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Oral findings in coeliac disease and Sjögren's syndrome

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OBJECTIVE: Both coeliac disease (CD) and Sjögren's syndrome (SS) have an autoimmune background and increased risk of oral mucosal and dental abnormalities. Individuals suffering concomitantly from CD and SS could even be at a higher risk.

STUDY DESIGN: Oral mucosal and dental abnormalities were examined in 20 patients with CD + SS (mean age 61 years) and compared with age- and sex-matched controls with either CD or SS.

RESULTS: Oral mucosal changes were most common in SS (80%), followed by CD + SS (65%) and CD (40%). Coeliac-type dental enamel defects were found in 89% in CD + SS and in 88% in CD compared with only 25% in SS ($P < 0.001$). The median number of teeth was six in the CD + SS, 24 in the CD and 22 in the SS group. The DMF index was higher ($P < 0.005$) in the CD + SS than in the CD group. CD + SS was characterized by higher salivary flow rate ($P < 0.001$) and lower inflammatory focus score in the salivary glands ($P < 0.01$) than SS.

CONCLUSIONS: The co-occurrence of CD and SS should be recognized because of its effects on dental and oral mucosal health. A lower salivary gland inflammatory focus score and higher salivary flow rate in CD + SS than in SS suggests that a gluten-free diet treatment may alleviate autoimmune inflammation.

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Keywords: coeliac disease; Sjögren's syndrome; caries; enamel defects; focal sialadenitis; gluten-free diet

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Introduction

Coeliac disease (CD) is an autoimmune disorder caused by wheat gluten and related cereal peptides in genetically predisposed individuals (Mäki and Collin, 1997). It is characterized by small intestinal mucosal inflammation, villous atrophy and crypt hyperplasia, which improve with a gluten-free diet. Clinical spectrum of CD varies from overt intestinal symptoms and severe malabsorption to subclinical disease. Its prevalence can be as high as one in 100 (Fasano *et al*, 2003; Mäki *et al*, 2003). The patients are also prone to have associated autoimmune disorders such as type I diabetes and Sjögren's syndrome (SS). Previously, although we found that 3% of the patients with CD had associated SS (Collin *et al*, 1994), subclinical CD is not uncommon among the patients with SS (Iltanen *et al*, 1999). Both conditions have similar immunogenetic background, i.e. are associated with human leucocyte antigen (HLA) DR3-DQ2, and present either with circulating tissue-type transglutaminase or SSA/SSB antibodies (Gottenberg *et al*, 2003; Green and Jabri, 2003).

Extraintestinal manifestations such as dermatitis herpetiformis and osteoporosis are common in CD (Corazza *et al*, 1995; Collin *et al*, 1997). Oral involvement consists of coeliac-type dental enamel defects in permanent teeth of 50–80% of adult patients (Aine *et al*, 1990; Aquirre *et al*, 1997) and mucosal inflammatory changes including recurrent aphthous ulcers and angular cheilitis (Lähteenoja *et al*, 1998). As to SS, the condition is characterized by chronic inflammation in salivary glands resulting in dryness of mouth and increased risk for dental caries (Konttinen *et al*, 1997; Najera *et al*, 1997; Pertovaara *et al*, 1999). As oral manifestations occur frequently in individuals suffering from CD or SS, subjects having concomitantly both disorders might even be at higher risk, and require thus additional preventive measures and thorough treatment. Therefore,

we compared oral mucosal and dental findings in the patients with CD + SS with those in the age- and sex-matched patients with either disorder alone.

Patients and clinical examinations

Twenty patients with CD + SS were examined (Table 1). The mean duration from the diagnosis of CD was 9.3 years and that of SS 8.2 years. Fourteen patients were on a strict gluten-free diet and six had occasional deviations in the diet. Four patients took prednisone every day (daily dose 10 mg or lower) for SS. The age- and sex-matched controls were 20 patients for CD and another 20 patients for SS (Table 1).

The diagnosis of CD was based on the demonstration of subtotal or partial villous atrophy with crypt hyperplasia in small bowel mucosal biopsy. SS was diagnosed according to the American–European consensus group (Vitali *et al*, 2002). In the patients with CD + SS, the disease was classified as primary SS (Pertovaara *et al*, 1999). The Ethical Committee of Tampere University Hospital approved the study and an informed consent was obtained from all patients.

A complete medical history was recorded for all 60 patients. Oral mucosal abnormalities were recorded according to the World Health Organisation International Classification of Diseases to Dentistry and Stomatology (WHO ICD-DA) (WHO, 1978) and changes observed were grouped topographically (Roed-Petersen and Renstrup, 1969). A thorough dental examination was performed and caries status recorded using the DMF index (WHO, 1997). Coeliac-type dental enamel defects occurring in a systemical manner in incisors without crowns were graded as previously described (Aine *et al*, 1990). The four grades were; grade I, defect in colour of enamel; grade II, slight structural defects with typical horizontal grooves; grade III, evident structural defects with deep horizontal grooves and large vertical pits; and grade IV, severe structural defects where the shape of the tooth may be changed. Paraffin-stimulated salivary flow rates measured as previously described (Patinen *et al*, 1995). The resting salivary flow was very low in many patients with SS or CD + SS and enough saliva could not be collected. Schirmer's test was used to measure the tear fluid flow rate.

Table 1 Characteristics of patients with coeliac disease (CD) and an associated Sjögren's syndrome (SS) compared with age- and sex-matched controls with either CD or SS

	CD + SS group	*CD group*	*SS group*
Number of patients (women)	20[a] (19)	20[a] (19)	20 (19)
Age [years; mean (range)]	61 (48–78)	61 (50–80)	62 (47–79)
Disease duration from the diagnosis			
CD [years; mean (range)]	9.3 (1–25)	9.2 (1–25)	–
SS [years; mean (range)]	8.2 (1–13)	–	11.8 (5–19)
Treatment			
Gluten-free diet	20	20	0
Systemic glucocorticoids	4	0	0

[a]Three patients with concomitant dermatitis herpetiformis.

Methods

An incision biopsy was taken from minor salivary glands in the lower lip of all 60 patients under local anaesthesia (lidocaine with 2% epinephrine). An inflammatory focus score was calculated by counting from 5-μm sections the number of mononuclear cell infiltrates containing at least 50 inflammatory cells in 4-mm^2 glandular section under light microscope using a graticule and 40× magnification (Segerberg-Konttinen *et al*, 1986). When clinically indicated, a 6-mm punch biopsy was taken from mucosal lesions for histopathological examination.

A panoramic radiograph was taken from all 60 patients and the state of alveolar bone was evaluated by using a panoramic mandibular index (PMI; Benson *et al*, 1991). This was obtained by dividing the height of the inferior cortex on the right side of the mandible with the distance from the lower border of the mandible to the inferior edge of the mental foramen. Alveolar bone resorption index (Packota *et al*, 1998) was calculated for 45 patients with teeth by dividing the distance from the inferior border of the mandible to alveolar crest with the distance from inferior border of mandible to the lower edge of mental foramen.

The results are expressed as means and standard deviations or for skewed parameters as medians and interquartile ranges (IQR). The normality of variables was evaluated by the Shapiro–Wilk statistics. Statistical comparison between the groups was made using Kruskal–Wallis test, chi-square test, Fisher's exact test or Fisher–Freeman–Halton test as appropriate. *Post hoc* testing of several univariate comparisons was made with Hommel adjustments or the Dwass–Steel–Chritchlow–Flinger method at a significance level of 0.05. The α level was set at 0.05 for all tests.

Results

Oral mucosal findings

The patients with CD + SS (90%) and with SS (95%) had more often ($P < 0.001$) a history of mouth dryness compared with the patients with CD (40%; Table 2). The frequency of macroscopic mucosal lesions was high in SS (80%), lower in CD + SS (65%) and lowest in CD (40%, $P = 0.043$) group. Six patients with CD + SS, six with SS and one with CD had mucosal ulcers. The mean number of affected mucosal locations was 1.7 (range 1–4) in CD + SS, 2.0 (range 1–3) in CD and 3.1 (range 1–5) in SS ($P > 0.05$).

Salivary and lacrimal flow rates and salivary gland focus score

The patients with CD + SS had higher ($P < 0.001$) stimulated salivary flow rate compared with the patients with SS (Table 2). Salivary gland inflammatory focus score was highest (median 5.5) in the SS, lower in the CD + SS (3.7) and lowest ($P = 0.002$) in the CD (2.1,

Table 2 Oral mucosal, salivary and dental findings in coeliac disease (CD) with an associated Sjögren's syndrome (SS) and controls with CD or SS alone

	Group				
	CD + SS	*CD*	*SS*	P *value*	*Multiple comparison*
Oral mucosal findings					
History of mouth dryness [*n* (%)]	18 (90)	8 (40)	19 (95)	<0.001	CD + SS/CD, CD/SS
Mucosal abnormalities [*n* (%)]	13 (65)	8 (40)	16 (80)	0.043	CD/SS
Patchy redness	8	3	13		
Ulcers	6	1	6		
Lichenoid/hyperplastic	3	4	7		
Leukoplakia	1	2	5		
Salivary and lacrimal findings					
Salivary flow rate [ml min^{-1}; median (IQR)]	0.8 (0.4–1.0)	1.4 (1.0–1.8)	0.2 (0.1–0.5)	<0.001	CD + SS/CD, CD + SS/SS, CD/SS
Inflammatory focus score [median (IQR)]	3.7 (2.6–5.3)	2.1 (1.0–3.1)	5.5 (2.6–9.1)	0.002	CD + SS/CD, CD/SS
Lacrimal excretion [mm $(5\ min)^{-1}$; median (IQR)]	3.7 (2.6–5.4)	8.2 (2.6–16.1)	1.5 (1.0–5.9)	0.003	CD/SS
Dental findings					
Patients with teeth [*n* (%)]	12 (60)	17 (85)	16 (80)	0.25	
Number of teeth [median (IQR)]	6 (0–25)	24 (14–27)	22 (9–25)	0.072	
DMF (28) [median (IQR)]	28 (25–28)	22 (21–28)	27 (23–28)	0.005	CD + SS/CD
Coeliac-type enamel defects [*n* (%)]	8/9 (89)	14/16 (88)	3/12 (25)	<0.001	CD + SS/SS, CD/SS
Grade I + II	6	10	2		
Grade III + IV	2	4	1		

IQR 1.0–3.1) group. The focus scores in the four patients in CD + SS group using systemic glucocorticoids did not differ from the rest of the patients in the same group.

Dental findings

Twelve patients with CD + SS had teeth compared with 17 with CD and 16 with SS ($P = 0.25$; Table 2). The median number of teeth was 6 in the CD + SS, 24 in the CD ($P = 0.072$) and 22 in the SS group. DMF index was similar in the CD + SS (28) and SS (27) groups but significantly lower (22, $P = 0.005$) in the CD group. Frequency of celiac-type enamel defects was 89% in the CD + SS and 88% in the CD group compared with 25% in the SS group ($P < 0.001$; Table 2).

Radiological findings

PMI index was 0.37 (range 0.13–1.0) in the CD + SS, 0.38 (0.13–0.6) in the CD and 0.40 (0.25–0.88) in the SS group ($P > 0.05$). Mandibular alveolar bone resorption index was 2.82 in the CD + SS, 2.83 in the CD and 2.94 in the SS group ($P > 0.05$).

Discussion

More than a half of the adult patients with CD present with oral mucosal abnormalities (Lähteenoja *et al*, 1998) and coeliac-type dental enamel defects (Aine *et al*, 1990, Aquirre *at al*. 1997). The patients with SS frequently have dental caries because of decreased salivary flow (Konttinen *et al*, 1997; Najera *et al*, 1997; Pertovaara *et al*, 1999). Individuals suffering concomitantly from CD and SS might be even at a higher risk of mucosal and dental abnormalities. In the present study, eight of the 20 patients with CD + SS had lost their teeth, and the median number of teeth in the CD + SS group was only 6 compared to 24 in the CD and 22 in the SS group. This difference did not reach statistical significance ($P = 0.072$). However, the DMF index was significantly higher in the patients with CD + SS than in those with CD, but as high as in the patients with SS, suggesting that the increased caries index is in part linked to impaired salivary gland function and xerostomia in SS (Pedersen *et al*, 1999). The stimulated salivary flow rate was, however, significantly less impaired in the patients with CD + SS than in those with SS only. It is therefore, possible that the coeliac-type dental enamel defects, the prevalence of which was as high as 89% in the CD + SS group, could have an additive effect on the caries risk.

History of mouth dryness was common in all three patient groups of the present study. The frequency was 40% in the patients with CD which is, however, almost the same as that (36.4%) reported in Finnish control subjects in a recent type 2 diabetes study (Collin *et al*, 2000). In agreement with Lähteenoja *et al* (1998) we found macroscopic mucosal changes in as many as 40% of the present patients with CD. Prevalence was even higher in the patients with CD + SS (65%) and highest (80%) in those with SS. This suggests that low salivary flow rate and concomitant dryness in the mouth in SS affect mucosal health more than the inflammation associated with CD only (Patinen *et al*, 1997; Lähteenoja *et al*, 1998). Falling in the line with lower frequency of mucosal changes and higher salivary flow rates, the patients with CD + SS had lower, although not satistically significantly different, salivary gland inflammatory focus score than the patients with SS only. The low-dose prednisone treatment in four of the 20 patients can hardly contribute to this finding (Malmström *et al*, 1983). It is unlikely that the difference of 3 years from

the diagnosis could explain the higher salivary flow rates in the patients with CD + SS compared with the patients with SS only. In both the groups, the follow-up time from the diagnosis of SS was relatively long, i.e. over 8 years. Furthermore, it is impossible to estimate when salivary gland inflammation in SS in fact starts to develop. One reason for the observed differences might be that the patients with CD + SS had adhered to a gluten-free diet for several years. The diet treatment had previously been suggested to prevent the development of associated autoimmune disorders in CD (Ventura *et al*, 1999). Moreover, diabetes-related and other organ-specific auto-antibodies have decreased or disappeared in the patients with CD after adherence to a gluten-free diet (Ventura *et al*, 2000). Whether gluten-free diet might alleviate autoimmune inflammatory process in the salivary glands of SS patients with associated CD or even in SS patients without CD is an intriguing hypothesis and subject of further studies.

Interestingly, the median focus score of the CD patient group was 2.1 and the interquartile range values being 1.0–3.1. This implies that several of the present patients with CD but without SS as diagnosed according to currently valid criteria could have a subclinical autoimmune focal sialoadenitis. Therefore, it is likely that the autoimmune exocrinopathy disease process characteristic for SS can start before the outbreak of the clinical disease. This also implies that the overlap between CD and SS maybe more extensive than is apparent at the first sight. It is also a matter of discussion whether SS in the patients with CD should be classified as secondary or primary SS.

Apart from many associated autoimmune conditions, such as thyroid disease, patients with CD have an increased risk for malignant lymphoma (Holmes *et al*, 1989) and osteoporosis (Corazza *et al*, 1995; Valdimarsson *et al*, 1996; West *et al*, 2003), which warrants the early diagnosis and dietary treatment. Panoramic radiographs detect osteoporotic changes, e.g. in postmenopausal women (Klemetti *et al*, 1993) but these patients with CD + SS or CD did not show such changes. It is, however, possible that more sensitive methods such as dual-energy X-ray absorptiometry (Valdimarsson *et al*, 1996) might have revealed signs of osteoporosis, which could be one additional reason for the impaired dental health as observed in the present patients with CD + SS.

In conclusion, the association of CD with SS comprises a high frequency of oral mucosal abnormalities, coeliac-type dental enamel defects and caries. Detection of concomitant CD in patients with SS is important: introduction of a gluten-free diet reduces the risks of complications in CD and might also alleviate inflammation and dysfunction of the salivary glands.

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References

Aine L, Mäki M, Collin P *et al* (1990). Dental enamel defects in coeliac disease. *J Oral Pathol Med* **19:** 241–245.

Aquirre JM, Rodriquez R, Oribe D *et al* (1997). Dental enamel defects in coeliac patients. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **84:** 646–650.

Benson BW, Prohoda TJ, Glass BJ (1991). Variations in adult cortical bone mass measured by a panoramic mandibular index. *Oral Surg Oral Med Oral Pathol* **71:** 349–356.

Collin P, Reunala T, Pukkala E *et al* (1994). Coeliac disease – associated diseases and survival. *Gut* **35:** 1215–1218.

Collin P, Reunala T, Rasmussen M *et al* (1997). High incidence and prevalence of adult coeliac disease. Augmented diagnostic approach. *Scand J Gastroenterol* **32:** 1129–1133.

Collin H-L, Niskanen L, Uusitupa M *et al* (2000). Oral symptoms and signs in elderly patients with type 2 diabetes. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **90:** 299–305.

Corazza GR, Di Sario A, Cecchetti L *et al* (1995). Bone mass and metabolism in patients with celiac disease. *Gastroenterology* **109:** 122–128.

Fasano A, Berti I, Geraduzzi T *et al* (2003). Prevalence of coeliac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. *Arch Intern Med* **163:** 286–292.

Gottenberg JE, Busson M, Loiseau P *et al* (2003). In primary Sjogren's syndrome, HLA class II is associated exclusively with autoantibody production and spreading of the autoimmune response. *Arthritis Rheum* **48:** 2240–2245.

Green PH, Jabri B (2003). Coeliac disease. *Lancet* **362:** 383–391.

Holmes GKT, Prior P, Lane MR *et al* (1989). Malignancy in coeliac disease – effect of a gluten-free diet. *Gut* **30:** 333–338.

Iltanen S, Collin P, Korpela M *et al* (1999). Coeliac disease and markers of celiac disease latency in patients with primary Sjögren's syndrome. *Am J Gastroenterol* **94:** 1042–1046.

Klemetti E, Kolmakov S, Heiskanen P *et al* (1993). Panoramic mandibular index and bone mineral densities in postmenopausal women. *Oral Surg Oral Med Oral Pathol* **75:** 774–779.

Konttinen YT, Platts LA, Tuominen S *et al* (1997). Role of nitric oxide in Sjögren's syndrome. *Arthritis Rheum* **40:** 875–883.

Lähteenoja H, Toivanen A, Viander M *et al* (1998). Oral mucosa changes in coeliac patients on a gluten-free diet. *Eur J Oral Sci* **105:** 899–906.

Mäki M, Collin P (1997). Coeliac disease. *Lancet* **349:** 1755–1759.

Mäki M, Mustalahti K, Kokkonen J *et al* (2003). Prevalence of coeliac disease among children in Finland. *N Engl J Med* **348:** 2568–2570.

Malmström M, Seppä A, Konttinen YT *et al* (1983). Sjögren's syndrome in systemic lupus erythematosus and rheumatoid arthritis: immune effector cells in salivary glands. *Rheumatol Int* **3:** 1–5.

Najera MP, al-Hashimi I, Plemons *et al* JM (1997). Prevalence of periodontal disease in patients with Sjögren's syndrome. *Oral Surg Oral Med Oral Pathol Radiol Endod* **83:** 453–457.

Packota GV, Hoover JN, Neufeld BD (1998). A study of the height of intact alveolar bone on panoramic radiographs of adult patients. *J Prosthet Dent* **60:** 504–509.

Patinen P, Björksten F, Malmström M *et al* (1995). Salivary and serum IgA antigliadin antibodies in dermatitis herpetiformis. *Eur J Oral Sci* **103:** 280–284.

Patinen P, Savilahti E, Hietanen J *et al* (1997). Intraepithelial lymphocytes bearing the gamma/delta receptor in the oral and jejunal mucosa in patients with dermatitis herpetiformis. *Eur J Oral Sci* **105:** 130–135.

Pedersen AM, Reibel J, Nordgarden H *et al* (1999). Primary Sjogren's syndrome: salivary gland function and clinical oral findings. *Oral Dis* **5:** 128–138.

Pertovaara M, Korpela M, Uusitalo H *et al* (1999). Clinical follow up study of 87 patients with sicca symptoms (dryness of eyes or mouth, or both). *Ann Rheum Dis* **58:** 423–427.

Roed-Petersen B, Renstrup G (1969). A classification of the oral mucosa suitable for electronic data processing its application to 560 leukoplakias. *Acta Odontol Scand* **27:** 681–695.

Segerberg-Konttinen M, Konttinen YT, Bergroth V (1986). Focus score in the diagnosis of Sjögren's syndrome. *Scand J Rheumatol* **61** (Suppl.)**:** 47–51.

Valdimarsson T, Löfman O, Toss G *et al* (1996). Reversal of osteopenia with diet in adult coeliac disease. *Gut* **38:** 322–327.

Ventura A, Magazzu G, Greco L (1999). Duration of exposure to gluten and risk of autoimmune disorders in patients with celiac disease. SIGEP Study Group for Autoimmune Disorders in Coeliac Disease. *Gastroenterology* **117:** 297–303.

Ventura A, Neri E, Ughi C, Leopaldi A, Citta A, Not T (2000). Gluten-dependent diabetes-related and thyroid-related autoantibodies in patients with celiac disease. *J Pediatr* **137:** 263–265.

Vitali C, Bombardieri S, Jonsson R *et al* (2002). Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* **61:** 554–558.

West J, Logan RF, Hill PG *et al* (2003). Seroprevalence, correlates, and characteristics of undetected coeliac disease in England. *Gut* **52:** 960–965.

WHO (1978). *Application of the International Classification of Diseases to Dentistry and Stomatology (ICD-DA)*, 2nd edn. World Health Organization: Geneva.

WHO (1997). *Oral health surveys basic methods*. World Health Organization: Geneva.