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Salivary gland and temporomandibular joint involvement in rheumatoid arthritis: relation to disease activity

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OBJECTIVES: To study temporomandibular joint (TMJ) involvement, salivary gland dysfunction and oral mucosal lesions in rheumatoid arthritis (RA), and to investigate the relationship to general disease activity.

SUBJECTS AND METHODS: The TMJ dysfunction index (D_i), mean salivary flow and disease activity score (DAS28), were calculated for 50 RA-patients, and 23 non-RA patients (controls).

RESULTS: Median D_i was 5.5 (range: 0–21) for the RA-patients compared with 2.0 (range: 0–9) for the controls ($P < 0.0001$). Pain on movement of the TMJ ($P = 0.015$), muscular pain ($P = 0.006$), TMJ pain ($P = 0.019$) and D_i as a total ($P = 0.009$), significantly correlated with DAS28. Mean resting whole saliva (RWS) flow was 2.6 (s.d. 2.4) ml per 15 min for the RA-patients and 4.5 (s.d. 3.0) for the controls ($P = 0.003$). RWS correlated positively with haemoglobin ($P = 0.021$) and negatively with Westergren erythrocyte sedimentation rate (ESR) ($P = 0.029$). No major differences in frequency of oral mucosal lesions were seen between RA-patients and controls.

CONCLUSIONS: Higher frequency of TMJ and salivary gland dysfunction in RA-patients compared with controls has been demonstrated. RA disease activity is associated with hyposalivation and TMJ dysfunction.

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Keywords: rheumatoid arthritis; saliva; oral mucosa; disease activity; temporomandibular joint

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disorder, characterized by synovial hyperplasia and chronic inflammation. The prevalence in the western population is 0.5–1% and the disease affects women about three times more than men (Symmons *et al*, 1994). The disease predominantly affects small joints in the hands, wrists and feet, but may involve any joint lined by a synovial membrane. Although evidence suggests that various microorganisms (Simelyte *et al*, 2000; Ebinger *et al*, 2003) may play a role in association with genetic predisposition (Albani *et al*, 1992), the aetiology and pathogenesis is not fully understood.

Involvement of the temporomandibular joint (TMJ) in RA was first scientifically described in 1874 (Garrod, 1874), where the investigator claimed that the disease had a peculiar tendency to select the TMJ. More recent studies have reported a prevalence of TMJ symptoms in the range of 4.7% (Ragan, 1949) to 85% (Friez and Le Goc, 1982), and a majority of the publications indicate that around half of RA-patients exhibit clinical involvement of the TMJ (Larheim *et al*, 1983; Gleissner *et al*, 2003). The most common clinical findings are pain and limited function of the joints, crepitation, pain during maximal opening and tenderness on palpation of both masticatory muscles and the TMJ (Laurell *et al*, 1989; Goupille *et al*, 1993). Radiological changes are also frequently present in the TMJ (Larheim *et al*, 1992; Suenaga *et al*, 2000).

Sjögren's syndrome (SS) is commonly associated with RA, and is characterized by xerostomia and keratoconjunctivitis sicca with focal sialadenitis. Although sicca symptoms are well-known features in other connective tissue diseases-like RA, systemic lupus erythematosus (SLE), progressive systemic sclerosis and dermatomyositis, the frequency of these symptoms is still under debate (Andonopoulos *et al*, 1987; Brun *et al*, 1994, 2003; Jensen *et al*, 1997; Uhlig *et al*, 1999).

Oral mucosal manifestations in SS and SLE are well-documented (Jonsson *et al*, 1984, 2001, 2002; Provost and Watson, 1992; Stinchi *et al*, 1998), but the nature and frequency of oral mucosal pathology in RA are not fully described. Antirheumatic treatment, including individually adapted doses of disease-modifying antirheumatic drugs (DMARDs), analgesics, non-steroidal

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anti-inflammatory drugs (NSAIDs) and glucocorticosteroids (Ince *et al*, 2000; Jones *et al*, 2003) have documented side-effects, and ulcers or toxic reactions may manifest in oral tissue (Gispen *et al*, 1987; Ince *et al*, 1996; Madinier *et al*, 2000). Consequently, it is often difficult to determine the actual pathogenesis behind the oral lesions in these patients.

Associations between TMJ involvement and general disease activity in RA have been demonstrated. TMJ involvement are claimed to be associated with age, duration of the disease, number of swollen joints, C-reactive protein (CRP), rheumatoid factor (RF) and Westergren erythrocyte sedimentation rate (ESR) (Tegelberg *et al*, 1987; Celiker *et al*, 1995; Yoshida *et al*, 1998; Nordahl *et al*, 2001). The hypothesis of this study was therefore that TMJ involvement and salivary gland dysfunction were more severe-, and that oral mucosal lesions were more frequent in RA compared with healthy individuals. It was also hypothesized that these oral parameters were significantly associated with general disease activity in RA.

Consequently, the purpose of the present investigation was to elucidate the frequency and character of TMJ-involvement and oral mucosal lesions in RA, to investigate the relationship between oral parameters and disease activity, and to evaluate the diagnostic value of hyposalivation in RA-patients.

Patients and methods

The RA group consisted of 50 consecutive hospitalized patients, all fulfilling the revised criteria according to the American College of Rheumatology (formerly the American Rheumatism Association) (Arnett *et al*, 1987). Thirty-nine (78.0%) were women and 11 (22.0%) were men. The mean age was 53.8 years (range: 27–77) for the women and 60.6 years (range: 41–73) for the men. The mean duration of the disease was 12.1 years (range: 1–55).

The control group consisted of 23 non-RA patients. Seventeen (73.9%) were women and six (26.1%) were men. The mean age was 52.1 years (range: 27–71) for the women and 60.3 years (range: 55–67) for the men.

Twenty-five (50%) of the RA-patients and eight (35.0%) of the control patients had additional medical diagnoses (Table 1). Twenty-six (52.0%) of the RA-patients were found to be RF positive, where cut-off levels for a positive RF were set at titres of ≥128 (Ulvestad *et al*, 2001). Three patients were positive to Sjögren's syndrome A antigens (SSA) and two for Sjögren's syndrome B (SSB).

Approval was given by the Ethical Committee, Faculty of Medicine, University of Bergen, and patients were included during the period from January 2002 to February 2003.

Medical treatment in both groups

Forty-eight (90.0%) of the RA-patients were treated with DMARDs, 38 (76.0%) with NSAIDs, 24 (48.0%) with oral steroids, 14 (28.0%) with analgesics, seven (14.0%) with anticoagulating drugs and three (6%) were treated for asthma and allergy. Four (8.0%) of the patients were treated with antibiotics at the time of enrolment into the study. Thirty-eight (76.0%) of the patients were treated with other drugs. Hormone supplements, gastrointestinal drugs or various heart and vascular drugs were recorded as other drugs. The most frequent oral steroid and DMARD given were prednisolone and methotrexate (MTX) respectively. All of the patients treated with MTX were simultaneously treated with folic acid.

Two of the control patients were medically treated for asthma and allergy and one with analgesics. Nine (39.1%) of the control patients were medically treated with other drugs.

Table 1 Additional medical diagnoses in RA-patients and controls

Parameter	*Number of RA*[a] *(%)*	*Number of controls*[b] *(%)*
Other inflammatory diseases[c]	7 (14.0)	4 (17.4
Heart, blood, and vascular disease[d]	6 (12.0)	3 (13.0)
Osteoporosis	6 (12)	0 (0)
Secondary SS	4 (8.0)	0 (0)
Asthma/allergy	3 (6.0)	2 (8.7)
Hypothyroidism	2 (4.0)	0 (0)
Other	2 (4.0)	3 (13.0)

[a]Three patients exhibited two different additional diagnoses, one patient three, and one patient four different additional diagnoses each.
[b]Three patients exhibited two different additional diseases each.
[c]Diagnosed psoriasis, thyroiditis, oesophagitis, phyonephritis, oral lichen planus, ulcerative colitis, gastroenteritis and dermatitis.
[d]Diagnosed hypo- and hypertension, leucopenia, anaemia and heart arrhythmia.
RA, rheumatoid arthritis; SS, Sjögren's syndrome.

General examination and blood analyses

The RA group were examined at the Rheumatology Clinic, Haukeland Hospital, Bergen, Norway. Recorded data from the clinical examination included number of swollen and tender joints (28 joint count), duration of morning stiffness (graded on a 30 min interval scale), and physician global assessment (PGA) score, graded on a 100 mm visual analogue scale (VAS). Health Assessment Questionnaire (HAQ) score and patient overall assessments of disease activity (VAS) were also recorded. In addition, a Schirmer eye test was performed according to published guidelines (Cho, 1993). All RA-patients responded separately to each of the six questions regarding sicca symptoms, which are used in the European Criteria for SS (Vitali *et al*, 2002). All patients were screened for extracted nuclear antibodies (ENA), however, minor salivary gland biopsies were not included in the study.

Serological data, obtained from routine laboratory analyses included ESR, haemoglobin (Hb), CRP, antinuclear antibodies (ANA), white blood cells count (WBC), platelet count (TC) and immunoglobulin G (IgG) concentration.

Disease activity score (DAS28) was calculated for all 50 patients according to published guidelines (van der Heijde *et al*, 1990; Prevoo *et al*, 1995), using tender 28

joint score, swollen 28 joint score, ESR and patient overall assessments of disease activity.

Patients using drugs with documented hyposalivary effects, patients wearing total or partial dentures and patients with documented tension myalgia or other muscular diseases were not included in the study population.

Examination of TMJ and oral mucosa

Clinical examinations of the RA-patients were performed at the Clinic for Oral and Maxillofacial surgery, Haukeland University Hospital, Bergen. The 23 patients in the control group consisted of sex-and age-matched patients who were all randomly selected from a population of consecutive patients at the Faculty of Dentistry, University of Bergen, Norway.

History of the following TMJ symptoms were recorded for all RA and control patients: pain or difficulties during occlusion or mouth opening, crepitus or joint clicking or locking of the TMJ, unprovoked pain from TMJ or masticatory muscles and a feeling of fatigue and stiffness in the TMJ region. RA-patients were all asked whether the TMJ symptoms did occur in relation to RA severity, and if they had persisted only once or periodically since the disease was diagnosed. Patient oral assessment (POA) included the total presence or absence of extraordinary symptoms originating from TMJ, masticatory muscles, salivary glands and oral mucosa, and was graded on a 100 mm VAS for all patients. Toothache, headache and pain in the neck and shoulders were not included.

Both patient groups were subjected to a detailed examination of their TMJ. The examination included maximal mouth opening (defined as the distance between one of the upper central incisors and one of the lower central incisors during maximal opening, added the individual vertical overbite), maximal protrusion, maximal lateral movement, deviation of the mandible from the midline during opening, and lateral or frontally open bite. Locked jaw, pain, crepitus and clicking on mandible movement were registered for each patient. The presence or absence of swollen and/or tender TMJ regions on lateral and posterior palpation was recorded. The following masticatory muscles were palpated bilaterally: profound and superficial masseter muscle, posterior and anterior part of the temporal muscle, insertion and origin of the temporal muscle, lateral and medial pterygoid muscle.

For each patient the Helkimo clinical dysfunction index (D_i) for the masticatory system was calculated (Helkimo, 1974a,b). The index was calculated on the basis of five subgroups, each judged on a three graded scale of severity using 0-, 1- and 5-points. 'No symptom' was awarded – 0; 'mild symptoms' – 1; and 'severe symptoms' – 5-points (Helkimo, 1974a,b). The five subgroups included: impaired range of movement of the TMJ, impaired function of the TMJ, pain on movement of the TMJ, muscular pain and TMJ pain.

A thorough clinical examination of the oral mucosa was performed. Sites examined were lips, buccal mucosa, alveolar mucosa, gingiva, palate, floor of the mouth, oropharynx, tonsills and tongue. Oral pathology was based on clinical observations and was recorded as either: White (leucoplakia, tobacco-associated lesions, etc.), red (hemangioma, erythroplakia, etc.), red-white (candidasis, oral lichen planus, etc.), nodular (fibromas, polyps, etc.), vesiculobullous (pemphigus, herpes simplex, etc.), ulcerative (aphtous or chemotherapeutic ulcers, etc.) and oedematous lesions (other tumours). Geographical tongue, Fordyce's spots, leucoedema, linea alba buccalis or morsicatio buccarum were recorded as normal variations.

Resting whole saliva

Resting whole saliva (RWS) was most commonly collected from each patient during morning hours before noon. Patients had not eaten, smoked, swallowed liquids or rinsed their teeth for at least 1 h before the test. They were seated on a chair and protected from gustatory or other stimulation. RWS was collected per 15 min by passive spitting into a plastic cup (Sterilin, UK), then aspirated into a sterile single-use syringe (Omnifix®; 5 or 10 ml: Omnifix, B. Braun, Helsungen AG, Germany) and measured. Salivation for each patient was registered as mean per 15 min. The limit for reduced RWS production was set to >1.50 ml per 15 min.

Microbial counts and salivary buffering effects

Tests for detecting oral fungi, *Streptococcus mutans*, and lactobacilli (Dentocult CA®, Dentocult SM® and Dentocult LB®; Orion Diagnostica, Espoo, Finland) were performed. All microbial tests were carried out according to the instructions from the manufacturer. *Candida* colonies were scored on a scale from 0 to 4 indicating an increasing number of colonies (0: no growth, 1: 1–9 colonies, 2: 10–24 colonies, 3: 25–50 colonies and 4: >50 or confluent colonies). Lactobacilli were scored on a scale from 1 to 4, indicating bacteria per ml saliva (1: 10^3, 2: 10^4, 3: 10^5 and 4: 10^6). In the same way *S. mutans* was scored on a scale from 0 to 3 indicating bacteria per ml saliva (0: no growth, 1: $<10^5$, 2: 10^5–10^6, 3: $>10^6$). The buffering effect (Dentobuff®; Orion Diagnostica) was scored according to the colour changes of the strip as 1: yellow, 2: green and 3: blue, indicating poor, medium and good buffering effect.

Statistical analysis

Statistical analysis of the differences between the RA group and the control group were carried out using the Mann–Whitney *U*-test. The level of significance was set at $P < 0.05$. The association between each variable were analysed by use of Spearman's rho correlation coefficient. The statistical analyses were performed using SPSS release 12.0.1 software (SPSS Inc., Chicago, IL, USA).

Results

TMJ involvement in RA

Thirty-eight (77.6%) of the RA-patients compared with four (8.0%) of the controls, reported symptoms of TMJ pain or dysfunction during the course of the disease or

Table 2 Number of RA-patients with a history of TMJ symptoms[a]

Patient history	*Number of never (%)*	*Number of once (%)*	*Number of periodic (%)*	*Number of total (%)*
Dependent on RA disease severity		7 (14.3)	19 (38.8)	26 (53.1)
Independent on RA disease severity		4 (8.1)	8 (16.3)	12 (24.5)
Total	11 (22.4)	11 (22.4)	27 (55.1)	49[b]

The numbers in the table are based upon patient self-reported TMJ symptoms since debut of disease (RA).
[a]Pain or difficulties during occlusion or mouth opening, feeling of crepitus or joint clicking or locking of the TMJ, feeling of unprovoked pain from the TMJ or masticatory muscles and a feeling of fatigue and stiffness in the TMJ region.
[b]One patient excluded.
RA, rheumatoid arthritis; TMJ, temporomandibular joint.

during adulthood respectively (Tables 2 and 3). Eleven (22.4%) of the RA-patients had experienced symptoms once, and 27 (55.1%) several periods during the course of the disease (Table 2). Twenty-six (53.1%) patients related these symptoms to a general disease activity and 12 (24.5%) did not (Table 2). Eleven (22.4%) of the RA-patients had never experienced any symptoms from the TMJs during the course of the disease. One of the patients answered these questions improperly and was excluded regarding this issue. Two (4.0%) of the RA-patients had swollen TMJs bilaterally during the oral examination and unilateral open bite was registered in two (4.0%) of the patients. No open bite or swollen joints were found among the patients in the control group.

TMJ-involvement, and the relation to DAS28

The distribution according to the clinical dysfunction index is given in Table 4. Twenty (40.0%) of the patients had mild symptoms (D_i I) on examination, 20 (40.0%) had moderate symptoms (D_i II) and nine (18.0%) had severe dysfunction (D_i III) according to the index system (Helkimo, 1974a,b). One (2.0%) of the patients examined did not have symptoms of dysfunction (D_i 0). The median D_i was 5.5 (range: 0–21) for the RA-patients compared with 2.0 (range: 0–9) for the controls, $P < 0.0001$. Three of the subgroups in the index system was significantly elevated in the RA-group compared with controls; impaired range of movement of the TMJ ($P = 0.010$), muscular pain ($P = 0.048$) and TMJ-pain ($P = 0.003$).

The mean calculated DAS28 was 5.7 (s.d. 1.1), the median HAQ was 2.3 (range: 1.0–3.8), and the mean PGA was 43.2 (s.d. 26.9). Positive and statistic significant correlations were found between three of the five subgroups and DAS28; pain on movement of the TMJ ($r = 0.357$, $P = 0.015$), muscular pain ($r = 0.409$, $P = 0.006$) and TMJ pain ($r = 0.345$, $P = 0.019$). A significant and positive correlation was also found between D_i and DAS28 ($r = 0.387$, $P = 0.009$).

Salivary gland involvement and the relation to disease activity score

The mean RWS secretion was 2.6 (s.d. 2.4) ml per 15 min for the RA-patients compared with 4.5 (s.d. 3.0) for the controls, $P = 0.003$ (Table 8). Twenty (40.0%) of the patients in the RA group and three (13.0%) of the patients in the control group had a salivary flow of < 1.5 ml per 15 min. There was a significant negative correlation between RWS and POA ($P = 0.001$), RWS and HAQ ($P = 0.002$), between RWS and D_i ($P = 0.031$) and between RWS and ESR ($P = 0.029$). A positive correlation was found between RWS and Hb ($P = 0.021$) (Table 5). RWS did not correlate with any of the variables PGA, morning stiffness or patient overall assessment of disease activity.

Seven (14.0%) of the RA-patients reported dry eyes (Table 6) and 10 (20.0%) reported feeling of sand in the

Table 3 Number of control patients with a history of TMJ symptoms[a]

Patient history	*Number of patients (%)*
Never	19 (82.6)
Once	0 (0)
Periodically	4 (17.4)
Total	23

Numbers in the table are based upon patient self-reported TMJ symptoms during their entire adulthood.
[a]Pain or difficulties during occlusion or mouth opening, crepitus or joint clicking or locking of the TMJ, unprovoked pain from TMJ or masticatory muscles and a feeling of fatigue and stiffness in the TMJ region.
TMJ, temporomandibular joint.

Table 4 Clinical dysfunction index (D_i) for the RA-patients and the controls

	Patients	
Index (D_i)	*Number of RA (%)*	*Number of controls (%)*
0	1 (2.0)	2 (10.5)
I	20 (40.0)	13 (68.4)
II	20 (40.0)	4 (21.1)
III	9 (18.0)	0 (0)

The table is based on Helkimo's clinical dysfunction index system (D_i), for the masticatory system, where 0 is indicating no dysfunction, I mild dysfunction, II moderate dysfunction and III is indicating severe dysfunction.

Table 5 Production of resting whole saliva (RWS) associated with other parameters in rheumatoid arthritis (RA)-patients

Parameter vs RWS	*P-value*	*r-value*
Age	NS	–
Duration of disease	NS	–
Clinical dysfunction index (D_i)	0.031	−0.298
Health assessment questionnaire (HAQ)	0.002	−0.441
Patient oral assessment (POA)	0.001	−0.387
Disease activity scores (DAS28)	NS	–
Antinuclear antibodies (ANA)	NS	–
Immunoglobulin G (IgG)	NS	–
C-reactive protein (CRP)	NS	–
Erythrocyte sedimentation rate (ESR)	0.029	−0.316
Haemoglobin (Hb)	0.021	0.329
Thrombocyte count (TPC)	NS	–
Leucocyte count (LPC)	NS	–

Differences between the RA group and the control group were carried out using the Mann–Whitney *U*-test (*P*-value). The level of significance was set at $P < 0.05$. Associations between RWS the other parameters were analysed by use of Spearman's rho correlation coefficient (*r*-value).

Table 6 Feeling of dry mouth and dry eyes last 3 months associated with reduced salivary and lacrimal fluid production

	Clinical observation, # Patients (%)		
Subjective feeling	*Hypofunction*[a]	*Normal*[b]	*Total*
Feeling of dry mouth	11 (22.0)	6 (12.0)	17 (34.0)
Feeling of normal mouth	9 (18.0)	24 (48.0)	33 (66.0)
Total			50
Feeling of dry eyes	5 (10.4)	2 (4.2)	7 (14.6)
Feeling of normal eyes	14 (29.2)	27 (56.2)	41 (85.4)
Total			48[c]

[a]Rest salivary production < 1.50 ml per 15 min, and reduced lacrimal fluid production defined as < 5 mm according to Shirmer I test.
[b]Rest salivary production > 1.50 ml per 15 min.
[c]Shirmer I test missing from two patients. All patients responded separately to each of the six questions regarding sicca symptoms, which are used in the European Criteria for Sjögren's syndrome (SS) (Vitali *et al*, 2002).

eyes. Two (4.0%) had been using tear substitutes the last 3 months. Seventeen patients (34%) reported xerostomia during the last 3 months (Table 6), and 10 (20.0%) were using salivary substitutes. Four (8.0%) of the RA-patients had secondary SS according to existing criteria (Vitali *et al*, 2002). In one of the secondary SS patients, anti-SSB antibodies were detected. The mean Shirmer I was 7.0 mm for the right eye and 9.0 mm for the left eye. Eleven (22.0%) of the patients had a score less than normal on both eyes.

Among the 17 RA-patients that reported xerostomia, 11 showed decreased salivary production (Table 6). Xerostomia was also reported in six patients with normal salivary production. Of the 33 patients that did not report xerostomia, nine were found to have salivary hypoproduction. Among the seven patients with a subjective feeling of one or two dry eyes, five were shown to have reduced lacrimal fluid production and two were shown to have normal flow. Fourteen patients that characterized themselves as normal were found to have reduced lacrimal fluid production (Table 6).

Table 7 Clinically observed oral mucosal lesions in rheumatoid arthritis (RA)-patients and controls

	Patient group	
Oral mucosal pathology	*Number of RA (%) (n = 50)*[a]	*Number of controls (%) (n = 23)*
White lesions	4 (8.0)	2 (8.7)
Red lesions	2 (4.0)	0 (0)
Red-white lesions	1 (2.0)[b]	0 (0)
Nodular lesions	9 (18.0)	1 (4.3)
Vesiculobullous lesions	0 (0)	0 (0)
Ulcerative lesions	4 (8.0)	3 (13.0)
Oedematous lesions	0 (0)	0 (0)
Normal	33 (66.0)	16 (69.6)

[a]Two patients exhibited two and three different lesions each.
[b]Patient with diagnosed oral lichen planus.

Table 8 Oral microbiology counts for rheumatoid arthritis (RA)-patients and controls

	Patient group (mean)	
Microbiology	*RA*	*Controls*
Resting whole saliva	2.60* (s.d. 2.4)	4.51 (s.d. 3.0)
Streptococcus mutans colonies	1.0 (range: 0–4)	0.0 (range: 0–4)
Lactobacilli colonies	1.0 (range: 0–4)	0.0 (range: 0–4)
Candida colonies	1.0 (range: 0–4)	1.0 (range: 0–4)
Buffering capacity	2.0** (range: 1–3)	3.0 (range: 2–3)

Dental tests used in the study were Dentocult CA®, Dentocult SM® and Dentocult LB®; Orion Diagnostica, Espoo, Finland. Differences between the RA group and the control group were carried out using the Mann–Whitney *U*-test.
$*P < 0.01$, $**P < 0.0001$. All values are in median (range) except for resting whole saliva; mean.

Oral mucosal lesions

Oral mucosal lesions were found in 17 (34.0%) of the RA-patients. Nodular lesions were found in nine (18.0%) of the patients, white lesions in four (8.0%), ulcerative lesions in four (8.0%) red lesions in two and red and white lesions in one of the patients (Table 7). Among these 17 patients, saliva content < 1.5 ml per 15 min was found in nine (58.8%) of the patients. In the control group, oral mucosal lesions were found in six (26.1%) of the patients. Ulcers were found in three, white lesions in two and nodular lesions in one of the patients (Table 7).

Microbial counts and buffering capacity in saliva

The median microbial counts in saliva were higher in RA-patients than in the control-group, but the differences were not statistically significant (Table 8). The median salivary buffering capacity was significantly higher in the control group compared with the capacity found in the RA-patients ($P < 0.01$). There were no significant association between buffering capacity and the amount of RWS. Although not significantly different ($P = 0.052$),

a negative association was demonstrated between the median number of *Candida* colonies and RWS.

Discussion

In the present study, the frequency and nature of TMJ involvement, oral mucosal lesions and salivary function was investigated in a group of adult RA-patients and compared with the findings in a healthy control group. Further, the relationship between oral parameters and RA disease activity has been investigated.

Although most of the RA-patients investigated were medically treated with anti-inflammatory drugs, a difference in TMJ and salivary gland disease severity was detected between the RA group and the controls. This strengthens the assumption that these clinical symptoms are rather common in RA and are not easily masked by the use of antirheumatic drugs. It should be expected that TMJ symptoms occur frequently in the general population. However, in this study we clinically demonstrated a higher frequency of both mild, moderate and severe symptoms and dysfunction related to the TMJ and masticatory system in RA.

Associations have been shown between TMJ involvement in RA and disease activity parameters-like CRP, RF and ESR (Tegelberg *et al*, 1987; Celiker *et al*, 1995; Yoshida *et al*, 1998; Nordahl *et al*, 2001). In the present study, an association between TMJ involvement and DAS28 has been demonstrated. DAS28 is constructed on the basis of ESR, patient general assessment of disease activity and the number of tender and swollen joints at the time of examination, and its validity is well-documented (Prevoo *et al*, 1995). Three of the five subgroups and D_i as a total were found to be significantly associated with DAS28. This indicates that the traditional Helkimo dysfunction index can be used in order to determine TMJ disease activity in RA as well as in the normal population (Helkimo, 1974a,b). The findings in this study may further suggest that while TMJ related pain is associated with disease activity, impaired range of movement of the TMJ and impaired function of the TMJ, might be related to degenerative changes of the joint rather than inflammation. The index subgroups TMJ-pain and muscular pain were both elevated in RA-patients compared with controls and correlated significantly with the DAS28. This demonstrates that these two parameters are particularly strong indicators of the TMJ association in RA, also during a non-acute phase of the disease. The TMJ and surrounding connective tissue are also anatomically closely sited to the parotid and the submandibular glands, and exocrine tissue inflammation might be experienced as symptoms from connective tissues or vice versa. More research is warranted in order to evaluate these aspects of the disease.

Manifestation of dry mouth and eyes in RA have been discussed by various investigators since Henrik Sjögren presented his findings 70 years ago, and the frequency and nature of these sicca symptoms are still under debate (Andonopoulos *et al*, 1987; Brun *et al*, 1994, 2003; Jensen *et al*, 1997; Uhlig *et al*, 1999). In the present study, no association between reduced salivary and lacrimal flow was found and it may therefore be assumed that sicca manifestations of the eyes and mouth occur independent of each other in RA. Although xerostomia and hyposalivation are related to dry mouth, xerostomia do not always indicate hyposalivation. Six of 17 patients sensing dry mouth in this study, exhibited normal salivary flow. This is in accordance with another study showing that only 54% of the patients reporting xerostomia exhibited clinically dry mouth (Field *et al*, 1997). This may further indicate that xerostomia may be related to other parameters than salivary flow as well. The content of serous and mucous fluid in saliva or the change in buffering capacity (Table 8) are just some of the aspects that should be mentioned. Xerostomia is most commonly associated with cancer radiation treatment, medication or salivary gland dysfunction (Fox *et al*, 1985). Three of the control patients were found to have salivary production less than normal. This also indicates that factors as psychological stress, undocumented medical side-effects, undiagnosed rheumatic disease or normal variations are possible explanations for a reduced salivary flow.

The feeling of dry eyes also seemed to be a rare event in this study. Of 19 patients with clinically dry eye or eyes, five (26.3%) of the patients had the sensation of eye dryness. This could implicate that dry eyes are not considered a major problem among RA-patients and that the lacrimal film should be fairly dry before subjective symptoms occurs.

This study showed that decreased salivary flow was significantly correlated with ESR, HAQ, POA of disease activity and Helkimo's dysfunction index. A positive correlation between salivary production and the Hb was also demonstrated. Although not significant, other variables such as DAS28 and CRP were found to be associated with salivary production. Considering these data, it might be assumed that there is a possible connection between hyposalivation and disease activity in RA, and that hyposalivation may be considered as a disease activity measure for the degree of both local and systemic inflammation. The significant correlation between RWS and ESR supports the assumption of decreased salivary production as a consequence of higher disease activity in RA, and is further strengthened by the fact that these patients also showed significantly lower Hb levels.

Nodular lesions were more frequently observed in the oral mucosa among RA-patients compared with controls (Table 7). There have been case reports showing that SS patients and RA-patients may exhibit multiple nodular lesions in the skin and mucosa (Skov, 1987; Stinchi *et al*, 1998) suggesting a general lymphoproliferation of the minor salivary glands. Biopsies should be performed in a later study to elucidate this approach in more detail.

Although there have been evidence for a changed oral ecology with the focus on *Candida albicans*, *S. mutans* and other species, in patients with reduced salivary flow (Jensen and Barkvoll, 1998; Almståhl *et al*, 1999), the present study did not find evidence for such a difference

between RA-patients and normal subjects. This might demonstrate that the mean drop in salivary flow seen in RA-patients is not enough to create such a significant difference, or that more patients should have been enrolled into the study group. There has, however, been presented evidence that several bacteria could be associated with arthritis, either as triggering factors or to persist as an antigenic drive in the synovial inflammatory process (Simelyte *et al*, 2000; Ebinger *et al*, 2003). Other studies have shown that antibody levels against oral pathogenic bacteria in serum and synovial fluids (SF) are elevated in RA-patients compared with controls (Yoshida *et al*, 2001; Moen *et al*, 2003). Further investigations should be carried out in order to illuminate a possible triggering mechanism to joint inflammation.

In conclusion, evidence has been demonstrated for a significantly higher frequency and greater severity of TMJ-involvement in RA-patients compared with healthy controls. It has further been shown that Helkimo dysfunction index (D_i), and pain in the TMJ system in particular, correlates well with the DAS28. The present study has demonstrated that dry mouth and dry eyes are frequent events in RA, and that hyposalivation might depend on the degree of disease activity. This study strongly demonstrates the importance of oral examination in RA-patients in order to optimize medical treatment, and correctly manage the TMJ and the oral mucosa problems in these patients.

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