

Original Article

Oral manifestations in inflammatory bowel disease: A cross-sectional study in Isfahan

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ABSTRACT

Background: Various systemic diseases can cause oral manifestations, such as inflammatory bowel disease (IBD). This study is designed to investigate the frequency of oral manifestations in patients with IBD referred to health centers and offices in Isfahan in 2018.

Materials and Methods: This cross-sectional study was done among 161 patients suffering from IBD in Isfahan, Iran. They were chosen by the systematic randomized sampling. Finally, the data were analyzed using the logistic regression test in the SPSS software. Significance was assigned at $P < 0.05$.

Results: The number of patients with ulcerative colitis and Crohn's syndrome was, respectively, 119 persons (73.9%) and 42 persons (26.1%). Oral manifestations were seen among 52 (32.3%) of the samples. The frequency of oral manifestations was 35.6% (31 cases) in males and 28.4% (21 cases) in females. Oral manifestations were seen in 29.4% of patients with ulcerative colitis and 40.5% of patients with Crohn's disease. Based on the logistic regression, there was a statistically significant relationship between the use of azathioprine and mesalazine with oral manifestations ($P < 0.05$), whereas the severity of disease and smoking were not statistically significantly related to oral manifestations ($P > 0.05$).

Conclusion: The severity of the disease was not significantly correlated with oral manifestations, which are in agreement with the results of previous studies. It was also found that among patients with IBD, the oral aphthous ulcers can appear 1–3 years before the diagnosis of the disease. Besides that, some of the drugs used to treat the disease have a significant relationship with oral manifestations.

Key Words: Colitis, Crohn disease, inflammatory bowel disease, oral manifestations, ulcerative

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic disease related to intestinal immunity, which is divided into ulcerative colitis and Crohn's disease.^[1] In Iran, 11,000 cases for IBD have been reported up to now.^[2]

Several oral manifestations are associated with IBD, but the involvement of the oral cavity does not necessarily coincide with gastrointestinal disease. Oral manifestations of Crohn's disease may appear several months to several years before the bowel

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symptoms.^[3-6] The frequency of oral ulcers in patients with Crohn's disease is higher than patients suffering from ulcerative colitis.^[5] Aphthous ulcers occur in 20% of patients with ulcerative colitis. Oral manifestations occur among 5%–60% of patients with Crohn's disease, particularly in pediatric cases and men.^[3-5,7-9] The frequency of oral ulcers in ulcerative colitis varies widely, from 2% to 34%.^[4,10] Pyostomatitis vegetans is the most pathognomonic oral sign for patients with ulcerative colitis.^[3,6,10] Previous studies clarified a significant statistical relationship between oral signs (tongue coating and oral ulceration) and oral symptoms such as halitosis, dry mouth (xerostomia), acidic taste, and taste changes in patients suffering from severe ulcerative colitis compared to the control group.^[11] There is no significant relationship between the disease activity and the frequency of oral ulcers neither in Crohn's disease nor in ulcerative colitis.^[4,7] Some authors have cited that many of the oral manifestations are relatively nonspecific and may be associated with other conditions such as the medications used for the treatment. For example, there are many reports about the association between lichen planus and autoimmune diseases such as ulcerative colitis.^[12-14] Oral cancer and precancerous oral conditions have been reported in patients with IBD. Patients with IBD have increased the risk for these ulcers, so annual oral examination is recommended in these patients.^[15]

There is a significant dose-dependent association between active smoking and extra-intestinal manifestations (chronic skin disorders and joint manifestations) in both Crohn's disease and ulcerative colitis.^[16] Patients with IBD taking thiopurine drugs should be examined periodically due to the increased risk of oral cancer such as squamous cell carcinoma.^[17] Oral ulcers such as oral lichen planus could exist in IBD patients treated with anti-tumor necrosis factor α drugs.^[16,18] Sulfasalazine or 5-amino acids which are used by patients with IBD can induce lupus-like syndrome.^[19] The most common extraintestinal manifestation in patients with IBD is arthritis.^[9] Joints are involved in approximately 30% of patients suffering from Crohn's disease so that the temporomandibular joint could be affected too.^[20] A previous study indicated that gingivitis, periodontitis, and Decayed, Missing and Filled Teeth index was higher among patients with ulcerative colitis and Crohn's disease than the control group.^[21] Gingivitis was significantly higher among patients with Crohn's disease than ulcerative colitis.^[16]

Oral manifestations can be helpful in the early diagnosis of IBD, and dentists are the first members in the health-care systems who can diagnose them. As there were no comprehensive previous studies about the oral manifestations of IBD in Iran, this study is designed to assess and declare the frequency of different oral manifestations related to IBD among the patients in the Isfahan, Iran.

MATERIALS AND METHODS

This cross-sectional study was done among 161 patients suffering from IBD in Isfahan, Iran. The study was permitted by the Ethics Committee of the Isfahan University of Medical Science, and the ethical code is 1397.282. Patients suffering from IBD whose their profiles were recorded on the website of the "National Inflammatory Bowel Disease Research Center of Iran" and "Gastrointestinal health Center in Isfahan University of Medical Sciences" until 2018 were recruited by systematic randomized sampling at this cross-sectional study with a 95% confidence interval and 0.20 standard deviation ($n = 161$). The written consent has taken from all of them. Patients who had other systemic diseases that caused the same oral manifestations (diabetes, hepatitis, end-stage renal disease, tuberculosis, bronchitis, recurrent aphthous stomatitis that happen due to something like hormones changes during puberty ages (not 1–3 years before the diagnosis of IBD), hematologic diseases, Behcet's disease, scleroderma, rheumatoid arthritis, high blood pressure, Vitamin B12 deficiency, and iron deficiency) were excluded from this study. Besides that, patients using drugs that produced similar oral manifestations except drugs prescribed for the treatment of IBD were not recruited in this study. Eighty-seven patients were excluded from the study.

Data were collected by studying patient's documents, interviews, oral examinations, and completing related information forms. Oral examinations were done by an oral medicine specialist in a dental clinic in Isfahan, and oral manifestations such as cobblestone, mucogingivitis, indurated tag-like lesions, deep linear ulcerations, granulomatous inflammation, aphthous stomatitis, pyostomatitis vegetans, angular cheilitis, persistent submandibular lymphadenopathy, recurrent buccal abscesses, perioral erythema with scaling, and lip swelling were recorded in the information form. Since the disease has different severity, the frequency

of oral manifestations may include divers in different degrees of illness, the severity of ulcerative colitis and Crohn’s disease assessed by the simple clinical colitis activity index (SCCAI) index and Crohn’s disease activity (CDAI) index.^[22]

The frequency and distribution of various oral manifestations were evaluated using the IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA) software. Furthermore, the relationship between the severity of illness, smoking, type of drug used, and frequency distribution of oral manifestations were statistically analyzed by using logistic regression.

RESULTS

Descriptive results

A total of 161 patients with IBD in the age range of 19–77 years (mean age of 42 ± 11.71) participated in this study, 87 (54%) were males, and 74 (46%) were females. The number of patients with ulcerative colitis was 119 (73.9%), and 42 patients (26.1%) had Crohn’s disease. Oral manifestations were seen among 52 (32.3%) patients. The frequency of oral manifestations was 35.6% (31 cases) in males and 28.4% (21 cases) in females. The frequency of oral manifestations among patients suffering ulcerative colitis and Crohn’s was, respectively, 29.4% (35 cases) and 40.5% (17 cases). The frequency of oral manifestations was 22.2% in smokers and 32.9% in nonsmokers ($P > 0.05$).

Results based on studying clinical signs

In the examination of the lips, tongue, the floor of the mouth, and perioral tissues, all patients were normal.

In the examination of the oral mucosa, buccal mucosa, and mucogingival, one patient (0.6%) had aphthous ulcers. The patients were asked about the first time of having recurrent aphthae and other ulcers that could occur periodically, and it was mentioned in the symptoms survey section.

Twenty-eight participants (17.4%) had joint problems (such as clicks, crepitus, and trismus) in the temporomandibular joint examination. Twenty-four participants (14.9%) had clicking, and four participants (2.5%) had deviations. None of them had pain or trismus alone.

Salivary glands (parotid-submandibular-sublingual) and lymph nodes (jaw and facial regions) were normal in all participants.

Frequency distribution of oral manifestations based on the type of drug used and the pharmaceutical group is presented in Tables 1 and 2.

Results based on patient complaints

The frequency of dry mouth (xerostomia), taste changes, and acidic taste sensation in patients was, respectively, 31.1% (50 people), 6.2% (10 people), and 6.2% (10 subjects).

The frequency of other taste problems was 4.3% (7 patients). Two cases (1.2%) reported bitterness sensation, and five participants (3.1%) reported changes in the taste sensation after taking the drug.

Seventeen patients (10.6%) had subjective halitosis.

The frequency of oral manifestations (such as aphthae, ulcer, or irritation) before the diagnosis of the disease

Table 1: Frequency distribution of oral ulcers based on the type of drug used

Type of drug used	Number of persons, frequency (%)	
	Have ulcers	Do not have ulcers
Just using mesalazine	19 (36.6)	65 (59.6)
Mesalazine - azathioprine	15 (29)	8 (7.3)
Azathioprine - corton	2 (3.8)	1 (0.9)
Mesalazine – corton	2 (3.8)	8 (7.4)
Just using azathioprine	2 (3.8)	1 (0.9)
Mesalazine - mercaptopurine	1 (1.9)	2 (1.8)
Mesalazine – azathioprine - corton	1 (1.9)	8 (7.4)
Just using sulfasalazine	1 (1.9)	0 (0)
Just using mercaptopurine	0 (0)	0 (0)
Mesalazine – sulfasalazine - azathioprine	0 (0)	2 (1.8)
Using no drug	9 (17.3)	14 (12.9)
Total	52 (100)	109 (100)

Dosage of drugs used in patients: 1 mg/kg for corton, 3 g for mesalazine, 50 mg for azathioprine

Table 2: Frequency distribution of oral ulcers based on the pharmaceutical group

Pharmaceutical Group	Frequency (%)		
	Have ulcers	Do not have ulcers	Total
One of his medications is mesalazine	38 (29)	93 (71)	131 (100)
One of his medications is azathioprine	20 (45.5)	24 (54.4)	44 (100)
One of his medications is sulfasalazine	1 (33)	2 (67)	3 (100)
One of his medications is mercaptopurine	1 (33)	2 (67)	3 (100)
One of his medications is corticosteroid	5 (22.7)	17 (77.3)	22 (100)

was 24.2% (39 patients). The duration of the ulcers was short term in three participants (7.9%), recurrent in 24 participants (63.2%), and continuous in 11 patients (28.9%). Oral ulcers of 21 patients (53.8%) were reduced after diagnosis and treatment, and they were not recovered among 18 patients (46.2%). Among 28 patients (71.8%), ulcers were presented during <1 year before the diagnosis. Among eight patients (20.5%), ulcers were presented over the past 2 years before the diagnosis. Oral manifestations precede gastrointestinal involvement in three patients (7.7%) for 3 years or more. The ulcers were still present among 28 patients (71.8%) who had oral manifestations before the diagnosis [Figures 1 and 2]. In addition, the frequency of oral manifestations before the diagnosis was 24.4% (29 cases) among patients suffering from ulcerative colitis and 23.8% (10 cases) among patients suffering from Crohn's disease.

Furthermore, the prevalence of oral manifestations before the diagnosis in patients with ulcerative colitis (24.4%) was not significantly different from

those with Crohn's disease (23.8%). The SCCAI and the CDAI are the questionnaires used to assess the severity of symptoms in people suffering from ulcerative colitis and Crohn's disease.^[22] According to the SCCAI, the severity of the disease among patients with ulcerative colitis was mild among 69 patients (58%) and moderated among 50 patients (42%). The severity of Crohn's disease was mild in all patients based on the CDAI index. Frequency distributions of oral manifestations based on the severity of the disease are presented in Table 3.

Logistic regression was used to evaluate the effect of different factors on oral manifestations. There was a significant relationship between the use of Azathioprine and Mesalazine with oral manifestations ($P < 0.05$). The severity of illness and smoking were not statistically significantly related to oral manifestations ($P > 0.05$).

DISCUSSION

In this study, the overall frequency of oral manifestations was 32.3%. The frequency of oral manifestations was 29.4% among patients with ulcerative colitis and 40.5% among patients with Crohn's disease.^[5] The higher frequency of oral manifestations in Crohn's disease compared with ulcerative colitis was in agreement with previous studies.^[4,10] The frequency of oral manifestations in ulcerative colitis achieved 29.4% in this study, which is matched with a range of 2%–34% mentioned in previous studies. The frequency of oral manifestations in Crohn's disease in this study confirms the various frequencies of 5%–60% in previous studies. In the current study, the frequency of Aphthous ulcers in patients with ulcerative colitis was 15.1%, which is in agreement with the frequency reported in the previous studies. The frequency of aphthous ulcers in Crohn's disease was 23.8% in the current study, whereas the frequency of aphthous ulcers was reported from 4% to 24% among healthy people in Iran.^[11,23,24] The



Figure 1: Oral aphthous ulcers on the lip.



Figure 2: Oral aphthous ulcers on the oral mucosa.

Table 3: Frequency distribution of oral manifestations based on the severity of the disease

Severity of the disease	Number of persons, frequency (%)		
	Have ulcers	Do not have ulcers	Total
Mild ulcerative colitis	23 (33.3)	46 (66.7)	69 (100)
Moderate ulcerative colitis	12 (24)	38 (76)	50 (100)
Mild Crohn's disease	17 (40.5)	25 (59.5)	42 (100)

frequency of oral manifestations among patients with IBD was higher among men than women (35.6% vs. 28.4%), but the difference was not significant, which is in agreement with the previous studies.^[3-5,7-9,15,25]

Lips are the most frequent sites for oral ulcers, especially aphthous ulcers, in Crohn's disease [Figure 1]. Oral manifestations of Crohn's disease can be specific or nonspecific. Nonspecific ulcers are more prevalent than specific ones.^[5,7,8,26] In this study, specific ulcers were not seen, which confirms the lower frequency of these ulcers in the previous studies. Previous studies indicated that nonspecific ulcers could exist years before the diagnosis of the intestinal disease.^[5,7,8,26] The patients were asked if they had seen frequent ulcers in their mouth 1–3 years before the diagnosis of IBD. This clarified that the oral aphthous ulcers appeared for the first time in 1–3 years before the diagnosis of the disease among 24.2% of participants. The highest frequency of the presence of the aphthous ulcers among patients was 1 year before the diagnosis. The 2 years before the diagnosis was in the second place, and just a few of them reported presenting aphthous ulcers 3 years and more before the appearance of intestinal disease. Furthermore, the frequency of oral manifestations before the diagnosis in patients with ulcerative colitis (24.4%) was not significantly different from those with Crohn's disease (23.8%), which indicates that oral ulcers before the diagnosis can appear in both diseases with almost equal frequency. Oral manifestations in IBD, such as stomatitis, glossitis, oral aphthae, and angular cheilitis, can be caused by malnutrition due to the disease or drugs used to treat the disease. For example, IBD can lead to a deficiency of Vitamin B, albumin, iron, folate, niacin, and other essential elements. These deficiencies can cause aphthous ulcers and some other oral manifestations. Besides that, Sulfasalazine and Azathioprine can cause folate and niacin deficiency.^[5]

Of all patients with oral manifestations, 3.8% were smokers since the years before the diagnosis of IBD. The frequency of oral manifestations in smokers (22.2%) was less than nonsmokers (32.9%), which is in contrast with the previous studies stated that oral manifestations are more common among smokers.^[16] This could be because of presenting a small number of smoker patients in the study.

In a previous study, 30.8% of patients had clicked in the temporomandibular joint, but TMJ dysfunction

was observed only in 7.3% of patients.^[27] In this study, 17.4% of all patients had problems in the temporomandibular joint, which is more than healthy people. Click was seen among 14.9% of them, and 2.5% of them had deviations. None of them had pain or trismus. These findings were less frequent in comparison with the frequency reported in other studies.^[20] In a previous study in Iran, the frequency of joint problems and clicks was reported 6.2% and 4.4% among healthy people.^[28]

In this study, the frequency of dry mouth was 31.1% among patients (obtained by observation and asking patient history in the question), which was consistent with the results of previous studies.^[29] In a previous study, acid taste and taste changes were reported among 40% of patients with pancolitis, and it was about 20% among patients suffering ulcerative colitis.^[11] However, in this study, the frequency of taste changes was 6.2%, and the frequency of acidic taste was obtained 6.2% among patients with IBD. The frequency of taste changes and acidic taste sensation were, respectively, 8.4% and 5.9% among patients with ulcerative colitis, which are less than the frequency reported in the previous studies. The probable reason for this difference is that the findings are subjective. The frequency of other taste sensation problems was 4.3%. Bitterness sensation was reported by two patients (1.2%), and five patients (3.1%) reported taste changes after taking the drugs. The frequency of subjective halitosis was 10.6%. In a previous study in Iran, the frequency of halitosis, acid taste, and taste changes were 6%, 2%, and 0%, respectively among healthy people.^[11] One another study in Iran reported the frequency of 7.8% for having dry mouth among healthy individuals.^[30] Granulomatous inflammation of salivary glands was reported in some previous case reports while it was not observed in this study. It clarifies that salivary gland involvement is a rare manifestation in patients suffering from IBD.^[5,31]

While lymph node involvement was not observed in this study, submandibular and cervical lymph node involvement was reported in some previous case reports. It illustrates that salivary gland involvement is a rare manifestation in patients suffering from IBD.^[5,32]

Previous researches illustrated that oral manifestations are not necessarily related to the severity of bowel involvement, which is in agreement with the results

of this study ($P > 0.05$).^[4,7] The frequency of oral manifestations among patients with moderate ulcerative colitis (24%) was less than patients with mild ulcerative colitis (33.3%) [Table 3]. Although systematic random sampling was performed, no severe case was found among them because severe cases usually visit a gastroenterologist to reduce the severity of the disease.

Drugs prescribed to treat IBD can cause side effects in the mouth [Tables 1 and 2]. For instance, sulfasalazine can cause lichen planus, or immunosuppressive drugs such as azathioprine and corticosteroids can cause clinical signs and symptoms in the mouth.^[11]

Logistic regression was used to evaluate the effect of different factors on oral manifestations. There was a statistically significant relationship between the use of azathioprine and mesalazine with oral manifestations ($P < 0.05$), and this result was mentioned for the first time in this study.

CONCLUSION

Based on the findings of the present study, the severity of the disease was not significantly correlated with oral manifestations, which is in agreement with the results of previous studies. It was also found that oral Aphthae can appear for the first time in 1–3 years before the diagnosis of the disease among patients with IBD. Besides that, some of the drugs used to treat the disease (mesalazine and azathioprine) have a significant relationship with oral manifestations.

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Conflicts of interest

The authors of this manuscript declare that they have no conflicts of interest, real or perceived, financial or non-financial in this article.

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