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ORIGINAL ARTICLE

Oral and salivary parameters in patients with rheumatic diseases

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Abstract

We studied the presence of secondary Sjögren's syndrome (SS) and the composition of saliva, prevalence of oral pathogens, periodontitis, mouth mucosa, and teeth in patients with various rheumatic diseases and in healthy controls. The hypothesis was that different rheumatic diseases might cause differences in oral health characteristics because of the liability of secondary SS in the patients. The study involved 77 patients and 77 age-matched and sex-matched controls. Twenty patients were suffering from spondylarthropathy (SPA), 18 from ankylosing spondylitis (AS), 24 from rheumatoid arthritis (RA), and 15 from mixed connective tissue disease (MCTD). Clinical and radiographic oral health status was recorded and salivary flow rates were measured. Selected salivary proteins and immunoglobulins were analysed by routine methods. Minor salivary gland biopsy samples were taken from the patients for assessment of inflammatory focus scores. Differences between patients and controls and in between the different rheumatic diseases were analysed statistically. Secondary SS was diagnosed in 39% (30/77) of the patients. A severe periodontal condition (community periodontal index of treatment needs score 3 or 4) occurred in 58% (45/77) of the rheumatic patients compared with only 26% (20/77) of the controls ($p < 0.0001$). The severity of focal sialadenitis (focus score) correlated significant with salivary IgA, IgG, and IgM concentrations. Salivary albumin, total protein, IgG, and IgM concentrations were higher in all patient groups than in the controls. The number of patients with low salivary flow rates was higher in all patient groups compared to controls. Oral yeast counts were significantly higher in the patients than in the controls ($p < 0.001$). In a subgroup analysis, patients with SS had higher values for salivary IgA and IgM than patients without SS. Dental caries and oral lactobacilli were more frequent in patients with SS, but SS was not associated with periodontitis. No major differences were noted in other salivary biochemical parameters between these two groups. Patients with rheumatic diseases, irrespective of specific diagnosis, thus had various alterations in salivary flow and composition and oral health. The findings may reflect the autoimmune inflammation of the salivary glands frequently observed in these patients.

Key Words: *Arthritis, dental health, periodontitis, rheumatic disease, saliva*

Introduction

Oral infections have been associated with systemic diseases such as rheumatoid arthritis (RA) [1], and the risk of periodontal disease is substantially increased in patients with long-standing rheumatoid arthritis [2,3]. However, data on the periodontal condition in seronegative arthritides or mixed connective tissue disease (MCTD) are few, and no studies have been conducted on periodontal disease in patients with spondyloarthropathy (SPA). We have previously shown that saliva secretion, which is the principal defensive factor in the oral cavity, is affected by these rheumatic diseases [4], with subsequent detrimental effects on the teeth and mouth mucosa. Reduced salivary flow enhances oral microbial colonization, in particular yeasts, which, in turn, are an infectious burden on the patient and may worsen the systemic condition [5]. Salivary secretion depends on the general state of hydration, but is mostly affected by systemic diseases and drugs [5].

Secondary Sjögren's syndrome (SS) occurs in association with various rheumatic diseases [6–9]. In

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primary SS, incidences of caries and changes in the oral mucosa are relatively high [10–13]. Daniels & Whitcher [14] reported a correlation between reduction of parotid salivary flow rate and inflammatory focus score in lip biopsy specimens from patients with primary SS. Mandel & Baurmash [15] found higher salivary IgA concentrations in patients with primary SS than in control subjects. 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 [14].

Information on the composition of saliva in patients with mixed connective tissue disease (MCTD), an autoimmune disease in which SS is also often seen [8], is sparse. Only a few reports have been published on sialochemistry in patients with ankylosing spondylitis (AS) and SPA, diseases that may also be associated with focal sialadenitis and SS [9].

The aim of the study reported here was to investigate oral health status, presence of focal sialadenitis, prevalence of dental pathogens and yeasts, as well as salivary flow rates and composition in patients with various rheumatic diseases (RA, MCTD, AS, and SPA), and to compare these findings with those of control subjects matched with respect to age and sex. Our hypothesis was that differences exist between the groups of patients with various rheumatic diseases, due to liability to secondary SS, and between the patients and controls with respect to oral health.

Material and methods

Patients and controls

We studied 77 consecutive patients with rheumatic disease (24 with RA, 15 with MCTD, 18 with AS, and 20 with SPA) and 77 matched controls (Table I). The patients were receiving treatment at the Rheumatological Outpatient Department of the Meilahti Hospital, Helsinki University Central Hospital, Finland. They were asked to participate irrespective of whether they were experiencing oral or ocular symptoms. The control subjects were randomly selected healthy volunteers from dental patients of the Institute of Dentistry, University of Helsinki, matched with respect to sex and age (± 2 years). No control had any history of diabetes, rheumatic disease, or any other disease affecting the masticatory system. All subjects gave their informed written consent and the Ethics Committee of the Helsinki University Central Hospital approved the study.

The patients met the current classification criteria relating to RA [16], MCTD [17], and AS [18]. Patients with seronegative oligoarthritis or spondylitis not meeting the diagnostic criteria for AS were classed as SPA patients and met the European Spondylarthropathy Study Group criteria [19]. European criteria [20] were used in connection with diagnosis of SS.

Clinical oral and X-ray examination, questionnaire, and interview

The patients and controls were examined by a single investigator (L.M.J.H.) 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 Community Index of Periodontal Treatment Need (CPI) was score 3 or more [21]. In the CPI index, the following variables are recorded at clinical examination: dental calculus, periodontal pockets, and gingival bleeding [21]. To assess dryness of the eyes, Schirmer's test was performed, as previously described [4].

All patients and controls completed a questionnaire relating to ocular and oral symptoms according to the European Community study group diagnostic criteria for SS, with slight modifications. In addition, the subjects were interviewed [22]. All patients and controls completed a questionnaire relating to ocular and oral symptoms and were interviewed. Panoramic tomography of the jaws was taken. The radiographs were analysed independently by two observers (L.M.J.H. and D.H.). D.H. was a blinded experienced radiologist. At the analysis, the clinical characteristics of the patients and controls were not available. Analysis of the tomograms focused particularly on signs of dental infection foci, 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. Only distinctly abnormal findings were recorded [23].

Use of medication was recorded (Table 1). Because sulfasalazine can induce autoimmune effects, use of sulfasalazine and glucocorticoids at the time of examination was also recorded [24].

Minor salivary gland biopsy

All rheumatic patients underwent minor salivary gland biopsy irrespective of subjective symptoms. The control group did not undergo biopsy for ethical reasons. The biopsy samples were analysed for the inflammatory focus score, as reported earlier [4]. A focus score was defined as the number of agglomerations of at least 50 mononuclear cells per 4 mm^2 of glandular tissue. Focal sialadenitis was defined as existing if the focus score was 1 or more [22]. If agglomerations of at least 50 mononuclear cells were observed, but there were less than 1 per 4 mm^2 of glandular tissue, the focus score was expressed as less than 1.

Sampling of saliva and determination of buffering capacity and pH

The patients and controls provided resting and stimulated saliva samples according to Vitali et al. [22].

Table I. Characteristics of the study groups

	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
Sex (M/F)	2/22	2/22	1/14	1/14	12/6	12/6	12/8	12/8
Age mean (SD), years	49.4 (11.5)	44.6 (12.7)	44.5 (15.3)	43.2 (15.3)	42.4 (11.6)	43.4 (12.2)	37.4 (9.1)	37.2 (9.4)
Duration of disease mean (SD), years	10.5 (2.6)	–	11.7 (12.0)	–	14.7 (8.9)	–	13.0 (9.2)	–
Peripheral arthritis	24 (100%)	–	13 (87%)	–	13 (72%)	–	18 (90%)	–
History of use of antirheumatic drugs								
Sulfasalazine	18 (75%)	–	0 (0%)	–	17 (94%)	–	16 (80%)	–
Prednisolone	11 (46%)	–	14 (93%)	–	11 (61%)	–	13 (65%)	–
Current use of antirheumatic drugs								
Sulfasalazine	3 (13%)	–	0 (0%)	–	7 (39%)	–	8 (40%)	–
Prednisolone	7 (29%)	–	12 (80%)	–	8 (44%)	–	8 (46%)	–
Others	21 (88%)	–	8 (53%)	–	7 (39%)	–	6 (30%)	–
Present use of other medications								
Antibiotics and antimicrobial drugs	0	0	0	0	0	0	1	0
Cardiovascular drugs	5	2	0	2	1	2	3	3
Respiratory drugs	0	2	0	0	0	3	1	0
Gastrointestinal drugs	0	0	2	1	1	1	0	0
Sex hormones and gynecological drugs	1	1	1	7	0	0	0	1
Psychiatric drugs	2	0	1	1	1	0	0	2
Neurological drugs	1	1	0	0	0	0	0	0
Drugs for allergy	1	1	0	0	0	1	0	2
Endocrinological drugs	0	1	2	3	0	1	2	2
Dermatological drugs	0	0	0	0	0	0	0	1
Analgesics	9	0	5	1	12	0	14	0
Hematological drugs	0	0	0	0	0	0	0	1
Vitamins	1	0	0	0	0	1	0	0
Ophthalmological drugs	0	1	0	1	0	0	0	0
Otorhinological drugs	1	0	0	0	0	0	0	1
Current use of drugs known to decrease salivary flow	5/24 (21%)	4/24 (16%)	1/15 (7%)	2/15 (13%)	1/18 (6%)	0/18 (0%)	1/20 (5%)	2/20 (1%)

Values for resting flow rates equal or less than 0.1 ml/min and for stimulated flow rates equal or less than 0.7 ml/min were taken to indicate reduced flow rates [22]. 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 pH indicator paper and the values were classified as normal if 6.5 or more. The remaining salivas were centrifuged and deep frozen (−70°C) until further analysis.

Oral microbiological analyses

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 Meurman et al. [25] and Wahlfors et al. [26].

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 [27] using human serum albumin standards. Salivary IgA, IgG, and IgM levels were determined by means of the enzyme immunoassay [28]. Results were based on at least duplicate assays and standards and controls were used in all the analyses.

Serum samples

Venous blood samples were collected from the patients and serum concentrations of IgA, IgG, and IgM were determined by means of immunoturbidometry. Antibodies to extractable nuclear antigens (ENA), including specific antibodies to ribonuclear protein (RNP), SSA (SSA), SSB (SSB), and Smith antigen (Sm) were analysed by counter-immunoelectrophoresis. Sera were considered positive by precipitation line for the single antigen. All analyses were carried out in the hospital laboratory using routine clinical chemical procedures. For ethical reasons, no blood samples were taken from the controls.

Statistical analyses

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 χ^2-test when applicable, no adjustment was made for multiple testing. 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.

Results

Oral health characteristics

The oral health characteristics of the patients and controls are given in Table II. There were no statistically significant differences in the number of patients with missing teeth or clinically or radiographically detected caries lesions between the rheumatic patients and control subjects. The number of patients with CPI score 3 or 4 was significantly higher in rheumatic patients than in controls ($p<0.05$, $p<0.001$, respectively). 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 in controls ($p<0.001$) (Table II).

Salivary flow rates

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 III). The AS patients exhibited low resting salivary secretion rates significantly more often than controls (22% [4/18] vs. 0% [0/18], $p=0.03$). The MCTD patients significantly more often had reduced salivary flow both in the resting values (40% [6/15] vs. 0% [0/15], $p=0.0062$) and stimulated values (60% [9/15] vs. 0% [0/15], $p=0.003$) than controls. Eight patients and eight controls used drugs known to affect salivary flow (Table I). 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 (Table III).

Salivary composition

The patients as a group had significantly lower salivary amylase concentrations ($p<0.001$), while albumin ($p<0.01$), total protein ($p<0.001$), IgG ($p<0.001$), and IgM ($p<0.001$) concentrations were significantly higher than in controls. Concentrations of IgG and IgA were highest in the MCTD patients; the RA patients were characterized by significantly ($p<0.01$) lower salivary amylase concentrations. The MCTD patients had significantly higher salivary concentrations of total protein ($p<0.01$), IgA ($p<0.05$), IgG ($p=0.01$), and IgM ($p<0.001$) than matched controls. The AS

Table II. Oral health characteristics rheumatic patients and control subjects

	Rheumatoid arthritis ($n=24$)	Mixed connective tissue disease ($n=15$)	Ankylosing spondylitis ($n=18$)	Spondyloarthropathy ($n=20$)	Controls ($n=77$)
No. of patients with missing teeth	18/24 (75%)	11/15 (73%)	10/18 (56%)	7/20 (35%)*	41/77 (53%)
No. (mean) of the missing teeth/patients with missing teeth	95/18 (5.1)	82/11 (7.1)	62/10 (6.2)	16/7 (2.3)	160/41 (4.0)
No. of patients with dental caries at clinical examination	4/24 (17%)	3/15 (20%)	5/18 (28%)	3/20 (15%)	17/77 (22%)
Mean (range) of teeth with caries	0.3 (0–3)	0.8 (0–9)	0.7 (0–4)	0.1 (0–1)	0.5 (0–4)
No. of patients with dental caries detected by panoramic tomograms	4/24 (17%)	3/15 (20%)	5/18 (28%)	3/20 (15%)	15/77 (19%)
No. of teeth with caries	7	17	7	3	29
No. of patients with periapical lesions	6/24 (25%)	4/15 (27%)	7/18 (39%)	6/20 (30%)	19/77 (25%)
Mean (range) of periapical lesions	0.4 (0–2)	0.3 (0–1)	0.4 (0–2)	0.4 (0–3)	0.3 (0–3)
No. of patients with CPI[1]					
2	6/24 (25%)	7/15 (47%)	8/18 (44%)	11/20 (55%)	57/77 (74%)$^{\Psi}$
3	9/24 (38%)	8/15 (53%)	7/18 (39%)	7/20 (35%)	19/77 (25%)$^{\#}$
4	9/24 (33%)	0/15 (0%)	3/18 (17%)	2/20 (10%)*	1/77 (1%)$^{\Psi}$
No. of patients with furcation lesions[2]	2/24 (8%)	0/15 (0%)	3/18 (17%)	2/20 (10%)	3/77 (4%)
No. of patients with horizontal alveolar bone loss[2]	20/24 (83%)	8/15 (53%)	9/18 (50%)	6/20 (30%)*	28/77 (36%)$^{\#}$
No. of patients with vertical bone pockets[2]	16/24 (67%)	4/15 (27%)	5/18 (28%)	4/20 (20%)*	8/77 (10%)$^{\Psi}$
Mucosa membrane (no. of patients):					
Normal	14/24 (58%)	12/15 (80%)	13/18 (72%)	17/20 85%)	73/77 (95%)$^{\Psi}$
Varicoses	5	0	0	0	1
Geographic tongue	2	1	3	0	2
Fissura tongue	2	1	2	2	2
Lichen planus	2	2	0	1	1
Mucosal hyperlasia	0	1	1	0	0

[1] Community periodontal index for treatment need. Score 2 = gingivitis, score 3 = 4–6-mm-deep periodontal pocket, and score 4 = > 6-mm-deep periodontal pocket.
[2] Assessed from the panoramic tomograms.
$^{\Psi}$ Statistically significant difference between the whole patient and control group, $p<0.001$ (χ^2 test).
$^{\#}$ Statistically significant difference between the whole patient and control group, $p<0.05$ (χ^2 test).
* Statistically significant difference between patient groups, $p<0.05$ (χ^2 test).

patients had significantly higher salivary concentrations of total protein ($p<0.001$) and IgA ($p<0.05$) than the matched controls (Table IV).

Microbiologic data

Microbes referring to periodontal disease were more frequently observed in the controls than in the patients. A positive yeast count was significantly more common in the rheumatic patients than in the control subjects ($p<0.001$) (Table V). On the contrary, microbes referring to periodontal disease were more frequently observed in the controls than in the patients (Table V).

Relationship between salivary flow rates and focal sialadenitis

Fifty-two (68%) of the 77 patients had focal sialadenitis. Compared to patients in whom salivary gland biopsy findings were normal, the patients with focal sialadenitis more often had reduced resting salivary flow rates (11/52 versus 1/24, $p=0.059$) and stimulated salivary flow rates (12/52 vs. 1/24, $p=0.042$). Significant correlations were found between focus scores and salivary concentrations of IgA ($r_s=0.28$, 95% confidence interval (CI) 0.06 to 0.47), IgG ($r_s=0.34$, 95% CI 0.13 to 0.52), and IgM ($r_s=0.40$, 95% 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).

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 (Table IV). 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

Table III. Salivary values (median [IQR]), sialadenitis, dry mouth and diagnosed Sjögren's syndrome 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
Resting flow (ml/min)	0.3 (0.2–0.4)	0.3 (0.2–0.5)	0.2 (0.0–0.3)	0.2 (0.1–0.5)	0.4 (0.2–0.6)	0.5 (0.4–1.0)	0.4 (0.3–0.5)	0.2 (0.1–0.3)
No. (%) of patients with decreased flow	2 (8%)	0 (0%)	6 (40%)	0 (0%)	4 (22%)	0 (0%)	0 (0%)$^{\Phi}$	0 (0%)
Stimulated flow (ml/min)	1.5 (1.3–2.5)	1.6 (1.0–1.8)	0.7 (0.2–1.1)	1.4 (0.8–1.9)	1.8 (1.3–3.0)	2.0 (1.4–3.5)	2.1 (1.2–2.6)	1.4 (0.8–2.0)
No. (%) of patients with decreased flow	2 (8%)	0 (0%)	9 (60%)	0 (0%)	2 (11%)	1 (6%)	0 (0%)$^{\#}$	0 (0%)
No. (%) of patients with low buffering capacity	7 (29%)	9 (38%)	9 (60%)	5 (33%)	2 (11%)	2 (11%)	7 (35%)	6 (30%)
pH	4 (17%)	1 (4%)	3 (20%)	1 (7%)	1 (6%)	1 (6%)	1 (5%)	1 (5%)
No. (%) of patients with focal sialadenitis	20 (83%)	–	14 (93%)	–	10 (56%)	–	8 (40%)$^{\#}$	–
No. (%) of patients with subjective dry mouth	11 (46%)	2 (8%)	13 (87%)	1 (7%)	8 (44%)	0 (0%)	3 (15%)$^{\#}$	0 (0%)$^{\Psi}$
No. (%) of patients with Secondary Sjögren's syndrome*	10 (42%)	–	12 (80%)	–	6 (33%)	–	2 (10%)	–

$^{\Phi}$ Statistically significant difference between patient groups, $p=0.007$ (χ^2-test).
$^{\#}$ Statistically significant difference between patient groups, $p<0.001$ (χ^2-test).
$^{\Psi}$ Statistically significant difference between patient and control groups, $p<0.0001$ (χ^2-test).
* Fulfilling the European criteria for secondary Sjögren's syndrome.

Table IV. 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)$^{\clubsuit}$	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)$^{\xi}$	35.8 (26.0–54.6)	23.0 (16.0–34.0)$^{\xi}$	27.0 (18.8–67.0)$^{\Phi}$	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)$^{\Phi}$	7.4 (3.2–11.0)
IgM mg/l	3.1 (1.7–5.4)	1.7 (0.9–3.3)$^{\xi}$	6.6 (3.0–7.2)	1.8 (0.9–2.9)$^{\clubsuit}$	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)$^{\Psi}$	–
IgG g/l	10.3 (9.0–11.3)	–	18.1 (13.2–23.4)	–	12.9 (10.6–14.6)	–	14.7 (11.0–17.9)$^{\Psi}$	–
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)	–

$^{\Phi}$ Statistically significant difference between patient groups, $p<0.05$ (Kruskal-Wallis).
$^{\Psi}$ Statistically significant difference between patient groups, $p<0.001$ (Kruskal-Wallis).
$^{\xi}$ Statistically significant difference between the patient and matched control group, $p\leqslant 0.05$ (Mann-Whitney).
$^{\#}$ Statistically significant difference between the patient and matched control group, $p<0.01$ (Mann-Whitney).
$^{\clubsuit}$ Statistically significant difference between the patient and matched control group, $p\leqslant 0.001$ (Mann-Whitney).

Table V. Oral microbiological findings

	Rheumatoid arthritis ($n=24$)	Mixed connective tissue disease ($n=15$)	Ankylosing spondylitis ($n=18$)	Spondyloarthropathy ($n=20$)	Controls ($n=77$)
Mutans streptococci ($>10^5$ CFU/ml)	2/24 (8%)	4/15 (27%)	1/18 (6%)	4/20 (20%)	9/77 (12%)
Lactobacilli ($>10^6$ CFU/ml)	1/24 (4%)	3/15 (20%)	2/18 (11%)	3/20 (15%)	5/77 (6%)
Positive yeast count	12/24 (50%)	5/15 (33%)	7/18 (39%)	8/20 (40%)	17/77 (22%)*
A.a. positive	2/24 (8%)	0/15 (0%)	1/18 (6%)	1/20 (5%)	5/77 (6%)
P.g. positive	3/24 (13%)	0/15 (0%)	0/18 (0%)	1/20 (5%)	12/77 (16%)#
P.i. positive	15/24 (63%)	3/15 (20%)	11/18 (61%)	11/20 (55%)Φ	58/77 (75%)#
P.n. positive	15/24 (63%)	4/15 (27%)	11/18 (61%)	11/20 (55%)	41/77 (53%)
B.f. positive	0/24 (0%)	0/15 (0%)	0/18 (0%)	0/20 (0%)	2/77 (3%)

A.a. = Actinobacillus actinomycetemcomitans, P.g. = Porphyromonas gingivalis, P.i. = Prevotella intermedia, P.n. = Prevotella nigrescens, B.f. = Bacteroides forsythus (Tannerella forsythensis).
* Statistically significant difference between the whole patient and control group, $p<0.001$ (χ^2-test).
# Statistically significant difference between the whole patient and control group, $p<0.05$ (χ^2-test).
Φ Statistically significant difference between patient groups, $p<0.05$ (χ^2-test).

AS patients who had and who had not taken sulfasalazine medication (data not shown).

Comparison between patients with and without Sjögren's syndrome

When patients were divided into two groups with respect to presence or absence of secondary SS, those with secondary SS had significantly higher salivary immunoglobulin A and M concentrations, more often positive lactobacilli and more often dental caries compared with patients without secondary SS (Table VI). On the contrary, while the patients had more severe periodontitis (Table II), there was no association of periodontitis with SS (Table VI).

Discussion

This study was the first comprehensive investigation of oral health and saliva in patients suffering from different types of rheumatic disease. The results confirm our hypothesis showing considerable differences in oral health characteristics and salivary parameters between patients with different rheumatic diseases. Some, but not all, of the changes were associated with secondary SS observed in 39% of the patients. To our knowledge, there are no previous data on the frequency of periodontal disease or periapical lesions in patients with spondyloarthritides (AS and SPA).

In primary SS, incidences of caries and changes in the oral mucosa are relatively high [10–13]. Controversial data exist as to whether SS increases the risk of

Table VI. Oral health characteristics in rheumatic patients with respect to the presence or absence of Sjögren's syndrome

	Sjögren's syndrome+	Sjögren's syndrome−	*p*-value
Resting flow (ml/min) (median, IQR)	0.16 (0–0.32)	0.42 (0.3–0.6)	<0.004 (Mann-Whitney)
Stimulated flow (ml/min) (median, IQR)	1.00 (0.5–1.9)	2.00 (1.36–3.0)	<0.001 (Mann-Whitney)
Salivary:			
Amylase; U/ml (median, IQR)	77.5 (63–126)	56 (38–87)	0.06 (Mann-Whitney)
Albumin; mg/l (median, IQR)	163 (104–195)	138 (109–200)	0.64 (Mann-Whitney)
Total protein; mg/ml (median, IQR)	1.1 (0.85–1.41)	0.98 (0.65–1.54)	0.06 (Mann-Whitney)
IgA; mg/l (median, IQR)	46.3 (34–85)	30 (18.4–45)	<0.001 (Mann-Whitney)
IgG; mg/l (median, IQR)	19.7 (6.4–30.5)	9.7 (5.7–15.1)	0.058 (Mann-Whitney)
IgM; mg/l (median, IQR)	3.8 (2.5–7.2)	2.5 (1.1–5.4)	0.049 (Mann-Whitney)
Positive yeast count	15/30 (50%)	18/47 (38%)	0.3 (χ^2-test)
Streptococcius mutans ($>10^5$ CFU/ml)	15/30 (50%)	14/47 (30%)	0.07 (χ^2-test)
Lactobacilli ($>10^6$ CFU/ml)	14/30 (47%)	10/47 (21%)	0.02 (χ^2-test)
No. (%) of missing teeth (median, IQR)	2 (0–5)	0 (0–3)	0.09 (Mann-Whitney)
No. (%) of patients with periapical lesions	10/30 (33%)	12/47 (26%)	0.5 (χ^2-test)
No. (%) of patients with horizontal alveolar bone loss	20/30 (67%)	22/47 (47%)	0.09 (χ^2-test)
No. (%) of patients with vertical bone pockets	14/30 (47%)	15/47 (32%)	0.2 (χ^2-test)
No. (%) of patients with furcation lesions	4/30 (13%)	3/47 (6%)	0.3 (χ^2-test)
No. (%) of patients with dental caries	9/30 (30%)	5/47 (11%)	0.05 (χ^2-test)
No. of patients with CPI score			
2	11/30 (37%)	23/47 (49%)	0.3 (χ^2-test)
3	13/30 (43%)	16/47 (34%)	0.4 (χ^2-test)
4	6/30 (20%)	8/47 (17%)	0.7 (χ^2-test)

periodontal disease [13,29]. However, 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 [2,3]. In the present study, periodontal disease commonly affected patients with spondyloarthritides. It was common: 75% of RA patients, 56% of AS, and 45% of SPA patients showed a CPI score of 3–4, indicating serious periodontal condition. Periodontal disease was as common in MCTD as in other patient groups (53%). The MCTD patients also had a high frequency of positive yeast counts (98%) and 20% mucosal alterations. With the exception of RA [2,3], there is a scarcity of information in the literature about periodontal disease in arthritis patients. Konttinen et al. [8] 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 mucosa. Interestingly, bacteria responsible for periodontal disease were less frequently isolated in patients than in controls (Table V). This might indicate that other factors contributing to inflammation might be playing a role in periodontitis.

We have previously reported that salivary secretion rates correlated negatively with lip-biopsy focus scores in our patient cohort [4]. A close correlation between minor salivary gland inflammation and whole salivary secretion has also been observed [30]. 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, the majority of whom had secondary SS. Focused glandular sialometry and sialochemistry might be more sensitive for detecting early inflammation in the salivary glands, as shown by Kalk et al. [31]. Focus score is one of the diagnostic criteria used for secondary SS. Thus, it seems that use of focal sialadenitis alone is not sufficient to diagnose secondary SS. On the other hand, it is possible that focal sialadenitis may appear as the first sign of developing secondary SS, and actual parenchymal dysfunction will appear later.

Amylase is the most important digestive enzyme in saliva, and a major component of parotid saliva. Amylase activity in saliva is a marker of protein synthesis in acinar cells [32]. The patients with rheumatic diseases had lower activity of salivary amylase than the controls. This finding was most pronounced in the RA and MCTD patients, indicating impaired function of the salivary gland acini in these individuals. We have previously reported that focal sialadenitis is more frequently observed in these groups than in the AS or SPA patients [4]. In accordance with our present observations, van der Reijden et al. [12] have reported that concentrations of salivary amylase in cases of secondary SS are similar to those in controls.

Elkon et al. [33] 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. High levels of IgA, IgG, and IgM have also been reported in whole saliva from patients with secondary SS [33–35]. In a normal population, concentration of IgA in saliva is inversely related to salivary flow rate. Stimulating flow results in dilution of IgA in the parotid and whole saliva [34]. In the study reported here, 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 accordance with our findings, Ben-Aryeh et al. [10] 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 [36]. High numbers of IgG-producing plasma cells have been observed in lymphocytic infiltrates of minor salivary gland biopsy specimens in patients with secondary SS [37]. High serum IgA concentrations are characteristic in active AS [38]. It has been suggested that it results from stimulation of the gut immune system by Gram-negative bacteria in the gut [39]. Use of sulfasalazine by patients with active AS has been shown to restore the levels to normal of IgA in serum [37] and of secretory IgA in the gut [38]. However, in 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 with rheumatic disease 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, just as is seen in the gut of AS patients [40]. High salivary albumin concentrations have previously been reported in RA, SS, and control subjects [33] and, for example, in patients treated for lymphoma [23].

In conclusion, signs of periodontal disease and abnormalities in salivary flow and composition were more common in patients with rheumatic diseases as compared to healthy control subjects. Differences between the patient groups were further observed, thus confirming our study hypothesis. In a subgroup analysis, patients with secondary SS more frequently had lactobacilli in oral culture and more often dental caries compared with the rest of the patients. However,

most salivary biochemical markers did not differ significantly between patients with and without secondary SS. Thus, it is possible that indeed the different rheumatic diseases may influence oral health also by mechanisms other than secondary SS.

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