

# Oral mucosal changes in coeliac patients on a gluten-free diet

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Oral mucosal lesions or dental enamel defects may be the only presenting features of coeliac disease. A series of 128 patients with coeliac disease (CD) on a gluten-free diet (GFD), 8 patients with a newly diagnosed CD, and 30 healthy controls participated in a clinical and histopathological study of their oral mucosa. Oral mucosal lesions occurred in 71/128 GFD-treated CD patients, in 4/8 untreated and in 10/30 controls, and oral symptoms in 85/128, in 6/8 and in 10/30, respectively. Five CD patients had aphthous ulcers. Moderate to severe lymphocytic inflammation occurred in 36/117 and in 14/117 of the biopsy specimens of GFD-treated CD patients, in 1/8 and 2/8 of untreated CD patients, and in 3/30 and in 1/30 of controls, respectively. Intraepithelial T-cells were significantly more frequent in GFD-treated CD patients than in controls. There was no difference between untreated CD patients and controls. In the lamina propria of the GFD-treated CD patients, T-cells were more frequent than in the other groups. Mast cells were significantly more frequent in patients with GFD-treated CD. Nine GFD-treated CD patients had raised serum endomysium IgA antibody titres, although five of them reported to follow a strict GFD. A lack of strict compliance with a GFD may be related to the high prevalence of oral changes and symptoms. In addition, T-cell infiltration in the oral mucosa tends to increase with a longer duration of CD, independent of GFD-treatment. Clinically, it is important to study the oral cavity of patients suspected of having CD where the only clue to the disease may reside, since no less than 66% of the patients in this study had oral symptoms.

**Hannu Lähteenoja<sup>1</sup>,  
Auli Toivanen<sup>1</sup>, Markku Viander<sup>2</sup>,  
Markku Mäki<sup>3</sup>, Kerttu Irjala<sup>4</sup>,  
Ismo Rähä<sup>5</sup>, Stina Syrjänen<sup>6</sup>**

<sup>1</sup>Department of Medicine, <sup>2</sup>Department of Medical Microbiology, University of Turku, Turku, <sup>3</sup>Department of Pediatrics, University Hospital of Tampere and Institute of Medical Technology, University of Tampere, Tampere, <sup>4</sup>Central Laboratory, University Hospital of Turku, <sup>5</sup>Turku City Hospital, Turku, <sup>6</sup>MediCity Research Laboratory and Institute of Dentistry, University of Turku, Turku, Finland

Hannu Lähteenoja, University Hospital of Turku, Department of Medicine, Kiinanmyllynkatu 2–5, FIN-20520 Turku, Finland

Telefax: +358–22612030  
E-mail: hannu.lahteenoja@tyks.fi

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Coeliac disease (CD) is characterised by villous atrophy and crypt hyperplasia in the mucosa of the small bowel. Patients with CD recover completely if they adhere strictly to a gluten-free diet (GFD) for life (1, 2). GFD may protect against malignancy of the gut (3), which is a known sequel of untreated CD.

The pathogenesis of CD is still poorly understood, but genetic and immunologic factors seem to be involved (2, 4–6). Currently, much attention has been paid to the identification of subclinical CD, because the disease may often be clinically atypical, and all patients may not have the abdominal symptoms and signs of malabsorption of classical CD; the disease may even be clinically silent in older children and adults (7–8). Serologic screening of high-risk patients for CD may be appropriate

(9), and antibody-positive patients with no or minor mucosal abnormalities should be regularly followed up (10).

COLLIN *et al.* (11) showed that patients with CD have certain concomitant diseases more often than control patients. Insulin-dependent diabetes mellitus, autoimmune thyroid disease, connective tissue diseases and Sjögren's syndrome are more frequent among CD patients than in the general population (11). CD and these associated diseases can lead to oral symptoms and signs. Dental hypoplasia is associated with CD (12). Enamel defects occur in 96% of the children and in 83% of the adults with CD. These enamel defects may follow a specific symmetrical or chronological distribution (13–14). The pathogenesis of these oral lesions is not fully understood (15).

Oral lesions may provide a valuable clinical clue for CD (16). CD patients may have oral ulcers similar to those seen in patients with recurrent aphthous stomatitis (RAS) (21). The detection of CD in 4% of RAS patients implies that all iron-deficient and folate-deficient patients should undergo intestinal biopsy to exclude CD (17).

We have studied the mucosal lesions and other oral manifestations of a population of CD patients and studied the associations between the oral mucosal changes with epidemiological, clinical and biochemical variables and with the CD-associated serologic findings and the patients' adherence to a GFD. Special attention was paid on the histological findings of the oral mucosa.

## Patients, materials and methods

### Patients

Patients with treated CD were enrolled among the members of the Coeliac Association of Turku, Finland. All members of the association with a diagnosis of CD were invited to participate in the study regardless of age or sex or any other demographic circumstance. The invitation included a questionnaire and a brief summary of the study. The invitation was accepted by 168 patients out of 402 to whom it was sent. Forty patients had the diagnosis of CD based on serological positivity for

CD alone and were excluded, since it was required that the diagnosis of CD must be confirmed by small-intestine biopsy (partial or subtotal atrophy); this was the case in the remaining 128 patients, which were enrolled into the study. The mean age of the patients was  $42.7 \pm 14.7$  yr (mean  $\pm$  SD) (range 3–86 yr), and the female:male ratio was 4.3:1. The duration of CD was less than 5 yr for 58/127 patients (45.6%) and more than 5 yr for 69/127 patients (54.3%) (Table 1).

In addition, 8 consecutive, newly diagnosed patients with CD (2 males and 6 females; mean age  $44.6 \pm 10.2$  yr, range 21–73 yr) were invited to the study. Their diagnosis of CD was also based on a positive coeliac serology and a small intestine biopsy with total or subtotal atrophy (Table 1).

The control group consisted of 30 subjects without CD as determined on the basis of a normal small intestine biopsy specimen obtained by gastro-duodenoscopy or of a negative coeliac serologic study (Table 1). The control patients were matched for the two other investigation groups.

The study was approved by the Ethics Committee of the Faculty of Medicine, University of Turku.

### Clinical examination and questionnaire

At study entry, a clinical examination was performed and all subjects filled in an extensive, struc-

Table 1  
*Characterisation of the subjects studied*

	CD-patients (newly diagnosed) <i>n</i> = 8	CD-patients (previously diagnosed) <i>n</i> = 128	Healthy control subjects <i>n</i> = 30	Level of significance, CD patients <i>n</i> = 128 versus controls <i>n</i> = 30
Sex: female:male ratio	3:1	4.3:1	19:11	
Age: mean years $\pm$ SD	$44.6 \pm 10.2$	$42.7 \pm 16.7$	$47.9 \pm 14.3$	
Small intestine biopsy:				
total/subtotal villous atrophy	8	128	0	
Gluten-free diet:				
strictly holding	–	102	0	
rather holding	–	23	0	
do not follow	–	2	0	
Oral symptom:				
soreness or burning sensation in tongue	2	38 (29.6%)	3 (10.0%)	0.027
dryness of the mouth	1	29 (22.6%)	7 (23.0%)	0.937
soreness of the mouth	1	34 (26.5%)	5 (17.0%)	0.258
Oral lesion:				
mucosal erythema	2	12 (9.4%)	5 (17.0%)	0.246
mucosal ulceration	1	38 (29.6%)	0 (0.0%)	0.001
erythematous tongue	0	6 (4.5%)	1 (3.0%)	0.746
atrophy in tongue	1	5 (3.9%)	1 (3.0%)	0.883
aphthous ulcer	1	4 (3.1%)	0 (0.0%)	0.327
Number of patients with oral symptoms	5	85 (66.4%)	10 (33.0%)	0.001
Number of patients with oral mucosal lesions	4	71 (55.5%)	7 (23.0%)	0.002

tured questionnaire on the medical history, associated diseases, oral changes and other manifestations that the subject was aware of. A careful clinical examination of the entire oral cavity was carried out by one of the authors (HL).

#### Biopsies and immunohistochemical staining

A biopsy, approximately 4 mm in diameter, was taken by punching/incision from the buccal mucosa adjacent to the second upper molar under local anaesthesia (Xylocain<sup>®</sup> adrenaline; ASTRA, Södertälje, Sweden) of each subject. The specimen was fixed in formalin, embedded in paraffin, and stained using haematoxylin-eosin (H-E) and with toluidine blue, the latter for identification of mast cells. T- and B-lymphocytes were identified with monoclonal antibodies in sequential sections. The monoclonal antibodies were purchased from Dako (Copenhagen, Denmark). Formalin-fixed and paraffin-embedded sections placed on organosilane-coated slides were deparaffinised in xylene and dehydrated with graded alcohol. The sections were then treated with pepsin at 37°C for 10 min. Endogenous peroxidase activity was blocked with 5% H<sub>2</sub>O<sub>2</sub> for 5 min. The sections were first incubated with 1.5% normal goat serum (Vector Laboratories, Burlingame, CA, USA) for 15 min (to reduce non-specific antibody binding), and then incubated with the primary antibody (in blocking serum) overnight at +4°C. Then the sections were incubated with the secondary biotinylated antibody (antimouse IgG; Vector Laboratories) for 30 min, followed by incubation with avidin-biotin-peroxidase complex (Vectastain Elite ABC Kit; Vector Laboratories) for 30 min. The immunoperoxidase reaction was developed using 3,3'-diaminobenzidine (DAB; Sigma Chemical Co., St. Louis, MO, USA) for 5 min. Finally, the sections were counterstained with Meyer's haematoxylin, dehydrated and mounted with permount. Positive and negative control sections were included in all stainings. Sections treated with blocking serum without primary antibodies served as negative controls, and formalin-fixed, paraffin-embedded sections from the tonsils and minor salivary glands of patients with Sjögren's syndrome were used as positive controls. CD 20-positive B-cells showed strong immunostaining.

The intensity of the inflammation in the H-E stainings was graded as none or low (1), moderate (2) or intense (3). These biopsy specimens were assessed by one of the authors (SS).

The total count of the positively stained mast cells, B-cells and T-cells in the epithelium and lamina propria were then counted under a light microscope through a calibrated graticule at  $\times 400$

magnification. Ten fields (0.12 mm  $\times$  0.12 mm) were counted in the buccal epithelium and twenty fields in the lamina propria. The first ten fields (named as the first layer) in the lamina propria were examined just below the basement membrane and the other ten fields (named as the second layer) the width of the graticule (=0.012 mm) below the first layer. The results are given as cells/mm<sup>2</sup>. The counting was performed by one of the authors (HL).

#### Biochemical tests

The following blood tests were performed: haemoglobin, mean corpuscular volume (MCV), serum iron, serum ferritin, serum vitamin B<sub>12</sub>, red cell folate, serum IgA, IgG and IgM. Antibodies to gliadin (AGA) were assayed by a solid-phase enzyme linked immunosorbent assay (ELISA) (18) using commercial purified gliadin (BDH, Poole, UK). Serum IgA and IgG antibodies against reticulin (ARA) were measured using an indirect immunofluorescence method (19–20). Fixed rat stomach, liver and kidney were used as the antigen for reticulin antibody testing. The first serum dilution for reticulin was 1:5. The conjugate was purchased from Dako. Serum antiendomysial antibodies (EmA) were also measured with an indirect immunofluorescence test (21) using commercial monkey oesophagus as the antigen (Biosystems, Barcelona, Spain).

#### Statistical methods

The  $\chi^2$ -test (Tables 1 and 2) and the one-sided/two-sided *t*-test (Tables 3 and 4) were used to compare differences between CD patients and the healthy control subjects.

Table 2  
Results of histopathologic analysis of buccal biopsies

Series	Degree of grading	Inflammatory cell infiltration
CD-patients (gluten-free diet treated)* <i>n</i> = 117	none or mild	67
	moderate	36
	intense	14
CD patients (untreated)* <i>n</i> = 8	none or mild	27
	moderate	2
	intense	1
Healthy control subjects <i>n</i> = 30	none or mild	5
	moderate	2
	intense	1

\*CD patients versus healthy controls, significant difference ( $P = 0.001$ ).

Table 3

*Intraepithelial B-cells, T-cells, plasma-cells and mast cells in the oral mucosa of patients with CD and healthy control subjects*

	B-cells	T-cells	Mast-cells
Untreated CD patients ( $n=8$ ), median ( $\pm$ SD) (cells/mm <sup>2</sup> )	0	22.9 $\pm$ 30.4*	0
CD patient on a gluten free diet ( $n=52$ )	1.4 $\pm$ 6.94	92.3 $\pm$ 107.6**	0.7 $\pm$ 4.6
Healthy control subjects ( $n=27$ )	0	42.3 $\pm$ 41.6	0

\*untreated CD patients versus GFD-treated CD patients, significant difference ( $P=0.0363$ ).

\*\*GFD-treated CD patients versus healthy controls, significant difference ( $P=0.0001$ ). *t*-test procedure.

## Results

A total of 128 treated CD patients (GFD), 8 newly diagnosed CD patients, and 30 healthy control subjects were included. The patients filled in a questionnaire, but as they were not always able to give exhaustive answers, the numbers of patients responding to the various questions on their disease histories were variable. Some of the biopsy specimens were of poor quality, and the number of acceptable specimens was also therefore variable.

The duration of CD among the treated CD patients was reported as <1 yr by 7 (5.5%), 1–2 yr by 17 (13.3%), 2–5 yr by 34 (26.5%), 5–10 yr by 38 (29.6%), and >10 yr by 31 patients (24.2%)

( $n=127$ ). One hundred and three of 128 (80.4%) of the CD patients reported that they adhered strictly to the GFD and 23/128 (18.0%) almost strictly. Only two patients (1.6%) did not follow diet recommendations.

Fifteen of 126 CD patients with treated disease (11.9%), none of the 8 CD patients with untreated disease and four control subjects (13.3%) were smokers. Seventy-eight of 124 CD patients (62.9%), 5/8 of CD patients with untreated disease, and 16 control subjects (53.3%) reported slight or moderate alcohol intake, but there were no heavy drinkers. Neither smoking nor alcohol intake had any significant association with the prevalence of oral symptoms or lesions.

Lactose intolerance was common among CD patients. Of the 128 treated CD patients, 53 patients (41.4%), one of the controls, and none of CD patients with a untreated disease had lactose intolerance as confirmed by a laboratory lactose tolerance test.

Table 1 summarises the most common oral symptoms and clinical lesions in the 128 treated CD patients, in 8 newly diagnosed CD patients, and the 30 control subjects. The tongue (soreness or burning sensation) was most frequently affected; this was the case in 38/128 of the treated CD patients (29.6%) and in 3/30 (10.0%) of the control subjects ( $P=0.027$ ). Six of the 8 newly diagnosed CD patients admitted to having oral symptoms. Totally, oral mucosal lesions were present in 71 of 128 patients (55.5%) and in 7 of 30 control subjects (23.0%) ( $P=0.002$ ), whereas 4/8 of newly diagnosed CD patients had oral lesions. Oral lesions

Table 4

*B-cells, T-cells, plasma cells and mast cells in lamina propria in the oral mucosa of patients with CD and healthy controls*

	B-cells	T-cells	Mast-cells
Untreated CD patients ( $n=8$ ), median ( $\pm$ SD), (cells/mm <sub>2</sub> )			
Layer 1	0	304.7 $\pm$ 419.2	54.8 $\pm$ 62.5 <sup>5</sup>
Layer 2	0	107.6 $\pm$ 129.8	34.7 $\pm$ 23.6 <sup>3,4</sup>
CD patient on a gluten free diet ( $n=52$ )			
Layer 1	27.8 $\pm$ 125.6	414.3 $\pm$ 962.6	113.8 $\pm$ 70.1
Layer 2	17.4 $\pm$ 125.6	119.4 $\pm$ 247.0 <sup>1</sup>	109.0 $\pm$ 83.1
Healthy control subjects ( $n=27$ )			
Layer 1	0	183.2 $\pm$ 186.0	104.1 $\pm$ 77.0
Layer 2	0	44.4 $\pm$ 68.7	81.2 $\pm$ 50.0

<sup>1</sup> CD patients on a GFD versus healthy controls, significant difference ( $P=0.0611$ ).

<sup>2</sup> CD patients on a GFD versus healthy controls, significant difference ( $P=0.0005$ ).

<sup>3</sup> untreated CD patients versus healthy controls, significant difference ( $P=0.0497$ ).

<sup>4</sup> untreated CD patients versus CD patients on a GFD, significant difference ( $P=0.0301$ ).

<sup>5</sup> untreated CD patients versus CD patients on a GFD, significant difference ( $P=0.0002$ ).

were defined as strong erythema, lingual atrophy or ulcers. Some of the subjects had prostheses and the associated erythema, if present, was not taken into account. The lesions were located in the buccal mucosa, lips, palate or tongue. Ulcers were the most common type of oral lesion and they were purpuric, papular, or erosive in nature, often surrounded by erythematous margins (Figs. 1 and 2). Non-aphthous buccal mucosal ulcers were present in 38 CD patients with treated CD (29.6%), in none of the control subjects ( $P=0.001$ ), and in 1/8 of patients with untreated CD. At the time of examination, 4 patients treated for CD had aphthous ulcers but none of the control subjects ( $P=0.327$ ).

Oral changes were as common in the group who followed a strict GFD (in 57/103 patients, 55.3%) as in the group who followed a GFD almost strictly (in 13/23 patients, 56.2%).

Eleven patients with treated CD had oral mucosal lesions at a three sites or more. Seven had also lactose intolerance. One patient (a 52-yr-old



Fig. 1. An erosive ulcer in oral mucosa of a 50-yr-old woman with CD.



Fig. 2. A micrograph of a biopsy sample taken from the buccal mucosal lesion shown in Fig. 1. The epithelium is atrophic and a dense lymphocytic inflammatory cell infiltration is seen in the connective tissue. H-E staining, original magnification  $\times 136$ .

woman) had ulcers of the lower lip, tongue and buccal mucosa. The palate was erythematous. At the time of diagnosis of CD she had had severe oral lesions. Her villous atrophy of the small intestine healed, and the coeliac specific antibodies disappeared after she had stood on a strict GFD, but the oral manifestations persisted. Six CD patients treated for B<sub>12</sub>-vitamin deficiency had oral symptoms more often than the other GFD-treated CD patients ( $\chi^2$ ,  $P<0.050$ ). In general, women (87/106; 82%) had oral symptoms more often than men (11/22; 50%) ( $P<0.001$ ). The medication used by the patients was not related to oral clinical lesions or symptoms. Clinically and statistically, the oral lesions or symptoms could not be associated with any other disease or with mechanical irritation. Therefore, the high prevalence of oral afflictions was considered to be associated with CD.

Only severe grade III-IV (Aine's classification; 13) enamel defects were recorded. Such defects occurred in 13/128 patients (10.1%) (Fig. 3). The mean age of the patients with enamel defects was  $37.3 \pm 13$  yr (mean  $\pm$  SD) (range 12–55 yr).

Serum ferritin values below 20 mg/l indicate iron deficiency anaemia. The mean ferritin value was  $49 \pm 44$  mg/l and the mean haemoglobin values  $133 \pm 10$  g/l. Values that were below either of these averages occurred in 26/95 of the treated CD patients (27.3%), 7/30 of the 30 controls (23.0%) and 3/8 of the untreated CD patients. One 36-yr-old woman among the untreated CD patients had a low haemoglobin value (115 mg/l) and the ferritin value was undetectable, which implies that she lacked iron stores in the bone marrow. Still she had no oral lesions, although she did claim to have a burning sensation in tongue. The erythrocyte folate content was low ( $<445$  nmol/l) in three GFD-treated CD patients (3.2%) and in one control subject, but in none of the CD patients with untreated disease.



Fig. 3. Coeliac dental enamel changes in a 64-yr-old woman with CD.

Six CD patients (6.3%) had antimitochondrial antibodies, three patients (3.2%) had antibodies against the cell membrane, and one patient had antinuclear antibodies. IgA-AGA was elevated in 8/95 treated CD patients (8.4%) and IgG-AGA in 12/95 treated CD patients (12.6%). IgA-ARA was elevated in 4 treated CD patients (4.2%) and IgG-ARA in none. Nine treated CD patients (9.5%) had raised IgA-EmA. Seven of 8 untreated CD patients had strongly raised IgA-EmA and IgA-ARA values. One woman with subtotal villous atrophy in her small intestine had normal IgA-EmA value, but the IgA-ARA value was slightly raised.

None of the control subjects had raised AGA, ARA, or EmA values. Surprisingly, neither the biochemical blood values nor the coeliac antibody titres of the CD patients was significantly associated with the presence of oral lesions or symptoms.

Table 2 shows the histological findings. There was inflammatory cell infiltration of the buccal mucosa of the treated CD patients in 117 cases (103 lymphocytic, 12 lymphocytic and plasma cells, 2 plasma cells). In the untreated CD patients and control subjects, the inflammation was lymphocytic, if present. Oral symptoms occurred in 13/14 of the treated CD patients (92.9%) with severe inflammation, in 29/36 (80.5%) with moderate inflammation and in 48/67 (71.6%) with mild inflammation. Surprisingly, 3 control subjects (all female, age 72–76 yr) had moderate to severe inflammation in the oral mucosa in H-E-stained biopsy specimens. Only one of these 3 subjects had an erythematous buccal mucosa, the two others subjects were clinically healthy. One woman with a severe oral inflammatory lesion in the control group had mild gastroesophageal reflux. None reported use of any medication.

The number of B-cells, T-cells and mast cells in the oral mucosa of the CD patients and controls subjects are given in Tables 3 and 4. Intraepithelial T-cells were significantly increased in GFD-treated CD patients versus healthy controls ( $P=0.0001$ ) and in GFD-treated CD patients versus untreated CD patients ( $P=0.0363$ ) (Table 3). Table 4 shows that T-cells were clearly more present in the lamina propria of oral mucosa of GFD-treated CD patients than in that of healthy controls ( $P=0.0611$ ) (Fig. 4). The lamina propria of the healthy controls contained more abundantly mast cells than did the lamina propria of untreated CD patients ( $P=0.0497$ ), and GFD-treated CD patients more than untreated CD patients ( $P=0.0002$ ). Mast cells were most abundant around blood vessels, nerve endings and ducts.

There was no significant association between the number of oral lesions found at clinical examination

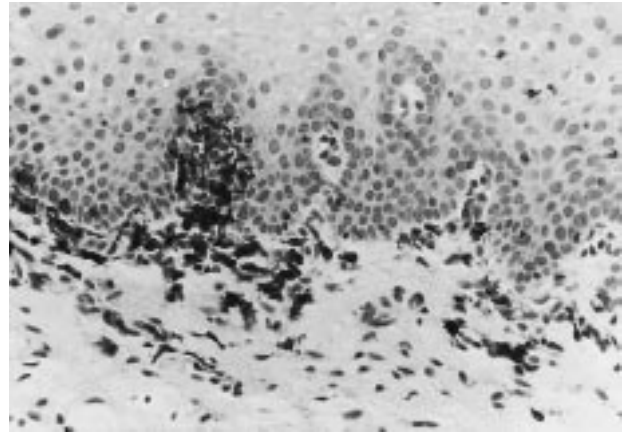


Fig. 4. Infiltration of T-cells lymphocytes as shown by immunocytochemistry. The patient was on a gluten-free diet. Original magnification  $\times 340$ .

and the grade of the inflammation or the number of inflammatory cells in the buccal biopsy of patients with CD or controls.

## Discussion

It is well known that CD affects the mucosa of the small intestine and that gastric diseases, especially atrophic gastritis, are associated with it. The involvement of the oral mucosa in CD has not attracted much attention, although the mouth is part of the gastrointestinal system. (6). There is a lack of data on the prevalence of oral mucosal changes in patients with GFD-treated CD. This study was conducted to determine the frequency and type of oral mucosal changes associated with GFD-treated CD.

In an earlier study by AINE *et al.* (13), 3% of adult CD patients had grade III or grade IV enamel defects. In our series, the figure was 10.3%, but this included paediatric patients. In the study of AINE *et al.* (13), 30% of their children with CD had grade III–IV enamel defects. The difference between the children and adults might indicate that the adults often develop CD after the critical age of 7 yr when the crowns of the permanent teeth have developed. It should be noted that the changes in the permanent teeth may be the only sign of an otherwise symptomless CD. None of the untreated CD patients had enamel changes.

Oral changes were common in patients with a known diagnosis of CD (totally in 55.5%), although all except two patients were on a GFD, 80.2% of them following the GFD strictly. Yet, 9 patients of this group had raised IgA-EmA and 5 of them reported that they were following a strict GFD and 4 an almost strict GFD. Many CD patients probably do not follow a GFD very strictly, and if this is the case, oral manifestations of CD might there-

fore be more common than expected. Interestingly, occasional dietary laxity was associated neither with the oral lesions and symptoms nor with changes in CD serology. This implies that also non-dietary factors may be involved in the clinical course of CD.

Oral soreness, burning sensations or xerostomia in GFD-treated CD patients seem to be common symptoms; the tongue is most often affected (Table 1). Eleven of the 71 patients with oral mucosal lesions (15.5%) presented with these changes at three or more sites. Six patients had B<sub>12</sub>-vitamin deficiency but were on a substitution therapy. The damaging effect of CD on the duodenal mucosa may affect the absorption of B<sub>12</sub>-vitamin, folate and iron. It is well known that redness and soreness of the tongue with atrophied papillae is occasionally accompanied by angular stomatitis and less frequently by cheilosis and this constellation is linked to these deficiency states (1). Therefore, CD may as such be the cause for the oral mucosal lesions of GFD-treated CD patients. Although the CD patients reported that they were following a strict GFD, exposure to small amounts of gluten is practically impossible to avoid, and even minute exposure may lead to oral manifestations, since ingested food first contacts the oral surfaces.

In the present study, cigarette smoking was not significantly associated with oral symptoms or lesions. Cigarette smoking protects against the development of symptomatic adult onset coeliac disease by obscure mechanisms (22).

In this study, the biopsy specimens were always taken from the same site of the buccal mucosa of every subject. Histology showed moderate to severe inflammatory cell infiltration (mainly lymphocytes) and epithelial atrophy as well as an increased amount of T-cells and mast cells in GFD-treated CD patients with subjective oral symptoms. Curiously, this association was not present regarding objective oral lesions. An explanation might be that the biopsy specimens were always taken from the same buccal area and that lesions were distributed between various sites of the oral mucosa. Subjective symptoms and identifiable oral lesions of GFD-treated CD patients were considered to be oral mucosal manifestations of CD ( $P=0.001$ ), since persistent oral symptoms could not be explained by other means. Since untreated CD patients did not have as often inflammatory changes in their oral mucosa as did the GFD-treated CD patients, duration of CD seems to be strongly involved in regulating inflammatory changes in the oral mucosa.

The amount of T-cells increases with the duration of CD (Table 3,4) may be related immunologic

phenomena. In CD, the small-intestinal intraepithelial T-cell population is increased, and there is a well known association between untreated CD and intestinal T-cell lymphomas (3). In CD patients who adhere to a GFD, the number of intestinal intraepithelial T-cells will decrease, but whether the same is true for the oral mucosa is not known. Nevertheless, the intra-epithelial T-cell population and the amount of T-cells in the lamina propria of the oral mucosa of CD patients seems to increase during the course of CD regardless of dietary intervention (Tables 3 and 4).

Mast cells increase in number in lamina propria of oral mucosa of CD patients with progressing of the disease (Tables 3 and 4). These cells may also be involved in the inflammatory process of oral mucosal surfaces, an issue that clearly needs further study.

The lesions of the oral cavity carry profound diagnostic importance in CD, an insidious and often latent disease (10). In fact, recurrent aphthous stomatitis or dental hypoplasia may be the only presenting features in adults with CD. Interestingly, some patients with oral ulceration respond to a GFD even in the absence of jejunal villous atrophy (23). In this study, even CD patients on a GFD had often oral manifestations that could not be explained by other causes than CD.

CD is a particular prominent cereal-induced entity, which has kept the final riddle of its pathogenesis unresolved to this day. However, the marked immunogenetic basis and the knowledge of proteins involved render CD a valuable model to understand diseases in which environmental factors, genetic factors, and an immune response interplay. Much research is needed before the reactions in the mouth and the oral mucosa in CD are clarified.

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