, and four had abnormalities in oral mucousa. In the present study, 53% of the MCTD patients had periodontal disease, 98% had positive yeast count, and 20% mucosal alterations. Similarly the rheumatic patients had slightly higher number of missing teeth per patient than among controls.

Patients with MCTD had low salivary flow rates, high concentrations of salivary IgG and IgA that differed most from those in the controls, but salivary flow rates were also low in the AS patients. In the saliva samples from the patients concentrations of amylase were lower while concentrations of total protein, albumin, IgA, IgM, and IgG were higher than those of controls.

Salivary secretion rates correlated negatively with lip-biopsy focus scores. A close correlation between minor salivary gland inflammation and whole salivary secretion has also been observed.

Similar to the situation in other organs, the salivary glands can compensate functionally for modest loss of parenchyma. In the early stages of disease, stimulated flow rates may therefore be normal or only slightly reduced. In later stages, however, there is a much greater loss of tissue and stimulated flow rates may be significantly reduced. AS patients may therefore experience subclinical minor salivary gland inflammation associated with low resting salivary secretion rates while MCTD patients may exhibit long-standing sialadenitis resulting in decreased secretion from the larger salivary glands. To confirm this, however, further studies are needed.

Amylase is the most important digestive enzyme in saliva, and a major component of parotid saliva. Amylase concentration is a marker of protein synthesis in the acinar cell (73). The patients had lower concentrations of salivary amylase than controls (Paper II, *Table 4*, page 6). This finding was most pronounced in the RA and MCTD patients indicating impaired functioning of the salivary gland acini in these individuals. Focal sialadenitis was more frequently observed in these groups than in the AS or SPA patients (Paper II, *Table 3*, page 6). In contrast to our observations van der Reijden et al. have reported that concentrations of salivary amylase in cases of secondary SS were similar to those in controls.

Elkon et al.(75) found that salivary IgA concentrations were higher in RA patients with dry eyes than in control subjects and that even RA patients without dry eyes had high concentrations of salivary IgG. High levels of IgA, IgG, and IgM have also been reported in whole saliva from patients with secondary SS (75, 78). In a normal population, concentration of IgA in saliva is inversely related to salivary flow rate. Stimulating flow results in dilution of IgA both in the parotid and whole saliva (78). Salivary IgA, IgG, and IgM concentrations were significantly higher in patients with rheumatic disease than in controls. Particularly high concentrations of both IgA and IgG in saliva were observed in the MCTD patients. In line with our findings, Ben-Aryeh et al. (80) have suggested a positive correlation between focus score and salivary IgA concentration. The

increases in salivary IgA and IgG concentrations detected in primary and secondary cases of SS could result from massive infiltration of salivary glands by B cells, or leakage from serum into the damaged glands (81). High numbers of IgG-producing plasma cells have been observed in lymphocytic infiltrates of minor salivary gland biopsy specimens in patients with secondary SS (82). High serum IgA concentrations are characteristic in active AS (83). It has been suggested that it results from stimulation of the gut immune system by Gram-negative bacteria in the gut (83). Use of sulfasalazine by patients with active AS has been shown to restore the levels to normal of IgA in serum (82) and of secretory IgA in the gut (84). However, in the our study no significant differences were seen between serum and salivary levels of IgA in the AS patients with respect to current consumption of sulfasalazine.

The patients had significantly higher concentrations of salivary albumin, a marker of plasma ultrafiltrate. This finding was most marked in the AS patients. The high levels of salivary albumin may indicate decreased mucosal integrity in the oral cavity, like what is seen in the gut of AS patients (78, 83). High salivary albumin concentrations have previously been reported in RA, SS and control subjects (76) and, for example, in patients treated for lymphoma (134).

### 6.4 HLA-alleles

MacGregor et al. (157) have investigated the association between allotypes of HLA-DR4 and radiological erosion in the peripheral joints of patients with RA. They found that in all patients with RA, DRB1*0401/0404 genotype was associated with a substantially increased risk of being rheumatoid factor positive, and of having subcutaneous nodules and radiological erosion. They suggested that HLA-DRB1*04 might be a marker of severe RA. However, in previous studies from Finland by Möttönen et al. (34) such an association was not observed.

The association between HLA-antigens and TMJ erosion has not been studied earlier. Our results showed that instead of HLA-DRB1*04, HLA-DRB1*01 was significantly associated with distinct

erosions in the TMJ in patients with rheumatic diseases (Paper II, results, page 26). In the subgroup of SPA patients, HLA-DRB1*01 carried a high risk for erosion, whereas DRB1*06 provided protection against it. This is in agreement with a recent report by Henry et al. (158) where internal derangement with severe TMJ symptoms in patients with various diseases were associated with HLA-DR1 and HLA-DR4. While our patients were collected from normal routine outpatient clinic, it is interesting that the genetic markers turned out to be the same as in the highly selected patients with severe TMJ disorders (158).

HLA-DRB1*04 was associated with increased salivary concentrations of IgG in the RA patients, while in AS patients, HLA-DRB1*04 was protective against increase in salivary IgA. We also observed a significant association between HLA-alleles and the presence of focal sialadenitis. While previous studies have presented evidence to genetic associations with immunological aberrations in both primary (159-160) and secondary (159-160) SS, we saw here evidence that the development of focal sialadenitis, as a feature of secondary SS, in patients with a wide spectrum of arthritides would be genetically determined.

### 6.5 Temporomandibular disorders

Patients suffering from the various rheumatic diseases exhibited higher prevalences of stomatognathic problems and radiographic evidence of TMJ destruction than the matched controls. The patients with MCTD exhibited lower prevalences of individual symptoms, abnormal findings on examination and erosions than the other patients. There were no major differences between the other groups of patients.

In previous studies, prevalences of clinically evident TMJ involvement in patients with RA have been reported to be between 2% and 98% (118). Results of most studies indicate that more than 50% of patients with RA exhibit clinically evident TMJ involvement (16,161). The prevalence of TMJ involvement in patients with AS has been found to range from 4% to 35%, depending on the

diagnostic criteria used, the population studied and the means employed to assess TMJ involvement (118, 125).

Crum and Loiselle (166) reported that 16% of patients with AS complained of pain and tenderness in the TMJ region, with limited jaw opening. Davidson et al. (125) reported that 10% of patients with AS exhibited restricted jaw opening. Ramos-Remus et al. (126) studied 65 AS patients and 22 control subjects. They found TMJ involvement to be common in the AS patients and associated with findings suggestive of more severe disease. Könönen et al. (117) have also reported that clinical signs of temporomandibular dysfunction are common in patients with RA, psoriatic arthritis and AS.

The patients in this study reported often sounds, pain, stiffness, and restricted condylar movement. They also complained of headache more often than the controls. Pain in the preauricular area is common, and often experienced as ear pain (90) (Paper IV, *Table* 2, page 457). The patients studied also reported auricular pain more often than the controls. It has been suggested that compression of retrodiscal tissue, in the bilaminar zone, may be the cause of such pain. Other suggested causes are inflammatory change secondary to internal derangement, stretching of the joint capsule and synovitis. Inflammation could explain the high prevalence of TMJ symptoms in our patients because the control subjects exhibited much lower prevalences of various symptoms. Another important source of pain is disorder of the masticatory muscles. If a joint is not functioning normally a patient will often develop muscle tenderness that can be experienced as facial pain. This was noted in the study described here, and has been recorded earlier by Könönen (117). It is often difficult to distinguish between muscle and joint pain on physical examination (90). Tenderness of the masticatory muscles in a patient with rheumatic disease is therefore a good indicator of TMJ inflammation. This is particularly true for inflamatory arthritis and other autoimmune diseases

where the muscles may also have a low grade inflamation (162). It could also reflect the existence of permanent TMJ destruction.

Other suggested causes of TMJ disorders are direct facial trauma. A history of facial trauma was reported by 12-25 % of the patients in our study and by 26% of the control subjects. However, 37% of the AS patients reported a history of facial trauma. Results of some studies suggest that TMJ abnormalities can result in changes in dental occlusion (117). In this study, an association between lateral excursion movement and erosion of the TMJ was found (Paper IV, *Table 5*, page 461). This was also in agreement with Könönen (117) who found no correlation between any dental factor studied and clinical signs of stomatognathic disorders. No statistically significant differences were found between the groups of patients and the controls in relation to prevalence of interference, confirming previous findings (117).

**6.6 Radiology**

Results of most studies indicate that the prevalence of radiographically evident TMJ abnormalities ranges from 50% to 80% in RA patients (16, 163, 164). In another study, Wenneberg et al. found panoramic radiographic changes more frequently in patients with RA (66%), psoriatic arthritis (38%) and AS (30%) than in controls (12%) (163). In AS patients Wenneberg and Kopp (17) also observed a good correlation between subjective symptoms and extent of radiological changes to the TMJ. Wenneberg et al. (165) found radiographic erosions of TMJ in 56% of RA and 18% of AS patients, and in 1% of control subjects. RA patients showed also commonly flattening of condyles, subcortical cysts and cortical sclerosis. Konttinen et al. (19) observed radiographic TMJ changes in seven out of ten MCTD patients, four of them with erosions. Locher et al. (166) found erosions of the TMJ in 20% of AS patients. There are only a few studies relating to SPA patients other than those with psoriatic arthropathy. In a recent study, it was found that patients with Reiter's disease

frequently exhibited TMJ symptoms and that 33% had erosions (164). These figures correspond fairly well with ours, although the occurrence of erosions in the TMJ was much lower in our RA patients (21%). The occurrence of TMJ erosions was highest among patients with HLA-B27 associated diseases (AS and SPA), and considerably higher than that reported by Wenneberg et al. (164).

In addition to standard TMJ radiography, panoramic and lateral panoramic radiography can be valuable in the initial screening for osseous abnormalities such as fractures and advanced degenerative joint disease. Such radiography can also be used to study inflammatory TMJ changes (90). Wenneberg et al. (163,167) used panoramic radiography to compare 90 patients with AS with age- and sex-matched controls. Radiographic changes were observed in 25% of patients and 11% of controls. In our study, we observed a high prevalence of erosion in both the AS and SPA patients but in only 1% of the controls. Despite the differences between the patients in our study and that of Wenneberg et al. (164) the associations between clinical findings (tenderness of the masticatory muscles and deviations in mouth opening) and radiographic TMJ erosions are very similar. We also found that abnormal opening of the mouth correlated with joint destruction as measured using lateral panoramic radiographs. Clinical examination would therefore seem to be a suitable method for screening patients for further examination and treatment of TMJ dysfunction.

In the only study, on MCTD patients, reported in the literature, radiographic TMJ changes were found in seven out of 10 instances (19). Erosion of the condyle similar to changes seen in RA patients was noted in four of 10 MCTD patients (19). Limited condylar function was noted in only one of the latter patients there was (19). Our findings are in accordance with those by Konttinen et al. (19). MCTD is a disease in which clinical features vary considerably between patients, and with time. Some patients end up with erosive peripheral arthritis (123). A high prevalence of TMJ changes was therefore to be expected.

It has been reported that in a patient with unilateral symptoms an asymptomatic contralateral joint often shows signs of internal derangement during clinical and radiographic examinations (167-169). These studies employed a variety of methods in addition to tomography.

Although complete condylar destruction or evident bone erosion at different locations within the joint may be considered typical of rheumatic disease involving the TMJ, the bone abnormalities may also be quite similar to those found in degenerative joint disease. Therefore, in previously reported series of rheumatic patients with TMJ problems it may not necessarily have been the results of the rheumatic process that were described (141).

**6.7 MRI**

In this study MRI images were evaluated for condyle and disk morphology and position (Table14) (Paper V). MRI of the TMJ allows direct visualisation of the disc before and after treatment (2). Perforations were identified when there was abnormal disk structure where the disk was severely destroyed that only remnance or no disc structure at all could be seen. The use of a contrast medium e.g. gadopentetate dimeglumine would have improved the detection of these perforations. However, the use of this contrast was not available at the time of the study. The use of CT-scan would have no doubt rendered better diagnostic results to identify bony erosions (170, 171). However, the risk of unnecessary exposure to high doses of radiation limited our choices when planned this study. The use of MRI is a non invasive alternative method compared to CT-scan. MRI is also better in showing the soft tissue damages, which is important in imaging patients with rheumatic diseases (16,168).

A good correlation between clinical symptoms and TMJ changes by imaging was observed. The association between clinical signs and symptoms of temporomandibular diseases and radiographic findings of the TMJ has been widely discussed, and conflicting results have been presented

(169,161). In epidemiological studies on adult populations, tenderness to palpation of the TMJ has been found in 10-45% of patients examined (170, 172). In patients with TMD, tenderness in the TMJ has been recorded in up to 75% of all patients examined (174).

Ramos-Remus et al. (172) studied 11 AS patients with severe cervical spine involvement. TMD were reported by seven of the patients and ten had abnormalities on MRI of which six were classified as grossly abnormal. In this study the clinical disease of 18 AS patients was less severe. Thus, the observed MRI findings were also mild to moderate.

Larheim et al. (37) studied 28 symptomatic patients with rheumatic diseases (21 with RA, four with psoriatic arthropathies, two with AS and one with Reiter's disease). MRI showed bony abnormalities in 27 of the 36 TMJs studied. The reported abnormalities included joint effusion, disc abnormalities, and condylar degenerative findings. The occurrence and findings were well in accordance with the present study for RA patients.

In the present study, both SPA and MCTD patients commonly showed articular, disc and bony abnormalities in MRI, although these findings were less frequent and usually also less severe than in RA and AS patients. However, MCTD patients frequently showed condylar osteophytes (60%), joint space narrowing (93%), and perforation of the disc.

# 7. CONCLUSIONS

1. Focal sialadenitis affects a high proportion of MCTD, RA, AS, and SPA patients. Its occurrence is significantly associated with RF, as well as with ANA, SS-A and SS-B antibodies. The association is most evident in RA and in MCTD. Because of the common problems in all the patient groups, the patients should be screened for ocular and oral symptoms and if symptomatic, should be referred to specialist care.

2. Signs of periodontal disease, and abnormalities in salivary flow and composition, were all more common in patients with rheumatic diseases as compared to healthy control subjects.

3. Pain, crepitation and decreased condylar movement were frequent clinical findings in the patient groups. The presence of these findings in Rheumatoid patients indicates the need for radiography (panoramic tomography and lateral panoramic tomography), which is usually sufficient to show rheumatic changes. There was a good correlation between panoramic radiographs and MRI. MRI was able to demonstrate articular cartilage changes, disc abnormalities and joint effusion. Thus, if panoramic radiographs in a symptomatic patient with rheumatic diseases are within normal limits, MRI can provide valuable additional information about the TMJ. MRI can be useful when planning a surgical intervention of the disc or synovial membrane. In addition, in a patient with acute arthritis and symptoms of TMJ, MRI could also be used to detect acute joint inflammation.

4. HLA-DRB01 alleles was associated with distinct radiographic erosions in the TMJ. HLA-DRB01*03 alleles was associated with the presence of focal sialadenitis, as well as increased concentrations of salivary immunoglobulins. Genetic background may contribute to the

development of TMJ erosions and is involved in salivary composition in patients with various rheumatic diseases. HLA-DRB1*01 antigen seemed to have an impact on the development of erosions in TMJ and especially in patients with spondyloarthropathies.

5. The prevalence for TMJ involvement in rheumatic patients varies from 0-75% based on radiological changes and depends on the type of rheumatic diseases. It is important for dentists to follow-up dental occlusion and TMJ disorders and to compare the disease activity in all rheumatic patients.

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## APPENDIX

1. Personal data (ID, adress, telephone number…)
2. Medication
3. Allergy
4. Questions

- Sounds from the TMJ (ie. clicking, crepitation)?
- Tiredness of jaw?
- Do you feel pain in the TMJ area and TMJ, when opening mouth as wide as you can (maximum opening)?
- Difficulties opening the mouth?
- Pain in the TMJ area and TMJ?
- Do you feel (or have you felt) pain or tiredness in jaws when chewing food or gum?
- Other different feelings in TMJ and jaw area? If yes, what?
- Contiquous headache?
- Ear problems? If yes, what?
- Eye problems? If yes, other questions were asked:

- Have you had daily: persistent, troublesome dry eyes?
- Do you have a recurrent sensation of sand or gravel in the eyes?
- Do you use tear substitutes?

- Oral symptoms? If yes, other questions were asked:

- Have you had a daily feeling of dry mouth?
- Do you frequently drink liquids to aid in swallowing dry food?

- Habbits:

- Bruxism

- Clenching of teeth
- chin or lip biting
- nail biting
- biting of pensil or something like that?

- Do you feel (or have you felt) pain temporal area?
- Have you ever get any hit to the face?
- How do you describe problems in the TMJ and jaws?

0= no problems at all

1= very light problems

2= light problems

3= moderate problems

4= nearly difficult problems

5= very difficult problems