

# Oral Manifestations of Celiac Disease

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**Introduction:** Contrary to early beliefs, celiac disease (CD) is relatively common; however, it still remains underdiagnosed since most cases are atypical, with few or no gastrointestinal symptoms and predominance of extraintestinal manifestations. As a consequence, the diagnosis of the disorder often requires a multidisciplinary approach. Also some oral ailments have been described in celiac patients. In this study, we review the papers that have reported oral manifestations in subjects with CD.

**Methods:** A comprehensive literature search was conducted in Medline and Embase databases using appropriate key words. Additional papers were selected by cross-referencing from the retrieved articles.

**Results:** Dental enamel defects are the oral lesions most closely related to CD. There are conflicting data on the association between CD and recurrent aphthous stomatitis. A correlation of CD with atrophic glossitis has been reported, although robust evidence in support of it is lacking. Patients with CD have caries indexes seemingly lower than healthy individuals, but they may experience delay in tooth eruption. Occurrence of other oral mucosal lesions in CD subjects is likely occasional.

**Conclusions:** Patients with systematic dental enamel defects should be screened for CD even in the absence of gastrointestinal symptoms. CD screening tests for patients with oral aphthae or idiopathic atrophic glossitis should be selectively considered during a medical evaluation that focuses on all aspects of the patient's status.

**Key Words:** atrophic glossitis, case-finding, celiac disease, dental enamel defects, recurrent aphthous stomatitis

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Celiac disease (CD) is a lifelong immune-mediated disorder triggered by the ingestion of wheat gluten and related proteins of rye and barley in genetically

susceptible subjects, which results in small intestinal mucosal injury and nutrient malabsorption.

Until recently considered a rare condition, CD is now well-known to be relatively common; its estimated prevalence in the general population of North America and Western Europe appears to be close to 1%, with a reasonable range of 0.71% to 1.25%.<sup>1</sup> The dramatic advances made during the last decade in the understanding of CD have revealed the disease to have a heterogeneous, wide, and often unsuspected range of clinical presentations. In fact, today it is apparent that the “classic” clinical form (characterized by a malabsorption syndrome, ie, chronic diarrhea, abdominal pain and distention, weight loss) is less common, and most patients have atypical CD, with few or no gastrointestinal symptoms and predominance of extraintestinal manifestations, such as short stature, iron-deficient anemia, abnormalities in liver function test.<sup>2</sup> CD patients are prone to develop long-term complications (eg, osteoporosis, infertility, autoimmune diseases, malignancies),<sup>3</sup> and some studies report an increased all-cause mortality compared with the general population.<sup>4,5</sup> Strict and lifelong adherence to a gluten-free diet (GFD) is the only treatment currently available, and usually results in remission. Compelling evidence suggests that GFD may prevent or reduce the risk of long-term complications.<sup>3</sup>

The wide range of the CD clinical manifestations should induce many different specialists to consider this disorder when a patient presents with those extraintestinal signs and symptoms that might be related to CD.<sup>6</sup> In this regard, also some oral ailments have been reported as possible atypical aspects of CD, mainly dental enamel defects (DEDs) and recurrent aphthous stomatitis (RAS). The aim of our study was to review the papers that have described oral manifestations in subjects with CD.

## METHODS

A comprehensive literature search was conducted in Medline and Embase databases using the key words “celiac disease,” “coeliac disease,” and “dermatitis herpetiformis” combined separately with the terms “oral cavity,” “oral lesions,” “dental enamel defects,” “recurrent aphthous stomatitis,” “oral ulcers,” “glossitis,” “Plummer-Vinson syndrome,” “oral lichen planus,” “dental caries,” “dental decay,” and “dental age.” Potentially relevant papers were selected on the basis of title and abstract, and the full manuscripts were retrieved and reviewed. For papers that were neither in English nor

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Italian, only the abstract was reviewed; if no abstract was available, the article was discarded. Additional papers were selected by a manual search of the reference lists of the retrieved articles.

## CD AND ORAL HARD TISSUE LESIONS

### DEDs

During enamel matrix deposition and calcification, genetic and/or environmental factors can cause DEDs, which may be quantitative or qualitative. Disturbances in matrix secretion can cause enamel hypoplasia, which presents as deficiency of enamel quantity, whereas qualitative defects present as enamel opacity and are due to disruptions occurring during the calcification phase of enamel formation.<sup>7</sup>

An association between gastrointestinal diseases and developmental defects of dental enamel was described since early 1900s, when the term “dental atrophy” was used for dental malformations owing to disorders interfering with a normal nutrition.<sup>8</sup> In 1955, pronounced DEDs were described in a 7-year-old girl with clinical features of CD,<sup>9</sup> and in 1956, 7 patients with CD were examined, 3 of whom exhibited DEDs of the permanent dentition.<sup>10</sup> Thereafter, other cases of DEDs in subjects with CD were reported,<sup>10,11</sup> and 8 out of 18 celiac children had DEDs of permanent teeth in a series reviewed in 1973.<sup>12</sup>

To the contrary, only 9 out of 252 patients with CD were described as having mild to severe enamel hypoplasia in a study realized in 1980.<sup>13</sup> Besides, the first controlled study available in English literature which investigated the presence of DEDs in CD patients reported no significant difference between celiac subjects and healthy controls.<sup>14</sup> However, in 1986 Aine<sup>15</sup> provided the strongest evidence that DEDs may be an extraintestinal manifestation of CD, reporting a 95.94% prevalence of DEDs of permanent teeth in 74 children with CD. In this study, the celiac-type DEDs were defined as “systematic,” as they were symmetrically and chronologically distributed in all 4 sections, reflecting the period in which disruptions interfered with amelogenesis. The author proposed a grading system (from grade I to IV) to classify the severity of the CD-related enamel lesions, from simple opacities to severe structural defects (Table 1).

Almost all the subsequent controlled studies reported prevalence values of DEDs significantly higher in CD patients than in nonceliac individuals, and confirmed that the celiac-type enamel defects are systematic, as differences for unspecific and unsystematic defects were not significant (Table 2).

The reason for the presence of DEDs in celiac patients still remains not clear. Hypocalcemia due to malabsorption could be a possible cause, in agreement with the unifying hypothesis on mechanism of enamel hypoplasia development.<sup>37</sup> However, no differences in mean serum calcium concentration were found between celiac children with and without dental lesions,<sup>27</sup> and celiac-type DEDs were also detected in healthy first-

**TABLE 1.** Grading of the CD-related DEDs According to Aine<sup>15</sup>

Grade	DED
Grade I	Defect in color of enamel Single or multiple creams, yellow or brown opacities with clearly defined or diffuse margins; a part or the entire surface of enamel is without glaze
Grade II	Slight structural defects Enamel surface rough, filled with horizontal grooves or shallow pits; light opacities and discoloration may be found; a part or the entire surface of enamel is without glaze
Grade III	Evident structural defects A part or the entire surface of enamel rough and filled with deep horizontal grooves which vary in width or have large vertical pits; large opacities of different colors or strong discoloration may be in combination
Grade IV	Severe structural defects The shape of the tooth changed: the tips of cusps are sharp-pointed and/or the incisal edges are unevenly thinned and rough; the thinning of the enamel material is easily detectable and the margins of the lesions are well defined; the lesion may be strongly discolored

degree relatives of celiac patients having normal small-bowel mucosal architecture.<sup>38</sup> So, a gluten-induced, immune-mediated enamel damage should seem a more likely cause of DEDs in celiac patients. Consistently with this hypothesis, CD-associated dental changes were found significantly related to HLA antigen DR3.<sup>22,27</sup> Furthermore, a strong association between the same HLA allele and celiac-type DEDs were also demonstrated in healthy first-degree relatives of celiac patients.<sup>38</sup> Hypocalcemia resulting from malabsorption could be nevertheless a contributing factor in inducing defective enamel formation.<sup>39</sup>

A few studies compared the prevalence of celiac-type DEDs in deciduous and mixed/permanent dentition, and all of these reported that they are more prevalent in the mixed/permanent dentition.<sup>16,23,27</sup> The overall prevalence of systematic CD-related DEDs in patients with mixed/permanent dentition ranges from 9.52% to 95.94% (with a mean value of 51.12%), whereas that for CD patients with deciduous teeth is 5.88% to 13.33% (mean: 9.60%). The higher prevalence for the permanent dentition could be explained by the fact that the development of crowns of permanent teeth occurs between the early months of life and the seventh year (ie, after the introduction of gluten), whereas the formation of deciduous teeth mainly occurs in utero. But the presence of DEDs also in deciduous teeth supports the hypothesis that immuno-genetical factors are more likely involved in development of CD-related dental defects rather than nutritional deficiencies, or at least these represent the main cause.

The distribution of different grades of DEDs (according to the classification of Aine) shows that grade I and II defects are on the whole most common (Table 3). It is unclear which factors affect the severity of enamel defects in CD patients. It was reported that the celiac-type

**TABLE 2.** Prevalence of DEDs in Patients With CD

Author, Year	Dentition	Type of DED	Study Group (Patients With CD)		Control Group (Subjects Without CD)		CD Diagnostic Criteria	P
			No. Patients	Prevalence of DED (%)	No. Subjects	Prevalence of DED (%)		
Bucci et al, <sup>16</sup> 2006	D, M, P	Systematic	70	20	159	5.66	Biopsy	< 0.001
	D	Systematic	17	5.88	14	0	Biopsy	NRb
Farmakis et al, <sup>17</sup> 2005	M, P	Systematic	53	24.53	145	6.20	Biopsy	NR
	D	Opac., hypopl.	13	92.30	13	46.15	NR	< 0.006
Ciacci et al, <sup>18</sup> 2005	P	NR	360	16.11	—	—	Biopsy	—
	M, P	Any	18	83.33	18	50	ESPGAN, 1970	< 0.03
Priovolou et al, <sup>19</sup> 2004	M, P	Systematic	18	44.44	18	11.11	ESPGAN, 1970	< 0.02
Rasmusson et al, <sup>20</sup> 2001	M, P	Opac., hypopl.	40	50	40	38	ESPGAN, 1970	0.26
Lähteenoja et al, <sup>21</sup> 1998	D, M, P	Systematic	128	10.16	—	—	Biopsy	—
Aguirre et al, <sup>22</sup> 1997	M, P	Any	137	52.55	52	42.30	Biopsy	0.2
	M, P	Unspecific	137	14.59	52	25	Biopsy	0.09
Rea et al, <sup>23</sup> 1997	M, P	Systematic	137	37.95	52	17.30	Biopsy	0.006
	D, M, P	Systematic	45	24.44	105	4.76	ESPGAN, 1990	0.002
	D	Systematic	15	13.33	NR	NR	ESPGAN, 1990	—
	M, P	Systematic	30	30	NR	NR	ESPGAN, 1990	—
Ventura et al, <sup>24</sup> 1997	M, P	Systematic	603	32.33	6949	0.74	ESPGAN, 1990	< 0.00001
Martelossi et al, <sup>25</sup> 1996	M, P	Systematic	90	53.33	6949	0.74	ESPGAN, 1990	NR
Bertoldi et al, <sup>26</sup> 1995	D, M, P	Systematic	32	37.50	—	—	ESPGAN, 1990	—
Mariani et al, <sup>27</sup> 1994	D, M, P	Systematic	82	28.04	189	14.81	ESPGAN, 1990	< 0.005
Ballinger et al, <sup>28</sup> 1994	P	Systematic	42	9.52	18	11.11	NR	> 0.05
Petrecca et al, <sup>29</sup> 1994	M, P	Systematic	29	75.86	29	0	Biopsy	NR
Aine et al, <sup>30</sup> 1992*	P	Any	30	100	66	92.42	—	NR
	P	Unspecific	30	46.66	66	90.90	—	NR
Aine et al, <sup>31</sup> 1990	P	Systematic	30	53.33	66	1.51	—	< 0.001
	P	Any	40	100	112	93.75	Biopsy	NR
	P	Unspecific	40	17.50	112	89.28	Biopsy	NR
	P	Systematic	40	82.50	112	3.75	Biopsy	< 0.001
Balli et al, <sup>32</sup> 1988	D, M	NR	49	34.69	—	—	SIP	—
Prati et al, <sup>33</sup> 1987	D, M	NR	10	33.33	15	0	Biopsy	NR
Aine, <sup>15</sup> 1986	P	Systematic	74	95.94	—	—	Biopsy	—
Andersson-Wenckert et al, <sup>14</sup> 1984	M, P	Any	19	68.42	19	63.16	Biopsy	NR
	M, P	Unspecific	19	15.78	19	15.78	Biopsy	NR
Shmerling et al, <sup>13</sup> 1980	M, P	Systematic	19	52.63	19	47.36	Biopsy	NR
Romankiewicz-Wozniczko et al, <sup>12</sup> 1973	NR	NR	252	3.57	—	—	NR	—
Miller, 1956†	M, P	NR	18	44.44	—	—	NR	—
Hertz, <sup>9</sup> 1955	P	NR	7	42.85	—	—	NR	—
	D, M	NR	27	3.70	—	—	NR	—

\*This study was performed on patients with DH.

†Data reported in Smith et al,<sup>10</sup> 1979.

D indicates deciduous; ESPGAN, European Society of Paediatric Gastroenterology and Nutrition (references of the diagnostic criteria: Meeuwisse,<sup>34</sup> 1970; Walker-Smith et al,<sup>35</sup> 1990); hypopl, hypoplasias; M, mixed; NR, not reported; Opac, opacities; P, permanent; SIP, Società Italiana di Pediatria (Italian Society of Pediatrics; reference of the diagnostic criteria: Italian Society of Pediatrics,<sup>36</sup> 1978).

DEDs in adults are much less severe than in children, despite a similar prevalence.<sup>31</sup> In fact, no grade IV and only 1 case of grade III defects were found out of 40 adult celiac subjects (with a mean age at diagnosis of 34y),

whereas nearly 30% of children with CD had grade III or IV DEDs. This considerable difference could indicate that the adult patients had had a clinically mild or atypical disease at childhood, which had led to a late diagnosis

**TABLE 3.** Distribution of Grades of CD-related DEDs

Author, Year	Dentition	No. CD Patients With DEDs	No. CD Patients With Grade I DEDs (%)	No. CD Patients With Grade II DEDs (%)	No. CD Patients With Grade III DEDs (%)	No. CD Patients With Grade IV DEDs (%)
Bucci et al, <sup>16</sup> 2006	D, M, P	14	7 (50%)	4 (28.57%)	2 (14.28%)	1 (7.14%)
Priovolou et al, <sup>19</sup> 2004	M, P	15	12 (80%)	1 (6.66%)	0 (0%)	2 (13.33%)
Aguirre et al, <sup>22</sup> 1997	M, P	52	32 (61.54%)	16 (30.77%)	3 (5.77%)	1 (1.92%)
Rea et al, <sup>23</sup> 1997	D, M, P	11	5 (45.45%)	4 (36.36%)	2 (18.18%)	0 (0%)
Martelossi et al, <sup>25</sup> 1996	M, P	48	8 (16.66%)	22 (45.83%)	14 (29.17%)	4 (8.33%)
Petrecca et al, <sup>29</sup> 1994	M, P	22	10 (45.45%)	9 (40.90%)	2 (9.09%)	1 (4.54%)
Aine et al, <sup>30</sup> 1992*	P	16	6 (37.50%)	10 (62.50%)	0 (0%)	0 (0%)
Aine et al, <sup>31</sup> 1990	P	33	15 (45.45%)	17 (51.51%)	1 (3.03%)	0 (0%)
Aine, <sup>15</sup> 1986	P	71	10 (14.08%)	39 (54.93%)	14 (19.72%)	8 (11.27%)

\*This study was performed on patients with DH. D indicates deciduous; M, mixed; P, permanent.

and slight dental lesions.<sup>31</sup> In support of this hypothesis, a correlation between the severity of CD clinical presentation and the grade of DEDs was also demonstrated.<sup>15</sup> However, a higher prevalence of enamel lesions in patients with atypical or asymptomatic CD was found,<sup>16</sup> and a study on patients affected by the CD-related dermatitis herpetiformis (DH) demonstrated no correlation between the degree of mucosal damage and the presence of DEDs.<sup>30</sup>

The hypothesis that late diagnosis and prolonged gluten exposure relate to the likelihood of DEDs was supported by a few studies, which demonstrated that mean age at diagnosis of CD is significantly higher in patients with dental defects,<sup>24,28</sup> although others failed to do so.<sup>16,27</sup> Furthermore, in a series of 360 adults with CD, no case of DEDs was described among patients with proved CD diagnosis in childhood and on a strict GFD since diagnosis, whereas DEDs were found in 18% of patients with early diagnosis but who were reexposed to gluten, and in 26% of adults with newly diagnosed CD.<sup>18</sup>

Concerning the location of the CD-related DEDs, incisors are the teeth most frequently affected, followed by molars, canines, and premolars.<sup>16,22</sup> This distribution should seem related to the chronology of development of the permanent dentition, as incisors and first molars are the first teeth that undergo calcification; the lesser involvement of teeth that calcify at a later stage could be explained considering that their calcification starts when CD has been possibly already diagnosed, and gluten removed from diet.<sup>22</sup> Instead, in nonceliac subjects dental defects seem to be equally distributed for all the teeth,<sup>16,22</sup> with significant difference with respect to the involvement of incisors as compared with CD patients.<sup>22</sup> In regard to the distribution of DEDs on the coronal surface, the incisal third resulted the most affected surface both in CD and control groups; however, involvement of the incisal two thirds or of the complete crown were also observed in celiac patients, whereas none of the control group showed this coronal involvement, and the difference resulted statistically significant.<sup>22</sup>

### Dental Caries

Several studies investigated the prevalence of dental caries in celiac patients. Some of these reported no difference in caries prevalence between celiac individuals and control healthy subjects.<sup>26,29,33,40</sup> Rather surprisingly, others found caries indexes significantly lower in CD subjects than controls.<sup>14,17,19,22</sup> No study reported higher dental caries prevalence among celiac patients. A possible explanation for these findings is that the need for a carefully controlled diet should make CD patients more diet-conscious, so that they maybe have a low cariogenic diet.<sup>14,17,22</sup>

### Dental Age

Dental age was studied in 49 children with CD<sup>32</sup>; delay in tooth eruption, estimated according to the dental standard of Schour and Massler,<sup>41</sup> was noticed in 28.57% of patients. Similarly, the dental age was delayed in relation to calendar age in one third of 38 children with CD examined in a Polish study.<sup>42</sup> Furthermore, we have recently observed delayed eruption in 26% of pediatric CD patients, as opposed to 7% of the controls (unpublished observations). These findings are likely related to the growth retardation, that is a typical sign of CD.

## CD AND ORAL SOFT TISSUE LESIONS

### RAS

RAS is characterized by painful, recurrent, single or multiple ulcers of the oral mucosa, which are round or ovoid and have an erythematous halos and a yellow or gray floor. It is one of the most common mouth diseases, affecting 5% to 60% of the population depending on the group studied<sup>43</sup>; it has been estimated that 20% of the general population will suffer from RAS at some time in their lives.<sup>44</sup> Approximately 80% of patients with RAS have minor aphthae, that are 2 to 8 mm in diameter and usually resolve spontaneously within 2 weeks. Major RAS is much less common, with ulcers that may exceed 1 cm in diameter and persist for several weeks. The least common type of RAS is termed “herpetiform” and is characterized

by clusters of small ulcers (as many as 100 or more, 1 to 3 mm in diameter) that tend to coalesce producing large irregular ulcerations.

The term “recurrent aphthous stomatitis” should be reserved for recurrent ulcers occurring in subjects without systemic diseases, whereas ulcers that resemble RAS but found in systemic disorders should be termed “aphthous-like ulcers.”<sup>45</sup> However, these 2 expressions are often used indistinctly, and all the papers we reviewed discussed RAS as a possible CD-associated oral disease. So, herein we use the term RAS as well, even though aphthouslike ulcers should be a more appropriate expression to describe recurrent oral ulcerations in celiac patients.

An association between oral ulcers, diarrhea, and weight loss has been described for more than 3 centuries,<sup>46</sup> and the early studies that investigated the prevalence of CD in patients affected by RAS reported very high values (Table 4). Notably, Ferguson et al<sup>46</sup> quoted a 24.24% prevalence of CD in 33 patients with RAS, and asserted the importance of performing jejunal biopsy in subjects with recurrent aphthae. Subsequent studies<sup>54–56</sup> lessened this matter, albeit they reported CD prevalence values higher than those expected for the normal population, and thus supported the hypothesis of a correlation between CD and RAS. On the contrary, in 1986 only 1 of 100 patients with RAS had histologic evidence of CD,<sup>53</sup> and no CD-affected patient has been recently described among 87 subjects with RAS.<sup>49</sup> However, in the only 2 controlled studies that have searched for CD in patients with RAS,<sup>47,48</sup> histologic signs of CD have been demonstrated in nearly 5% of patients with RAS, whereas none of the biopsies obtained from controls revealed the disease.

The evidence of a correlation between the 2 conditions was less robust when we considered studies, which examined the prevalence of RAS in CD patients (Table 5). In fact, 9.66%<sup>64</sup> to 26.53%<sup>32</sup> of celiac subjects resulted with RAS in uncontrolled studies, a prevalence similar to that estimated for the general population.

Furthermore, all the controlled studies<sup>14,16,21,60</sup> failed to demonstrate any statistically significant difference between CD and control groups, even though it is worth noting that prevalence values of RAS resulted constantly higher in celiac patients than controls.

A support for the hypothetical correlation between CD and RAS is provided by the observation that GFD may be effective in the management of RAS. In fact, several authors reported significant improvement, if not complete remission, of oral aphthae in most CD patients which had been placed on GFD,<sup>16,46,55,65</sup> and reappearance of recurrences with the reintroduction of gluten.<sup>52,54,62,63</sup> Furthermore, patients with RAS and no histologic evidence of CD showed a favorable response to GFD and a positive gluten challenge, suggesting the existence of a form of gluten-sensitive RAS.<sup>66</sup> On the other hand, a double-blind controlled study examined the effect of GFD in patients with RAS and without CD; 4 of the 11 subjects on GFD reported benefit as regards the oral aphthae, but no significant statistical difference was observed as compared with control subjects which underwent GFD supplemented by gluten given blind.<sup>67</sup>

Concerning the severity of aphthae in CD subjects, most papers assert that celiac patients with RAS suffer from minor aphthae.<sup>53,55,57,62,63</sup> However, cases of CD patients with major or herpetiform RAS were also reported.<sup>54</sup>

A possible explanation for the hypothetical correlation between CD and RAS is that oral aphthae in CD patients could be related to hematinic deficiencies (iron, folic acid, or vitamin B<sub>12</sub>). In fact, about 20% of subjects with RAS may have a hematinic deficiency,<sup>43</sup> and the serum levels of iron, folic acid, and vitamin B<sub>12</sub> are usually low in patients with untreated CD.<sup>68</sup> Consistently with this hypothesis, hemoglobin and serum folate levels were found significantly lower in patients affected by both RAS and CD than in nonceliac subjects with RAS.<sup>46,58</sup> Moreover, all the 5 cases of CD diagnosed in a series of

**TABLE 4.** Prevalence of CD in Patients With RAS

Author, Year	Study Group (Patients With RAS)			Control Group (Subjects Without RAS)		CD Diagnostic Criteria	P
	No. Patients	Type of RAS	Prevalence of CD (%)	No. Subjects	Prevalence of CD (%)		
Olszewska et al, <sup>47</sup> 2006	42	NR	4.76	42	0	Biopsy	> 0.05
Aydemir et al, <sup>48</sup> 2004	41	NR	4.88	49	0	Biopsy	NR
Robinson et al, <sup>49</sup> 2004	87	Minor	0	—	—	Biopsy	—
Nowak et al, <sup>50</sup> 2002	20	NR	5	—	—	IgA EMA	—
Jokinen et al, <sup>51</sup> 1998	27	NR	11.11	—	—	Biopsy	—
Tavarela Veloso et al, <sup>52</sup> 1987	24	NR	16	—	—	Biopsy	—
Merchant et al, <sup>53</sup> 1986	100	Minor	1	—	—	Biopsy	—
Tyldesley, <sup>54</sup> 1981	97	min., maj., her.	6.18	—	—	Biopsy	—
Ferguson et al, <sup>55</sup> 1980	50	Minor	4	—	—	Biopsy	—
Rose et al, <sup>56</sup> 1978	26	NR	3.84	—	—	Biopsy	—
Ferguson et al, <sup>46</sup> 1976	33	NR	24.24	—	—	Biopsy	—
Wray et al, <sup>57</sup> 1975	130	Minor	3.84	—	—	Biopsy	—
Ferguson et al, <sup>58</sup> 1975	35	NR	20	—	—	Biopsy	—

EMA indicates endomysium antibodies; her., herpetiform; min., minor; maj., major; NR, not reported.

**TABLE 5.** Prevalence of RAS in Patients With CD

Author, Year	Study Group (Patients With CD)			Control Group (Subjects Without CD)			CD Diagnostic Criteria	P Value
	No. Patients	Prevalence of RAS (%)	Type of RAS	No. Subjects	Prevalence of RAS (%)	Type of RAS		
Bucci et al. <sup>16</sup> 2006	72	33.33	NR	162	23.45	NR	Biopsy	> 0.05
Sood et al. <sup>59</sup> 2003	96	19.79	NR	—	—	—	ESPGAN, 1990	—
Sedghizadeh et al. <sup>60</sup> 2002	61	40.98	NR	62	27.41	NR	NR	0.1127
Lähteenoja et al. <sup>21</sup> 1998	128	3.12	NR	30	0	—	Biopsy	0.327
Petrecca et al. <sup>29</sup> 1994	29	17.24	NR	—	—	—	Biopsy	—
Corazza et al. <sup>61</sup> 1993	226	15.93	NR	—	—	—	Biopsy	—
Meini et al. <sup>62</sup> 1993; Majorana et al. <sup>63</sup> 1992	113	17.69	Minor	—	—	—	ESPGAN, 1990	—
Balli et al. <sup>32</sup> 1988	49	26.53	NR	—	—	—	SIP	—
Biamond et al. <sup>64</sup> 1987	414	9.66	NR	—	—	—	biopsy	—
Andersson-Wenckert et al. <sup>14</sup> 1984	19	31.58	NR	19	26.31	NR	Biopsy	NR

ESPGAN indicates European Society of Paediatric Gastroenterology and Nutrition (reference of the diagnostic criteria: Walker-Smith et al.<sup>35</sup> 1990); NR, not reported; SIP, Società Italiana di Pediatria (Italian Society of Pediatrics; reference of the diagnostic criteria: Italian Society of Pediatrics,<sup>36</sup> 1978).

130 patients with RAS were deficient in iron, vitamin B<sub>12</sub>, or folic acid.<sup>57</sup>

Immuno-genetical factors could be also involved in this presumptive association, as the prevalence of HLA antigens DRw10 and DQw1 was demonstrated significantly higher in patients with CD and RAS than in patients with CD only.<sup>62,63</sup> However, whether CD and CD-associated aphthous ulcers are the consequence of a similar immunopathologic mechanism remains a matter of conjecture.

### Atrophic Glossitis

A series of 128 patients with CD and 30 healthy controls was examined for oral mucosal lesions and symptoms in a Finnish study.<sup>21</sup> The tongue was most frequently affected, as 29.68% of CD patients referred soreness or burning sensation of the tongue (with a statistically significant difference as compared with control subjects) and 8.59% showed erythema or atrophy.

We can report the case of a man with erythema and atrophy on the dorsum of the tongue and without gastrointestinal complaints, whose serologic tests for CD were positive; the small-intestine biopsy confirmed the diagnosis of CD, and GFD resulted in resolution of the tongue lesion.<sup>69</sup>

We found no more paper that supports a correlation between CD and glossitis. However, iron and vitamin B<sub>12</sub> deficiencies are frequent in untreated CD patients,<sup>68</sup> and it is well known that such deficiencies may cause atrophic glossitis, often accompanied by soreness or burning sensation.<sup>70</sup> Furthermore, several reports describe cases of CD associated with Plummer-Vinson syndrome.<sup>71-77</sup> Plummer-Vinson syndrome (also referred as Paterson-Brown Kelly syndrome, or sideropenic dysphagia) is a rare condition that comprises the classic triad of dysphagia, iron-deficiency anemia, and esophageal webs; other clinical features may also be observed, among these atrophic glossitis.<sup>78</sup>

### Oral Lichen Planus

Oral lichen planus (OLP) is a chronic inflammatory disorder affecting the oral mucosa with a spectrum of clinical conditions, including keratotic, atrophic, erosive, and ulcerative lesions.<sup>79</sup>

In 1993, an unusual association of OLP and CD was reported.<sup>80</sup> This was the case of a 70-year-old male with a biopsy-proven erosive OLP; iron, folate, and vitamin B<sub>12</sub> deficiencies led to perform jejunal biopsy, that demonstrated CD. Surprisingly, GFD resulted in relief of OLP within 6 months. But the hypothesis of an association between CD and OLP was promptly refuted by Scully et al.<sup>81</sup> who 1 month later referred that they had investigated 103 patients with OLP and none had CD. So, they replied that OLP would seem only occasionally associated with CD.

In 1998, 39 consecutive patients with OLP were screened for CD; 12 were positive for IgA gliadin antibody test and 2 for endomysium antibody test, but only 1 had small intestinal signs of CD.<sup>51</sup> We found only another anecdotal report that describes OLP in a CD patient.<sup>82</sup> Thus, there is currently insufficient evidence to support an association between CD and OLP.

### Oral Manifestations of DH

DH is a pruritic bullous skin disease considered as a part of the spectrum of gluten-sensitive disorders. In fact, although patients with DH are unlikely to have gastrointestinal complaints, nearly all of them have some degree of small intestinal histopathologic changes identical to those of CD, and they share the same serologic antibody profile of celiac subjects.<sup>83</sup> Moreover, GFD is an effective therapy for DH, which confirms the role of an intestinal reaction to gluten in the pathogenesis of DH.<sup>84</sup> Typically, DH consists of symmetrical, erythematous, papulo-vesicular lesions that generally involve the extensor surfaces of the elbows, knees, buttocks, and scalp. Owing

to their intense itching, lesions often look as skin erosions secondary to scratching.

In a study on 15 patients with DH, oral lesions were found in 12 cases.<sup>85</sup> Oral involvement consisted of erythematous, pseudo-vesicular, purpuric, and erosive lesions, but only in 2 cases the direct immunofluorescence examination revealed the typical granular deposits of IgA along the basement membrane, that is a *sine qua non* for the diagnosis of DH. Similarly, 57% of 27 patients with DH were found as having oral lesions, which included ulcerations, erythemas, and atrophies<sup>86</sup>; however, no direct immunofluorescence study was performed.

To the contrary, no oral mucosal involvement was described in a large review of 926 cases of DH,<sup>87</sup> and only 1 case of small oral blisters was reported in a study on 149 DH patients.<sup>88</sup> Rather, in an old paper<sup>89</sup> the absence of oral lesions was referred as a diagnostic criterion for DH.

Actually, at present oral involvement in DH is considered very rare, and generally consists of vesicles and bullae that result in ulcers.<sup>90</sup> Reports that describe DH lesions in the oral cavity are sparse<sup>91–95</sup>; 2 of these<sup>91,95</sup> relate cases of oral manifestations appeared before the onset of the skin lesions.

### Other Oral Soft Tissue Lesions

Oral mucosal malignancies were described in celiac patients; these include carcinoma of the tongue<sup>72,96,97</sup> and oral T-cell lymphoma.<sup>98</sup> Occurrence of T-cell lymphoma in the oral cavity is uncommon for celiac patients, as CD-related lymphomas usually develop in the upper small intestine. In addition, 8 cancers of oral cavity and pharynx were detected out of 11,019 CD subjects.<sup>99</sup>

A case of oral mucosal melanosis was observed in a 32-year-old celiac woman, also affected by neuropathies and unspecified “dental irregularities”<sup>100</sup>; GFD resulted in improvement of neurologic findings, but not of oral hyperpigmentation.

An occasional association of CD and cicatricial pemphigoid with involvement of tongue, buccal mucosa, gingiva, and floor of mouth has been recently reported in a 14-year-old girl.<sup>101</sup>

## DISCUSSION

Contrary to early beliefs, CD is a relatively common disease, with a mortality rate higher than that of the general population, mainly owing to long-term complications (eg, autoimmune diseases, malignancies). Diagnosis of CD is relatively easy in cases with typical signs and symptoms (ie, chronic diarrhea, abdominal pain and distention, weight loss). However, the majority of patients suffers from atypical or silent forms, for which diagnosis is often difficult. As a consequence, although its estimated prevalence is nowadays significantly higher than previously thought, it is reasonable to presume that CD still remains underdiagnosed.<sup>102</sup>

CD fulfils the WHO criteria for mass screenings.<sup>103</sup> In fact, it is a common disorder with a significant morbidity and an effective treatment; its early detection could be difficult on a clinical basis; if not diagnosed, it

could result in severe complications difficult to manage. Moreover, although the small intestinal biopsy remains the gold standard for the diagnosis of CD, current diagnostic serologic tests (mostly endomysium antibodies and tissue transglutaminase antibodies) have optimal specificity and sensitivity approaching 100%.<sup>104</sup> Thus, they are suitable as screening tests. However, at present there is insufficient evidence to recommend mass screening for CD, while case-finding in high-risk groups (ie, subjects with clinical conditions well-known to be associated with CD) seems effective, and currently represents the best epidemiologic approach to detect atypical cases.<sup>105</sup> First-degree relatives of celiac individuals and subjects with type I diabetes, autoimmune thyroid disease, unexplained osteoporosis, unexplained abnormal liver biochemistry, irritable bowel syndrome, and unexplained infertility or miscarriage are considered at-risk groups<sup>105</sup>; for them serologic CD testing should be considered.

A few oral ailments have been described in celiac patients. Among these, systematic DEDs are those with the strongest evidence of a correlation with CD, and should be counted in the extraintestinal manifestations of the disease. Subjects with systematic DEDs should be considered at-risk for CD, and thus they should undergo serologic screening tests for gluten intolerance.

As regards aphthous ulcers, although an association with CD should seem plausible. Currently, we lack robust evidence-based data to recommend CD screening tests for subjects with recurrent aphthae. However, hematologic investigations (such as full blood cell count and measurement of serum iron, ferritin, vitamin B<sub>12</sub>, and folic acid) are often included in the standard diagnostic protocols for RAS,<sup>43</sup> albeit elements in support of routine hematologic testing in patients with aphthae are lacking.<sup>45</sup> At any rate, a suspicion of CD should arise in cases of RAS associated with hematinic deficiencies. Similarly, CD testing could be considered in those patients with idiopathic atrophic glossitis for which hematologic investigations reveal an underlying haematinic deficiency.

In summary, oral cavity may be involved in CD. DEDs are the oral lesions most closely related to CD; patients with systematic enamel defects have to be recognized as at-risk subjects, and they should undergo screening tests even in the absence of gastrointestinal symptoms. On the other hand, there is insufficient evidence to recommend routine CD screening tests for patients with RAS, and also for subjects with idiopathic atrophic glossitis. Nevertheless, we would alert physicians and dental practitioners to consider CD in managing these patients, especially if clinical conditions that could be the result of CD are present.

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