

# Patients-Reported Oral Manifestations in Coeliac Disease and Inflammatory Bowel Diseases: An Italian Survey

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**Abstract:** Inflammatory Bowel Diseases (IBDs), including Ulcerative Colitis (UC), Crohn's Disease (CD), Irritable Bowel Syndrome (IBS), and Coeliac Disease (CoD), primarily affect the intestinal tract but show some extra-intestinal manifestations affecting the skin, joints, liver, pancreas, and lungs. The aim of this survey was to define how often these intestinal conditions show oral manifestation. The study involved 46 patients of 56 recruited at the beginning, with a mean age of  $42 \pm 13.64$  and a sex distribution of 67.4% (31) female and 32.6% (15) male. Everyone was sent a questionnaire of four multiple-choice questions about the type of their bowel disease, the time of the diagnosis, the major symptoms which led to the disease discover, and finally their oral symptoms. According to the results, 65.52% referred to oral manifestations, especially canker sores and burning sensation. The oral involvement suggests that multidisciplinary management and therapy are mandatory, with close monitoring and follow-up interfacing with other specialists. Finally, dental practitioners have to be aware of this possible oral effect in IBDs and CoD patients.

**Keywords:** aphthous stomatitis; bowel inflammation; cobblestoning; extraintestinal manifestations; IBD; oral disease; oral health; oral pathology



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## 1. Introduction

Inflammatory bowel diseases (IBDs) are a group of nosological conditions that include two major phenotypes which affect the gastrointestinal tract (GI), Crohn's Disease (CD), and Ulcerative Colitis (UC), and other minor manifestations such as Irritable Bowel Syndrome (IBS), while Coeliac Disease (CoD) is considered as an immune-mediated disease. Although the etiopathology is still unknown, it is thought to be multifactorial, with the cooperation of environmental aspects, intestinal bacterial, genetic predisposition, and pathological immune response to the microbiota of the gut [1].

IBDs are characterized by inflammation of the intestinal mucosa [2] and may affect the entire GI tract: while CD can involve any location from the oral cavity to the anus (with primarily affection of the small intestine), and UC involves the rectum and part of the colon (the large intestine). Symptoms can occur at any age, with the onset usually occurring between fifteen and thirty years [3]: major symptoms are chronic and often bloody diarrhea, weight loss, abdominal pain, fever, and secondary anemia; however, IBDs not only affect the GI tract but may also involve other organs and body regions.

Extraintestinal manifestations (EIMs) of IBD, commonly involving the musculoskeletal system (e.g., arthritis), skin (e.g., erythema nodosum, pyoderma gangrenosum), eyes (episcleritis, uveitis), oral cavity (e.g., aphthous stomatitis and pyostomatitis vegetans), may interest lots of patients and occur even before or soon after the IBD diagnosis [4], with an important impact on patients' quality of life and functional status. Vavricka and co. in 2015 showed that a first EIM occurred before IBD diagnosis in 26% of cases (median time

five months before IBD was diagnosed) and after IBD diagnosis made in 74% of patients (median time: 92 months after) [5].

The oral cavity is frequently affected in patients suffering from IBD, especially CD, with a range prevalence of 5–50%, due to the heterogeneity of the studies (which included patients of different genetic backgrounds, ages, and ethnicities and were made by different authors with different knowledge and experience about the topic) [6].

Oral manifestations may occur before the IBD diagnosis or together with intestinal symptoms; sometimes oral lesions may anticipate GI symptoms, showing as the first sign of the disease [7,8]. Oral symptoms are usually more severe during the activity period of the intestinal disease, but approximately 1/3 of affected patients show oral manifestations after the remission of the IBD symptoms [9]. The prevalence of oral EIMs is higher in children [10,11] and males [12,13], and in CD patients than UC ones [14].

Oral manifestations can be considered a primary location of IBD or resulting in a nutritional deficiency due to intestinal malabsorption or even induced by medical treatments. Oral symptoms can be divided into specific and non-specific manifestations: if specific lesions are associated only with CD, non-specific lesions may occur in CD or UC patients; non-specific lesions are more common than specific ones, making differential diagnosis really difficult [15].

Specific oral lesions (Table 1) in CD patients include cobblestoning swollen oral mucosa, mucosal tags, deep and linear ulcerations, edema of the face, cheeks and lips and mucogingivitis [16]; furthermore, non-caseous granulomatous inflammation may be detected in such lesions at histological examination [10,12].

**Table 1.** Specific oral manifestations of IBD.

Specific Lesions	Description	CD *	UC **
Cobblestoning mucosa	Hyperplastic, fissured, and swollen mucosa with corrugation	YES	NO
Mucosal tags	Indurated tag-like lesions, with hyperplastic edges, boggy, or firm to palpation	YES	NO
Non-caseous granulomatous lesions	Granulomas (core of activated macrophages) surrounded by fibrotic tissue and lymphocytes	YES	NO
Mucogingivitis	Edematous, granular, and hyperplastic gingiva	YES	NO

\* Crohn's disease; \*\* Ulcerative colitis.

Non-specific oral manifestations (Table 2) associated with both CD and UC patients include aphthous stomatitis, pyostomatitis vegetans, angular cheilitis, glossitis, lichen planus [17]; they may be caused by chronic inflammation, malnutrition, and therapy drugs.

**Table 2.** Non-specific oral manifestations of IBD.

Non-Specific Lesions	Description	CD *	UC **
Aphthous stomatitis	Shallow round ulcerations with central fibrine membrane, surrounded by an erythematous halo	YES	YES
Angular cheilitis	Erythema with/without painful fissures and sores at mouth corners	YES	YES
Pyostomatitis vegetans	Small exophytic lesions with erythematous border and creamy surface with erosions	NO	YES
Glossitis	Swollen and inflamed tongue	YES	YES

\* Crohn's disease; \*\* Ulcerative colitis.

Moreover, the incidence of candidiasis, dental erosion, halitosis [18], and dental caries [19] is higher in IBD patients than in the healthy population. Traumatic lesions

(buccal trauma) may also be observed in patients with IBD (especially in those with CD) such as lymphadenopathy (in almost 50% of CD patients and 20% of UC patients) [20].

This survey aimed to evaluate the prevalence of oral manifestations in an Italian population of IBDs and CoD patients.

## 2. Materials and Methods

The current study was conducted in accordance with the Helsinki Declaration and patients were recruited from the Gastroenterology Unit of SS. Annunziata Hospital in Chieti, Italy.

### 2.1. Inclusion Criteria

IBDs and CoD patients older than 18 y.o., referring to the Gastroenterology Unit of SS. Annunziata Hospital in Chieti and who were able to provide informed consent were enrolled, without any other systemic conditions involving oral signs.

### 2.2. Exclusion Criteria

IBDs and CoD patients younger than 18 y.o., with oral lesions related to systemic conditions, and unable to provide informed consent were excluded.

Written informed consent was obtained after explaining the procedure to each participant and then every patient received a questionnaire (Table 3) on *SurveyMonkey.com* (*SurveyMonkey*<sup>®</sup>, One Curiosity Way, San Mateo, CA, USA) of four multiple-choice questions about which kind of intestinal disease they suffered from; how long since they discovered the disease?; the reason why they discovered it; if they have noticed any oral disorders. A dental professional was present during the survey filling to help patients with peculiar terms or specific questions, leaving them to freely express what they felt without affecting them in any way.

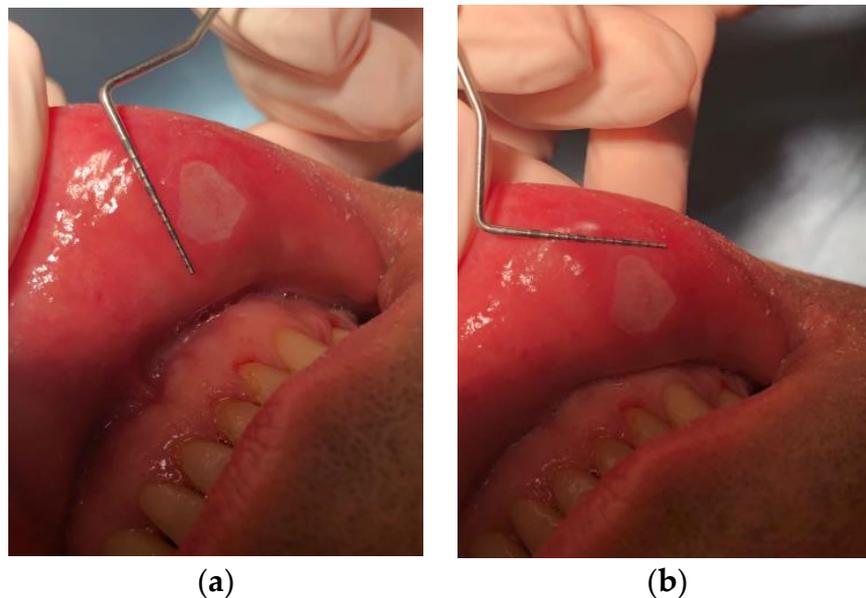
**Table 3.** Questions from the questionnaire on *SurveyMonkey.com*, accesses on 1 March 2021.

Questions	Options
Do you suffer from one of these diseases?	Crohn's Disease (CD) Ulcerative Colitis (UC) Coeliac Disease (CoD) Irritable Bowel Syndrome (IBS)
When did you discover your disease?	In early childhood (0–6 years old) In childhood (7–12 years old) In adolescence (13–19 years old) In adulthood (over 20 years old)
How did you discover your disease?	Weight loss Abdominal pain Blood or mucus in the stool Constipation or diarrhea
If you have noticed oral mucosa inflammation (pain, vesicles, burning) during acute phases, please describe it.	No options

The participants were able to leave the research at any time without any consequences and not to answer all the questions. Some symptomatic patients during the questionnaire filling agreed to be examined and photographed (Figures 1 and 2).



**Figure 1.** Vesicles outcome of a CD patient.



**Figure 2.** Canker sore on the labial mucosa of a CoD patient. (a,b) show the dimension of the lesion, using a parodontal probe.

### 3. Results

The initial recruitment provided 56 subjects with a mean age of  $48 \pm 17.04$  and a sex distribution of 66.1% (37) female and 33.9% (19) male. After the initial phase, a total of 46 patients, with a mean age of  $42 \pm 13.64$  and a sex distribution of 67.4% (31) female and 32.6% (15) male, decided to answer the questionnaire (Table 4). There was a 17.86% dropout rate, due to several factors: three patients had an exacerbation of the disease and were unable to answer the questionnaire in time; one patient reported being too busy with work and not being able to devote time to the survey; two other patients no longer showed interest in the study and withdrew, notifying it to the Gastroenterology Unit; four of them did not give any explanations and just dropped out.

**Table 4.** Questionnaire results.

Q1: Do You Suffer from One of These Diseases?		
Crohn's Disease (CD)	8	18.18%
Ulcerative Colitis (UC)	8	18.18%
Coeliac Disease (Cod)	20	45.46%
Irritable Bowel Syndrome (IBS)	8	18.18%
Q2: When did you discover your disease?		
In early childhood (0–6 yo)	4	8.89%
In childhood (7–12 yo)	4	8.89%
In adolescence (13–19 yo)	8	17.78%
In adulthood (over 20 yo)	29	64.44%
Q3: How did you discover your disease?		
Weight loss	10	22.22%
Abdominal pain	13	28.89%
Blood/mucus in the stool	7	15.56%
Diarrhea/constipation	15	33.33%
Q4: If you have noticed oral mucosa inflammation (pain, vesicles, burning . . . ) during acute phases, please describe it.		
No	9	31.03%
I don't know	1	3.45%
Yes	19	65.52%
• Canker sores	12	63.16%
• Vegetations	1	5.26%
• Burning	5	26.32%
• Stomatitis	1	5.26%
• Vesicles	2	10.52%

#### 4. Discussion

EIMs during the activity phase of an IBD are very frequent among patients (especially CD and UC patients) and they have been reported with frequencies ranging from 6% up to 47% [21]. EIMs may be more common in early onset IBD and in younger subjects [22], but this has not been confirmed in all studies: Stawarski et al. reported that 80% with CD and 50% of patients with UC had EIMs [23] while the SIBDCS group reported a 16.7% (55/329) prevalence of extraintestinal manifestations in pediatric patients with IBD [24]. Even Zervou et al. reported that patients with CD showed a higher rate of multiple oral manifestations than UC patients [20].

The aim of this survey was to evaluate the possible incidence of oral manifestations in IBD patients from the Gastroenterology Unit of SS. Annunziata Hospital in Chieti, Italy. It is important to underline that not all the patients that decided to participate to the survey answered all the four questions.

In this cohort, patients predominantly suffered from CoD (45.46%), which can be considered in a wide definition of Intestinal Bowel Disease as an IBD, sharing the same immune etiological involvement. Crohn's Disease, Ulcerative Colitis, and Irritable Bowel Syndrome showed the same incidence (18.18%). Although the etiology of these intestinal conditions has not been definitely found out that it is well known that the pathogenesis of the disease is triggered by factors including intestinal biofilm, genetical predisposition, pathological immune responses, and environmental aspects [25]. All of these factors are also involved in the onset of many common oral diseases, which may explain the link between these conditions.

Most of the enrolled patients (64.44%) discovered their intestinal disease in adulthood, while eight of them (17.78%) found it in adolescence; the other participants discovered their IBDs in early childhood or childhood (both 8.89%). According to previous studies, even if IBD can occur at any age from childhood to the elderly [26], the actual age of diagnosis or disclosure is 30–40 years [27,28]. Some papers stated that the peak age for UC onset is 30–40 years, while it is 20–30 years for CD; other studies have reported another peak occurring at 60–70 years, but this information needs to be confirmed [29].

The major symptoms that made these patients find out their intestinal problems were diarrhea or constipation (33.33%), abdominal pain (28.89%), weight loss (22.22%), and the presence of blood or mucus in the stool (15.56%), in accordance with other papers that showed the principal symptoms of IBDs (fatigue, fever, abdominal pain, diarrhea, and weight loss) [30]. These features are not always present in all patients: sometimes, only one symptom, usually abdominal pain alone, may manifest [31].

In 2011, a new classification of CD was implemented (the Oslo classification) and it recognized four clinical presentations: classic, subclinical, refractory, and potential forms [32]; the classical (or intestinal) form is usually detected in children (<3 years old) with symptoms like loss of appetite, diarrhea, abdominal distention, and growth difficulty [33]; older than three years children, adolescents, and adults may report symptoms like diarrhea, abdominal swelling, abdominal pain, constipation, and/or weight loss [34]. While the malabsorption syndrome (weight loss, chronic diarrhea, and asthenia) is quite unusual in adult patients, an IBS-like appearance is more common and shows symptoms like constipation and/or nausea and/or vomiting [35]. Patients with the subclinical form show very subtle signs and symptoms and they can be diagnosed with CD through the benefits of a gluten-free diet [32]. The potential form of CD may affect subjects with classical/non-classical symptoms or no symptoms, and it is characterized by normal/little inflamed intestinal mucosa and positive serological markers. The refractory CD form shows persistent symptoms plus atrophy of the intestinal mucosa after at least one year of a strict gluten-free diet.

Asking patients if they have noticed oral mucosa inflammation (pain, burning, vesicles, or other features) during the acute phase of their disease, nine subjects answered negatively, referring to no oral manifestations; only one patient answered that he could not connect the oral symptoms with an acute period of the intestinal disease, because he had always suffered from oral issues. 65.52% of this cohort of patients referred to suffer from oral manifestations during their active period of intestinal disease: major symptoms referred were canker sores (63.16%), burning sensation (26.32%), vesicles (10.52%) (Figure 1), stomatitis, and vegetations (both 5.26%); most of the subjects reported only one oral manifestation, while two patients described the contemporary presence of two oral symptoms (burning and vesicles, or burning and aphthae).

According to Scully et al., the most frequent oral manifestation of Inflammatory Bowel Diseases is aphthous stomatitis (canker sores with an atypical clinical course or presentation) [36]; these lesions cannot be recognized from regular aphthae without a biopsy, they are as frequent as in the healthy population, but they show a tendency of recurring in time [37]; they usually occur on the buccal and labial mucosa or the vestibular sulci (Figure 2a,b).

An interesting paper from Triantafyllidis et al. (2008) showed that a massive swelling of the lower lip as a result of granulomatous cheilitis could be the initial manifestation of CD, while the worsening of the lip lesions could represent a preliminary clinical feature of the intestinal disease's recurrence [8].

Treating oral lesions in patients with Inflammatory Bowel Disease is very important in order to reduce pain (which may be really disabling), to improve e speed up wound healing, and to prevent other secondary infections [38]. The therapy of oral conditions may be conditioned by the clinical presentation of the lesions, their etiology, and their symptoms. The treatment of oral lesions in CD aims to cure and control primary intestinal disease and these lesions tend to respond very well to the IBD therapy [39]. The treatment of

canker sores (aphthous stomatitis) consists of nutrition supplements (vitamin and mineral supplements) with the addition of topical and systemical (if required) medication therapy, based on the seriousness of the symptoms, type, and number of the lesions [38].

It is fundamental to emphasize that oral lesions in IBD patients may be caused by the medications used for treating the bowel disease: those medications (corticosteroids, 5-Aminosalicylic acid derivatives, antibiotics, immunomodulators, and others, based on the site, behavior, and activity of the primary disease) [40] may lead to modifications of the oral environment due to both direct (toxic) and indirect (immunosuppressive) effects, finally causing oral lesions.

#### *Limitation of the Study*

The methodological issues need to be assessed. The sample size of this survey has to be considered improvable, in order to gather more details about the oral situation in IBDs and CoD patients. Furthermore, surveys identify the personal perception of oral signs and symptoms not always evident during the recruitment phase.

### 5. Conclusions

Oral manifestations in IBDs and CoD patients are quite common EIMs that need to be considered and managed in a multidisciplinary work team, in order to improve patient's quality of life, although they seem to be poorly reported by patients who tend to underestimate them. As a result of the present survey, 65.52% of patients with IBDs and CoD referred an oral involvement during the active phase of their intestinal disease, and canker sores were the most frequent oral manifestation, followed by a burning sensation: with the limit of the small sample size, patients showed a high level of perception of oral inflammatory symptoms.

Dental professionals have to be aware of the possible oral implications in these clusters of subjects.

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