Salivary gland involvement and oral health in patients with coeliac disease

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Abstract
Coeliac disease (CD) is a chronic immune-mediated enteropathy triggered by ingestion of gluten. The aim of this study was to investigate if the salivary glands as a component of the mucosal immune system are involved in CD, leading to sialadenitis and salivary gland dysfunction and associated oral manifestations. Twenty patients with CD aged 49.2 (SD 15.5 years) and 20 age- and gender-matched healthy controls underwent an interview regarding general and oral health, serological analysis, a clinical oral examination including bitewing radiographs, Candida smear, assessment of salivary mutans streptococci and lactobacilli levels, unstimulated and chewing-stimulated whole and parotid saliva flow rates, analysis of secretory IgA, and a labial salivary gland biopsy. Xerostomia, mucosal lesions, dry/cracked lips and focal lymphocytic sialadenitis were more prevalent and extensive in patients with CD than in healthy controls. Moreover, the patients had less gingival inflammation and higher whole saliva flow rates than the healthy controls, but did not differ regarding dental health and levels of cariogenic bacteria and Candida. The major salivary gland function appears unaffected, contributing to maintenance of a balanced microbiota and oral health in CD patients. Xerostomia and labial dryness may be related to minor salivary gland inflammation and subsequent impaired mucosal lubrication.

KEYWORDS
aphthous stomatitis, caries, salivary dysfunction, sialadenitis, xerostomia

INTRODUCTION
Coeliac disease (CD) is a chronic autoimmune enteropathy caused by intolerance to gliadin in wheat gluten and related prolamins in barley and rye [1]. In CD, ingestion of gliadin-derived peptides leads to activation of immune cells in the lamina propria of the small intestine and recruitment of infiltrating T lymphocytes, which initiate an adaptive Th1 immune response and concomitant increased synthesis of interferon gamma (IFN-γ) and interleukins, for example, IL-10 and IL-15 [1—3]. This induces structural changes of the intestinal epithelium including a dense lymphocytic infiltration and villous atrophy resulting in abdominal discomfort and nutritional malabsorption [4]. There is a genetic predisposition to CD, which is mainly linked to the human leukocyte antigen (HLA) haplotypes HLA-DQ2, and to a
lesser extent HLA-DQ8 [5]. Environmental factors including the level of gluten intake, viral infections, and an aberrant intestinal microbiota changing the intestinal permeability are also considered to be involved in the aetopathogenesis [6]. CD can develop at any age. The estimated prevalence is about 1%–2%, but the condition is probably underdiagnosed [7], and diagnosis is often delayed.

Treatment of CD currently comprises a lifelong adherence to a gluten-free diet. If insufficiently treated, CD can lead to osteoporosis, infertility, and malignancies including T-cell lymphoma, which can explain the increased mortality rate amongst patients with CD [7,8]. Moreover, CD may be associated with an increased morbidity due to its concomitant occurrence with other autoimmune diseases, particularly type 1 diabetes mellitus, thyroid disease, and Sjögren’s syndrome [9].

Dental practitioners may play an important role in early diagnosis of CD, as a variety of oral manifestations can be indicators of CD including dental enamel defects, recurrent aphthous stomatitis, delayed dental eruption, angular cheilitis, itching and burning sensation in the oral mucosa, atrrophic glossitis and xerostomia [10–12]. Some of these oral manifestations most likely occur due to nutritional deficiencies that are particularly common at time of diagnosis, but they may also be related to affection of the salivary glands. It is well known that saliva plays a crucial role in the maintenance of oral health and that salivary gland dysfunction can lead to a variety of oral diseases [13,14]. A limited number of studies have investigated the involvement of the salivary glands in CD and the potential effect of a gluten-free diet on the salivary glands. A few studies have found reduced whole saliva flow rates in children with CD [15,16], whereas others found no differences in salivary flow rates between patients with CD and healthy controls [17–20]. One study, comparing minor salivary gland biopsies from patients with Sjögren’s syndrome and patients with both Sjögren’s syndrome and CD, demonstrated that the latter group had higher whole saliva flow rates and lower focal lymphocytic infiltration (focus score) in their salivary glands [21]. A recent study on non-obese diabetic (NOD) mice supports the view that a gluten-free diet seems to lower the degree of focal sialadenitis, in addition to infiltration of various immune cells [22].

Xerostomia appears to be a prevalent symptom in patients with CD [18,19]. It is therefore likely that involvement of the minor salivary glands in CD could lead to changes in sensory perception of the oral mucosa including xerostomia (i.e., the sensation of oral dryness).

The minor salivary glands are located in the oral submu-
scosa, particularly in the labial, buccal, palatal, lingual, and retromolar regions of the oral cavity. They secrete a relatively large fraction of lubricating proteins (e.g., mucins) to the oral mucosal surfaces [13,14,23]. The minor salivary glands also secrete 30%–35% of the secretory immunoglobulin A (sIgA) that enters the oral cavity and thereby play a substantial role in sIgA-mediated oral mucosal immunity [14,24]. The minor salivary glands are believed to be continuously stimulated by oral antigens due to their superficial location in the oral mucosa. Their short ducts may provide pathways for such antigens resulting in a local immune response. This local response may be ascribed to the presence of minor salivary gland duct-associated lymphoid tissue (DALT), which is comparable to gut-associated lymphoid tissue (GALT) with regard to organisation and function [25]. As in GALT, it is likely that the function of this local mucosal immune system is affected in CD due to repeated exposure to, for example, gluten, leading to formation of periductal focal lymphocytic infiltration. This could also affect the secretion of salivary IgA in CD.

The aim of this study was to determine if patients with CD display inflammatory and structural changes in their minor salivary glands. We hypothesised that inflammatory affection of the minor salivary glands reflects affection of the major salivary glands in terms of lower unstimulated and chewing-stimulated whole saliva flow rates, citric-acid-stimulated parotid saliva flow rates, and impaired secretion of sIgA. Furthermore, we investigated if the potential salivary gland involvement is associated with more oral discomfort, poorer oral and dental health, and higher levels of salivary mutants streptococci, lactobacilli, as well as Candida spores and hyphae in patients with CD than in healthy age- and gender-matched subjects.

**MATERIAL AND METHODS**

**Study participants**

Twenty-six patients with CD were screened, 20 of whom were eligible for enrolment in this cross-sectional study. The remaining six patients were not included due to breastfeeding, active infection requiring antibiotics or refusal to provide a biopsy. The inclusion criteria were age above 18 years and a diagnosis of CD, based on positive serology [i.e., IgA autoantibodies against tissue transglutaminase (anti-tTG) and against the endomysium of connective tissue (IgA EMA)] and biopsy (i.e., one from bulbus duodeni and two more from the distal part of duodenum, using the Marsh classification [4]). Exclusion criteria comprised pregnancy and breastfeeding, abuse of alcohol and drugs, active infection requiring antibiotics, and any acute medical condition. The patients were recruited amongst the group of patients undergoing regular follow-up examination at the Department of Internal Medicine, Amager Hospital, Copenhagen, Denmark, and through the Danish coeliac patient association. None of the patients had any signs of inflammatory bowel disease, including Crohn’s disease.

Twenty healthy age- and gender-matched controls were included via the Danish website for study participants.
Exclusion criteria were past or current history of systemic and oral diseases (e.g., inflammatory mucosal diseases such as lichen planus, pemphigoid, and pemphigus) as well as intake of medication. Use of contraceptives and hormonal replacement was accepted in addition to intake of dietary supplements. One of the healthy controls had recently been prescribed an antihypertensive agent (a calcium antagonist), but was otherwise healthy. She was included, as it proved difficult to recruit healthy matching control participants above the age of 65 years who did not take any sort of medication. Ten of the healthy controls did not undergo assessment of the salivary mutans streptococci and lactobacilli counts; bitewing radiographs and serologic analysis and were therefore not included in analyses pertaining to these measures. However, 10 controls were sufficient according to the power calculation.

The study was approved by the Regional Ethics Committee, Copenhagen, Denmark (no. H-1-2010067) and conducted according to the Declaration of Helsinki. All participants completed an informed written consent form prior to inclusion.

Two calibrated examiners (A.-K.J.L. and A.M.L.P.) conducted the oral clinical examination and the procedures mentioned below. All procedures were carried out in the same order (as mentioned in the following) and at same time of the day (between 9:00 and 11:30 am) to minimise the influence of circadian variation on the salivary flow measurements.

**Interview**

All study participants underwent a standardised interview regarding oral and general health, intake of medication, smoking history (never, current, and former smoker), and alcohol habits (abstainer, and weekly consumption, yes/no) and oral hygiene habits. According to the recommendations from the Danish Health Authority, low-risk alcohol consumption per week for women is seven units of alcohol and for men 14 units of alcohol [26]. One unit of alcohol is 1.5 cl pure alcohol. For the patient group, the interview also included the year of CD diagnosis, the duration and type of symptoms prior to gluten-free diet, diet compliance, and comorbidities.

**Assessment of oral symptoms**

Participants were questioned about (1) symptoms of the oral mucosa, including stinging, burning, roughness, and taste disturbances (the character of disturbances in taste perception); (2) presence and severity of oral dryness (xerostomia) [using four grades of severity (0–3)] [27], and any affection of oropharyngeal functions and diurnal variation in the sensation of oral dryness; and (3) current or past presence of recurrent aphthous stomatitis [the degree of related symptoms (scores 0–3), frequency, size, and number oral aphthous ulcers].

**Measurements of whole and parotid saliva flow rates**

In brief, the participants were asked not to eat, drink, smoke, brush, and floss their teeth, chew gum or eat (including use of pastilles) for 2 h prior to the examination, just as they were required not to use oral rinsing products 12 h before examination. Unstimulated and chewing-stimulated whole saliva flow rates were measured for collection periods of 15 and 5 min, respectively, followed by measurement of the citric-acid (2%)-stimulated parotid saliva flow rate for 5 min as previously described [28].

**Determination of salivary levels of mutans streptococci and lactobacilli**

The levels of *Streptococcus (Strep.) mutans* and lactobacilli in chewing-stimulated whole saliva was determined using Dentocult SM Strip and Dentocult LB Strip kits (Orion Diagnostica), respectively. The incubation times were 48 and 96 h for Dentocult SM and Dentocult LB, respectively. After incubation, the presence of *Strep. mutans* was evidenced by dark blue to light blue raised colonies on the strip. The levels of *Strep. mutans* were then evaluated by comparing the colony density against a chart provided by the manufacturer and divided into one of the following classes representing various numbers of colony-forming units per ml saliva (CFU/ml): 0 = <10^3 CFU/ml; 1 = <10^4 CFU/ml; 2 = 10^4–10^5 CFU/ml; and 3 = >10^5. The presence of lactobacilli was evidenced by white colonies on the agar surfaces; the levels were divided into following classes: 1 = 1000 CFU/ml; 2 = 10^3 CFU/ml; 3 = 10^4 CFU/ml; and 4 = 10^5 CFU/ml.

**Smear for oral candidiasis**

An oral smear was taken from the dorsal part of the tongue using a sterile wooden spatula. The smear was stained with Periodic Acid–Schiff and evaluated for presence of *Candida* hyphae and spores. The number of blastofores and hyphae were estimated semi-quantitatively: 0 = none; 1 = few; 2 = moderate; and 3 = many. The diagnosis of candidiasis was defined as a clinical lesion harbouring *Candida* hyphae verified by Periodic Acid–Schiff-stained smear from the site.
Clinical oral examination

The number of decayed, missing, and filled surfaces (DMFS) was recorded based on all teeth except third molars. Plaque (PI) and gingival indices (GI) were determined at four and six sites per tooth on six index teeth (16, 24, 21, 41, 44, and 36) as previously described [28,29]. Enamel defects were recorded according to the classification by Aine et al. [30]. Oral mucosal changes were also registered. Finally, four bitewing radiographs were obtained from the molar and premolar regions for caries diagnostics.

Labial salivary gland biopsy and histopathological analysis

A labial salivary gland biopsy was performed on all participants through normal-appearing mucosa in the lower lip under regional anaesthesia as previously described [29]. On average six glands were excised, fixed in 10% neutral buffered formalin (pH 7.3, 24 h, 20°C), embedded in paraffin, and routinely processed and stained with haematoxylin and eosin. A focus scoring system, which is routinely used in scoring labial salivary gland biopsies in Sjögren’s syndrome for the extent of focal sialadenitis, was applied [31]. A focus was defined as an aggregate (mostly periductal or perivascular localisation) of at least 50 mononuclear cells. To calculate the focus score, defined as the number of foci per 4 mm², the number of foci in the glandular section was divided with the total glandular area and multiplied by four. The major part of the foci should be surrounded by normal salivary gland tissue. Atrophic and fibrotic tissue evidently being part of the glands were included in the area measurement, while prominent infiltrating fat tissue was excluded from the area of focus scoring. The histopathological scoring, which also included assessment of diffuse chronic inflammation, acinar atrophy, fibrosis, and fatty tissue degeneration, was performed in a blinded manner (no information on the diagnosis). The histological assessment was performed by means of a light microscope (Leitz Orthoplan; Leitz) with a magnification of 100× and an ocular (Leitz Periplan GW10XM and GW10XMF; Leitz) by an oral pathologist (J.R.) and by a specialist in salivary gland histology (A.M.L.P.).

Peripheral blood samples and analysis

Peripheral blood samples were collected from all participants, processed and analysed at the same biochemical lab in Copenhagen, to determine any vitamin and mineral deficiencies. The analyses included haemoglobin, mean cell volume (MCV), erythrocyte width distribution width-coefficient of variation (RDW-CV), leucocytes including differential count, thrombocytes, p-transferrin, p-ferritin, homocysteine, p-iron, cobalamin, folate, 25-OH-vitamin D, C-reactive protein (CRP), alkaline phosphatase, p-calcium, and parathyroid hormone (PTH).

Analysis of secretory IgA (sIgA)

An indirect enzyme immunoassay kit was used to determine sIgA in the whole saliva samples according to the protocol supplied by the manufacturer (Salimetrics). As the levels of sIgA are dependent on the salivary flow rate, the output of IgA (μg/min) determined by each concentration was multiplied with the respective salivary flow rate (ml min⁻¹).

Statistical analysis

With alpha set at 0.05 and beta at 0.2, to provide 80% power to detect a difference of 60% in incidence of focal lymphocytic infiltration (focus score of 1) in labial salivary gland biopsy, 10 patients and 10 healthy controls were needed in each study group. The study included 20 patients and 20 healthy controls to strengthen additional statistical analyses. Differences in the salivary and clinical parameters between the CD patient and healthy control groups were analysed using the Wilcoxon rank-sum test, the Mann–Whitney U-test and the two-sample t-test (normal distributed numerical variables). Fisher’s Exact test (less than 10 in one category) and the chi-square test (more than 10) were used for analysis of distributions between the two groups. In addition, mean values and standard deviations were used to obtain the mean difference and 95% confidence interval (CI) for continuous data and odds ratios (OR) and 95% CIs were provided for dichotomous data. Associations between variables were analysed by the Spearman’s rank correlation test. P-values of ≤0.05 were considered statistically significant.

RESULTS

The demographic and clinical characteristics of the patients with CD and the healthy controls are presented in Table 1. Women comprised around 85% of the participants. The mean age (± SD) at time of diagnosis was 39.5 ± 12.0 years, and the mean duration from onset of symptoms to diagnosis was 14.8 ± 17.7 years. The average age of the patients was 49.2 years, and the disease duration (i.e., from diagnosis to current examination) was on average 10 years. At time of diagnosis, all patients had gastrointestinal symptoms and signs including diarrhoea, abdominal pain and distension, constipation, and weight loss, and 70% had extra-intestinal symptoms and signs including dry skin, hair loss, short menstrual cycle, memory
TABLE 1  Characteristics of the patients with coeliac disease (CD) and the healthy controls

|                                | Patients with CD  | Healthy controls | P-valuea |
|--------------------------------|-------------------|------------------|----------|
|                                | (n = 20)          | (n = 20)         |          |
| Age, years                     | 49.2 ± 15.5       | 48.0 ± 12.7      | 0.88     |
| Female/male ratio              | 16/4              | 18/2             | 0.66     |
| Age at time of CD diagnosis, years | 39.5 ± 12.0   | –                | –        |
| Symptom duration till diagnosis, years | 14.7 ± 16.8 | –                | –        |
| Medical conditions/comorbidities |                  |                  |          |
| Hypertension                   | 3 (15%)           | 1 (5%)           |          |
| Osteoporosis                   | 4 (20%)           | 0                |          |
| Osteoarthritis                 | 4 (20%)           | 2 (10%)          |          |
| Hypothyroidism                 | 3 (15%)           | 0                |          |
| Gastrointestinal reflux        | 3 (15%)           | 0                |          |
| Psoriasis                      | 1 (5%)            | 0                |          |
| Allergy                        | 2 (10%)           | 3 (15%)          |          |
| Daily intake of medication     | 10 (50%)          | 1 (5%)           | 0.001    |
| Antihypertensives              | 3 (15%)           | 2 (10%)          |          |
| Bisphosphonates                | 4 (20%)           | 0                |          |
| Analgesics, peripheral acting  | 3 (15%)           | 0                |          |
| Thyroid hormones               | 3 (15%)           | 0                |          |
| Proton pump inhibitors         | 3 (15%)           | 0                |          |
| Antidepressants                | 1 (5%)            | 0                |          |
| Oral antidiabetics             | 1 (5%)            | 0                |          |
| Daily intake of dietary supplements |       |                  | 0.01     |
| Vitamin D and calcium          | 18 (90%)          | 9 (45%)          |          |
| Multivitamin                   | 15 (75%)          | 4 (20%)          | 0.001    |
| B- or C-vitamin                | 8 (40%)           | 5 (25%)          | 0.31     |
| Fish oil                       | 5 (25%)           | 1 (5%)           | 0.10     |
| Weekly alcohol consumption     |                  |                  | 0.49     |
| <10.5 cl (F)/21 cl (M) alcoholb | 17 (85%)         | 10 (50%)         | 0.02     |
| >10.5 cl (F)/21 cl (M) alcoholb | 0               | 1 (5%)           | 0.07     |
| Abstainer                      | 3 (15%)           | 9 (45%)          | 0.05     |
| Smoking habits                 |                  |                  |          |
| Never smoker                   | 13 (65%)          | 12 (60%)         | 0.74     |
| Current (cigarettes, daily)    | 2 (10%)           | 1 (5%)           | 0.56     |
| Former (> 1 year ago)          | 5 (25%)           | 7 (35%)          | 0.43     |

Data presented as the number of participants (n) and proportions (%) and as mean values (± standard deviation, SD)

*aAccording to recommendations for female (F) and male (M) from the Danish Health Authority (for details see text).

Statistical significant differences between groups.

difficulty, headache, anaemia, and fatigue. At time of the current examination, all patients reported full adherence to gluten-free diet, and yet 50% had persisting symptoms such as abdominal pain, diarrhoea, constipation and bloating, weight loss, fatigue, dry and sensitive skin, and hair loss.

Eleven (55%) patients reported presence of medical diseases and conditions, predominantly thyroid hypofunction, gastrointestinal reflux, osteoporosis, osteoarthritis, and hypertension (Table 1). Daily intake of dietary supplements (e.g., vitamins and minerals) was statistically significantly higher amongst the patients with CD than the healthy controls (P = 0.01). A significantly higher number of patients (85%) than healthy controls (50%) (P = 0.02) had a weekly low-risk consumption of alcohol being within the recommendations from the Danish Health Authority. One healthy participant had an intake slightly above the recommendations. Two patients (10%) were daily smokers. Neither alcohol...
The oral symptoms are presented in Table 3. Xerostomia was the most prevalent oral symptom reported by the patients (60%), and 20% also reported xerostomia-related difficulties in swallowing dry food substances and/or difficulties in speech. In addition, a statistically significant higher number of patients than healthy controls reported a history of recurrent aphthous stomatitis (RAS) (85% vs. 60%, \( P = 0.002 \)), predominantly the minor type of RAS with several ulcers being present simultaneously. The patients also experienced more pain and discomfort related to outbreaks of aphthous ulcers than the healthy controls (55% vs. 20%). Seven (35%) patients reported having a persistent burning and itching pain/discomfort in the oral mucosa, whereas two healthy controls had an intermittent sensation of burning and itching on the tongue. Eight (40%) of the patients experienced impaired and altered taste (metallic or acidic) perception and three (15%) healthy controls reported impaired taste perception.

Table 3 presents the observed oral mucosal changes and lesions. In the patient group, signs of mucosal dryness were prevalent, particularly dryness and cracking of the lips and consumption nor smoking habits were significantly associated with xerostomia, saliva flow rates, DMFS, PI, GI or mucosal findings.

The findings of the serological analysis are presented in Table 2. Four patients had a leucocyte count above the normal level of \( 8.8 \times 10^{9} / \text{L} \) (i.e., 9.1–10.7 \( \times 10^{9} / \text{L} \)). Three patients had a p-cobalamin concentration below normal (i.e., 150–295 pmol/L). Two patients had a transferrin concentration above the normal of 41 \( \mu \text{mol} / \text{L} \) (i.e., 42 and 47 \( \mu \text{mol} / \text{L} \)). In three patients and two healthy controls, the homocysteine concentration was slightly elevated above the normal (i.e., 15.1–17.5 \( \mu \text{mol} / \text{L} \)). The patients had statistically significantly higher levels of vitamin D than the healthy controls (\( P = 0.02 \)). Three patients and five healthy controls had a slight vitamin D deficiency with serum values below 50 nmol/L. Three of the healthy controls with low vitamin D levels also had elevated levels of PTH (ranging from 8 to 10.7 pmol/L). They were advised to consult their physician for further evaluation and treatment.

| Table 2: Serological findings |
|-----------------------------|
|                            | Patients with CD \( (n = 20) \) | Health controls \( (n = 10) \) | 95% CI of the difference | \( P \)-value

| Parameter                        | Mean ± SD | Mean ± SD |             |          |
|----------------------------------|-----------|-----------|-------------|----------|
| Haemoglobin, mmol/L              | 8.4 ± 0.6 | 8.5 ± 0.6 | -0.10 (-0.58 - 0.38) | 0.67     |
| Mean cell volume (MCV), 10^{-15} L | 91.3 ± 3.7 | 110.5 ± 3.4 | -0.80 (-3.66 - 2.06) | 0.57     |
| Erythrocyte distribution width (RDW-CV), % | 12.8 ± 0.7 | 13.0 ± 0.6 | 0.20 (-0.33 - 0.73) | 0.44     |
| Leucocyte count, 10^9/L          | 7.1 ± 1.7 | 6.1 ± 1.7 | -1.00 (-2.35 - 0.35) | 0.14     |
| No. with deviation               | 4↑        | 1↑        |             |          |
| Thrombocyte count, 10^9/L        | 284.5 ± 73.0 | 254.0 ± 84.1 | -30.50 (-91.38 - 30.38) | 0.31     |
| No. with deviation               | 0         | 1↑        |             |          |
| P-transferrin, μmol/L            | 33.4 ± 5.0 | 30.7 ± 3.7 | -2.70 (-6.37 - 0.97) | 0.14     |
| No. with deviation               | 2↑        | 0         |             |          |
| P-ferritin, μg/L                 | 85.6 ± 54.2 | 82.8 ± 55.8 | -2.80 (-46.21 - 40.61) | 0.90     |
| Homocysteine, μmol/L             | 11.3 ± 3.2 | 10.1 ± 3.3 | -1.20 (-3.76 - 1.36) | 0.35     |
| No. with deviation               | 3↑        | 1↑        |             |          |
| P-iron, μmol/L                   | 18.5 ± 5.5 | 17.3 ± 7.2 | -1.20 (-6.04 - 3.64) | 0.62     |
| No. with deviation               | 0         | 1↓        |             |          |
| Cobalamin, pmol/L                | 380.7 ± 168.0 | 415.0 ± 179.6 | 34.30 (-102.01 - 170.61) | 0.61     |
| Folate, nmol/L                   | 23.0 ± 12.9 | 21.9 ± 10.5 | -1.10 (-10.76 - 8.56) | 0.82     |
| 25-OH-vitamin D, nmol/L          | 74.8 ± 26.5 | 56.1 ± 24.1 | -18.70 (-34.91 - 2.49) | 0.02     |
| No. with deviation               | 3↓        | 5↓        |             |          |
| C-reactive protein (CRP), mg/L   | <4        | <4        |             | NS       |
| No. with deviation               | 1↑        | 0         |             |          |
| Alkaline phosphatase, U/L        | 61.1 ± 15.9 | 65.5 ± 22.8 | 4.40 (-10.20 - 18.99) | 0.54     |
| No. with deviation               | 0         | 1↑,1↓     |             |          |
| P-calcium, mmol/L                | 2.4 ± 0.1 | 2.4 ± 0.1 |             | NS       |
| Parathyroid hormone, pmol/L      | 5.2 ± 2.3 | 6.2 ± 2.4 | 1.00 (-0.85 - 2.85) | 0.28     |
| No. with deviation               | 2↑        | 3↑        |             |          |

Data provided are mean values ± SD and 95% CI of the mean difference. The number of participants with deviation from normal reference values are also given.

Abbreviations: CD, coeliac disease; CI, confidence interval; OR, odds ratio; RDW-CV, red blood cell distribution width-coefficient of variation.

*aFor test of \( H_0: \text{mean}_{\text{cases}} = \text{mean}_{\text{controls}} \).
**TABLE 3** Absolute and relative frequency (%) of clinical oral mucosal changes and lesions and oral symptoms in cases and controls

| Condition                                                                 | Patients with CD (n = 20) | Healthy controls (n = 20) | OR (95% CI) | P-value*  |
|--------------------------------------------------------------------------|---------------------------|---------------------------|-------------|-----------|
| Dry and cracking lips                                                    | 7 (35%)                   | 0                         | 22.8 (1.2–432.6) | 0.03      |
| Mucosal erythema                                                         | 4 (20%)                   | 0                         | 11.2 (0.6–223.0) | 0.11      |
| Denture stomatitis (palatal erythema)                                   | 1 (5%)                    | 0                         | 3.2 (0.1–82.2)   | 0.49      |
| Presence or history of aphthous stomatitis Degree of disturbance 0/1/2/3 | 17 (85%)                  | 7 (35%)                   | 10.5 (2.3–48.8)  | 0.002     |
| Leukoplakia                                                              | 0                         | 1 (5%)                    | 0.3 (0.0–8.3)    | 0.49      |
| Fissured tongue                                                          | 4 (20%)                   | 2 (10%)                   | 2.3 (0.4–14.0)   | 0.38      |
| Geographic tongue                                                        | 0                         | 1 (5%)                    | 0.3 (0.0–8.3)    | 0.49      |
| Oral mucosal itching and burning sensation                               | 7 (35%)                   | 2 (10%)                   | 4.9 (0.9–27.2)   | 0.07      |
| Taste disturbances (diminished, enhanced, distorted)                     | 8 (40%)                   | 3 (15%)                   | 3.8 (0.8–17.3)   | 0.08      |
| Xerostomia                                                               | 0                         | 1 (5%)                    | 0.3 (0.0–8.3)    | 0.49      |
| Need of drinking water at night                                          | 7 (35%)                   | 1 (5%)                    | 10.2 (1.1–93.3)  | 0.04      |
| Problems with chewing, swallowing or articulation                        | 4 (20%)                   | 0                         | 11.2 (0.6–223.0) | 0.11      |
| Sensation of sticky saliva                                               | 5 (25%)                   | 0                         | 14.5 (0.8–283.4) | 0.07      |

Where relevant, the degree of severity is given. OR and 95% CI are also provided.

**Abbreviations**: CD, coeliac disease; CI, confidence interval; OR, odds ratio.

*For tests of $H_0$: $p_{\text{cases}} = p_{\text{controls}}$.

**TABLE 4** Dental and periodontal findings in patients with CD and healthy controls, given as mean values ($\pm$ SD) or frequencies (%)

| Condition                                   | Patients with CD (n = 20) | Healthy controls (n = 20) | OR (95% CI) | P-value* |
|---------------------------------------------|----------------------------|---------------------------|-------------|----------|
| No. of teeth                                | 26.8 $\pm$ 2.8             | 27.3 $\pm$ 1.3            | 0.5 (0.9–1.9) | 0.48     |
| Decayed surfaces                            | 2.7 $\pm$ 3.0              | 1.9 $\pm$ 2.0             | $-0.8$ (2.4–0.8) | 0.32     |
| Missed surfaces                             | 6.0 $\pm$ 14.3             | 7.1 $\pm$ 15.3            | 1.1 (8.4–10.5) | 0.82     |
| Filled surfaces                             | 24.5 $\pm$ 18.8            | 23.3 $\pm$ 18.0           | $-1.2$ (13.0–10.6) | 0.96     |
| DMF-surfaces                                | 33.0 $\pm$ 24.9            | 32.2 $\pm$ 21.5           | $-0.8$ (15.7–14.1) | 0.91     |
| Partial upper dentures                      | 2 (10%)                    | 0                         |             | 0.61     |
| Caries lesions on radiographs               | 2.2 $\pm$ 2.7              | 2.6 $\pm$ 2.3             | 0.4 (1.2–2.0)  | 0.63     |
| Plaque index                                | 0.21 $\pm$ 0.29            | 0.33 $\pm$ 0.24           | 0.1 (0.1–0.3)  | 0.16     |
| Gingival index                              | 0.12 $\pm$ 0.26            | 0.33 $\pm$ 0.33           | 0.2 (0.0–0.4)  | 0.03     |

**Abbreviations**: CD, coeliac disease; CI, confidence interval; DMF, decayed, missing, and filled; OR, odds ratio.

*For test of $H_0$: estimate$_{\text{cases}} = $estimate$_{\text{controls}}$.

The labial mucosa. In addition, mucosal erythema was more common amongst the patients and mainly on the dorsal part of the tongue.

There were no significant differences between patients with CD and healthy controls with regard to dental and periodontal health, apart from lower gingival inflammation scores in the CD group ($P = 0.03$) (Table 4). One patient with CD had dental enamel defects of grade 1 on the lateral incisors. Dental hygiene procedures/habits and regular dental follow-up visits did not differ between the two groups.

The mean values of the whole and parotid saliva flow rates were within the normal range for both patients and healthy controls (Table 5). The CD patients had significantly higher unstimulated and chewing-stimulated whole saliva flow rates than the healthy controls ($P = 0.01$ and $P = 0.05$). The stimulated parotid saliva flow rate was also higher, although not statistically significant ($P = 0.06$). In both groups, unstimulated and chewing-stimulated whole saliva flow rates were significantly correlated ($R = 0.68$, $P < 0.0001$ and $R = 0.59$, $P < 0.0001$), just as chewing-stimulated whole and citric-acid stimulated parotid saliva flow rates were positively correlated ($R = 0.80$, $P < 0.0001$ and $R = 0.55$, $P = 0.0003$). No significant correlations were found between age and salivary flow rates. Three patients and two healthy control
subjects had hyposalivation, defined as an unstimulated whole saliva flow rate equal to or below 0.10 ml\textsuperscript{-1} \[28\]. None of the participants had abnormal low stimulated whole saliva secretion. Patients who had hyposalivation also had an intake of ‘xerogenic’ medication (e.g., antidepressants and antihypertensives). Unstimulated whole saliva flow rates and number of diseases and medications were inversely correlated \(R = -0.43, P = 0.007\) and \(R = -0.33, P = 0.02\). No significant association was found between saliva flow rates and DMFS, although they were inversely correlated \(R = -0.38, P = 0.10\).

The salivary count of \textit{Strep. mutans}, lactobacilli, and the numbers of \textit{Candida} blastospores and hyphae did not differ significantly between patients and healthy controls (Table 6). Four (20%) of the patients, but none of the healthy controls, had counts of \textit{Strep. mutans} in class 3 (i.e., \(10^4\) CFU/ml). There were no associations between participants having oral mucosal lesions and those having \textit{Candida} blastospores and hyphae in the smears. No correlations were found between the levels of \textit{Strep. mutans}, lactobacilli, and the number of decayed or filled surfaces.

The mean concentration of salivary sIgA was significantly lower in patients with CD than in the healthy controls (139.1 ± 75.5 μg/ml vs. 180.5 ± 78.3 μg/ml, \(P = 0.03\)). The output values of sIgA, taking the salivary flow rates into consideration, however, did not differ (50.4 μg/min vs. 47.4 μg/min, \(P = 0.28\)).

The labial salivary gland tissue biopsies from patients with CD displayed significantly more changes in terms of more extensive, diffuse chronic inflammation, focal lymphocytic infiltration, acinar atrophy, and glandular fibrosis than those of the healthy controls (Table 7). Aggregations of more than 50 lymphocytes (foci) located around duct epithelium were observed in labial salivary gland biopsies from 13 (65%) patients. Thirteen (65%) patients had a focus score ≥ 1. One healthy participant had a labial salivary gland biopsy with a focus score of 1. No association was found between the focus score and the degree of xerostomia \((R = 0.11, P = 0.63)\).

### DISCUSSION

The aim of this cross-sectional study was to determine if the minor salivary glands as part of the oral mucosal immunity are involved in CD, and if the inflammatory and structural changes reflect involvement of the major salivary gland, leading to salivary gland dysfunction, which could compromise oral health.

Our findings suggest that the minor salivary glands are involved in CD. Thus, the immunohistochemical analysis revealed more extensive inflammation and more focal lymphocytic infiltration in the labial salivary glands of patients with CD than those of healthy individuals. The minor salivary glands of patients with CD were also characterised by acinar atrophy, fibrosis, and diffuse chronic inflammation, which are features of chronic sialadenitis, indicating presence of previous extensive immune-mediated inflammatory processes in the salivary gland tissue. Our finding of focal lymphocytic infiltrations (foci) in labial salivary glands of patients

### TABLE 5 Whole and parotid saliva flow rates in the groups of patients with CD and healthy controls, respectively

|                         | Patients with CD | Healthy controls | Difference (95% CI) | \(P\)-value<sup>a</sup> |
|-------------------------|------------------|------------------|---------------------|------------------------|
| **Unstimulated whole saliva flow, ml min\(^{-1}\)** | \(0.47 \pm 0.34\) | \(0.26 \pm 0.13\) | \(-0.21 (-0.37 to -0.05)\) | 0.01 |
|                         | \(0.35 (0.09-1.30)\) | \(0.26 (0.08-0.64)\) |                     |                       |
| **Stimulated whole saliva flow, ml min\(^{-1}\)** | \(2.39 \pm 1.06\) | \(1.81 \pm 0.74\) | \(-0.58 (-1.17-0.05)\) | 0.05 |
|                         | \(1.99 (0.90-5.74)\) | \(1.69 (0.79-3.66)\) |                     |                       |
| **Stimulated parotid saliva, ml min\(^{-1}\)** | \(0.80 \pm 0.53\) | \(0.55 \pm 0.23\) | \(-0.25 (-0.51-0.01)\) | 0.06 |
|                         | \(0.72 (0.32-2.86)\) | \(0.56 (0-1.07)\) |                     |                       |
| **Prevalence of hyposalivation** | 3 (15%) | 2 (10%) | OR 1.58 (0.24-10.71) | 0.63 |

Data presented as mean \(\pm SD\) and median (range). Mean differences and 95% CIs also provided.

<sup>a</sup>For testing \(H_0\): mean\(_{cases}\) = mean\(_{controls}\).
with CD supports the findings of Patinen et al. [21], who compared patients with Sjögren’s syndrome with patients having CD and patients having both Sjögren’s syndrome and CD. Interestingly, patients with both Sjögren’s syndrome and CD had lower salivary gland inflammatory focus scores and higher salivary flow rates than patients having Sjögren’s syndrome alone, which suggests that a gluten-free diet may alleviate autoimmune inflammation [21]. In a recent study on NOD mice, we found that a lifelong gluten-free diet reduces infiltration of monocytes/macrophages and T cells in salivary glands and inflammation in pancreatic islets, supporting the idea that autoimmune diseases like CD, type 1 diabetes, and Sjögren’s syndrome, which are associated and share pathogenic factors, can be alleviated by a gluten-free diet [22].

Our findings of structural and inflammatory changes in the minor salivary glands further indicate that the overlying oral mucosa may be affected by an inflammatory response, which could be elicited by small amounts of gluten or gluten-derivatives. A previous study showed that patients with CD displayed a more extensive infiltration of inflammatory cells, including lymphocytes and CD3+ and CD4+ T cells, in their buccal mucosa than that of healthy individuals [32]. Moreover, patients who were adherent to a gluten-free diet had a higher degree of inflammatory changes in their buccal mucosa than patients with untreated CD, suggesting that the duration of CD plays a role in the oral mucosal immune response [32]. The study also indicates that patients with CD have a lifelong immunological memory for gluten-hypersensitivity in terms of memory T cells, and that exposure to even small amounts of gluten/gluten-derivatives can activate these cells, leading to mucosal inflammation [32]. These findings can also explain the immune-mediated inflammatory changes in the underlying minor salivary glands observed in our study, despite adherence to a gluten-free diet.

The major salivary glands do not seem to be affected by inflammatory changes, or at least not to an extent that influences their function. Thus, the unstimulated and chewing-stimulated whole saliva flow rates were significantly higher in the patients with CD than in the healthy controls. Our findings of normal whole saliva flow rates are in line with findings of previous studies [17–19]. Some of the patients in our study had hyposalivation, which could be explained by their intake of xerogenic medication and a higher number of concomitant diseases (Table 1). The question is whether the location of the salivary glands can contribute to explain their various ways of affection. Although adherence to a gluten-free diet appears to reduce the degree of inflammation in the salivary glands, and thereby contributes to maintaining a normal or even higher salivary secretion, the minor salivary glands are continuously exposed to various factors, including small amounts of gluten/gluten-derivatives that can elicit an immune-mediated inflammatory response. The design of this study does not allow answering this question and such study would require a longitudinal approach, including patients in various stages of CD and sampling prior to gluten-free diet treatment and different time intervals during treatment with a gluten-free diet. Ethical considerations limit collection of repeated biopsies. Despite the findings of normal (and high) whole saliva flow rates, xerostomia was a prevalent symptom (65%) in patients with CD. Previous studies have also reported a high prevalence of xerostomia [21]. A study on self-reported xerostomia showed a significantly higher mean Xerostomia Inventory score in patients with CD than in a comparison group comprising acquaintances and partners (22.2 vs. 17.2) [33]. Furthermore, the patients with CD also reported more oral problems, including taste disturbances and problems with eating [33], which are in line with the findings in our study. It is well known that xerostomia can have a negative impact on the patient’s health-related quality of life. In our study, dry and/or cracked lips, erythematous oral mucosa and fissuring of the tongue were commonly observed. The fluid film thickness was not measured in this study. However, it is possible that the inflammatory changes of the salivary gland tissue affect the function of the salivary gland parenchyma, resulting in impaired secretion of lubricating and protective salivary proteins, like mucins, particularly from the minor salivary glands, which are affected in CD. This may lead to sensory disturbances in the oral mucosa as seen in other
Inflammatory autoimmune conditions [34–36]. The contribution of the minor salivary glands to the volume of whole saliva is small (below 10%), whereas their contribution to the production of salivary proteins, including lubricating proteins, is significant (about 70%) [13,14,23]. In a future study, it would be obvious to include assessment of minor salivary secretion and composition of the minor salivary gland secretions.

In our study, recurrent outbreaks of aphthous stomatitis were commonly reported by the patients (85%). Previous studies have also reported high prevalence of aphthous ulcers [10,12,37–39]. Aphthous ulcers often cause itching and burning sensation in the oral mucosa. The latter may also be present without aphthous ulcers, which could also explain higher presence of reported oral discomfort amongst the CD patients. The mean concentration of sIgA in whole saliva was significantly lower in patients with CD than in the healthy controls, but the output values of sIgA, which consider the individual salivary flow rates, did not differ. Neither the sIgA values nor the levels of Candida hyphae and blastospores were associated with any of the observed oral mucosal lesions or reported symptoms. It may also be speculated whether the oral mucosal lesions and symptoms could be ascribed to an increased immune-mediated inflammatory response in the oral mucosa. In a future study, it would be obvious to include analysis of oral mucosal tissue.

In this study, the number of caries lesions, filled and missing dental surfaces, and the dental plaque score did not differ between the patients with CD and the healthy controls. A previous study found significantly lower plaque index in children with treated CD compared to untreated CD patients and healthy controls, which also correlated to the frequency of in-between meals [40]. Results are conflicting with regard to the prevalence of caries. Some studies report a lower prevalence of caries in CD patients [15,20,41], while others report no difference in prevalence [19,42] or a higher prevalence compared to healthy controls [43,44]. Although not statistically significant, the patients in this study had a higher number of decayed dental surfaces. A higher prevalence of dental caries has been attributed to simultaneous presence of risk factors such as fragile hypomineralised enamel, reduction in salivary secretion, and changes in salivary composition [45]. In our study, the salivary flow rates were normal and even higher in the patient group than in the healthy control group. Furthermore, the levels of potentially cariogenic bacteria did not differ between the two groups. Results are conflicting with regard to the presence of potentially cariogenic bacteria. Thus, one study reported lower levels of Strep. mutans and lactobacilli [40], whereas another study found higher levels of lactobacilli [46].

Interestingly, patients with CD had a significant lower gingival inflammation score. In this respect, it has been suggested that adherence to a gluten-free diet leads to an oral microbiota favouring gingival health [10]. In addition, it has been shown that CD patients who do not follow a strict gluten-free diet display more systemic inflammation, which can be related to gingival inflammation [47].

In conclusion, the minor salivary glands seem to be affected in patients with longer-standing CD, despite adherence to a gluten-free diet. Further studies are needed to explore the immune-mediated inflammatory process in the labial salivary gland tissue, and whether it is related to an inflammatory response to small amounts of gluten-gluten-derivatives in the oral mucosa. Furthermore, it would be obvious to investigate the specific minor salivary gland secretion and composition of the secretions to elucidate whether aberrations can explain the high prevalence of oral mucosal lesions and symptoms in CD, despite no severe nutritional deficiencies. The function of the major salivary glands does not seem to be affected in CD, and the salivary sIgA did not differ between patients with CD and healthy controls. The number of enamel defects (hypomineralisation) was low, which can be ascribed to the age of the study participants, and the fact that the enamel lesions have been treated, or that the patients did not have vitamin- and mineral-deficiencies during formation of the permanent teeth. Neither the dental health nor the levels of potentially cariogenic bacteria differed between patients with CD and healthy controls. This could be due to the normal whole saliva secretion rate, which thereby maintained oral health and a balanced microbiota. The findings of xerostomia, labial dryness, and oral symptoms could be attributed to the inflammatory changes in the minor salivary glands caused by CD, leading to impaired secretion and lubricating properties. The potential quantitative and qualitative changes of minor labial salivary secretion need to be addressed in a future study.

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CONFLICT OF INTEREST
The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS
Conceptualization: AKJ Lundemann, AML Pedersen; Methodology: AKJ Lundemann, AML Pedersen; Investigation: AKJ Lundemann, AML Pedersen; Formal analysis: J Liu, J Reibel; Writing original draft: J Liu, AML Pedersen; Writing review & editing: AKJ Lundemann, J Reibel, AML Pedersen.
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