

Oral manifestations in mild-to-moderate cases of COVID-19 viral infection in the adult population

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Abstract

Background. Coronavirus disease 2019 (COVID-19) is a serious worldwide threat presented by a broad range of symptoms, from mild flu to severe pneumonia. A rising number of atypical infections have been reported. Thus, scientists and clinicians are doing hard work to unravel scientific knowledge about this novel pandemic.

Objectives. The aim of the present work was to highlight the oral manifestations which could be observed in mild-to-moderate cases of COVID-19.

Material and methods. A questionnaire survey was performed on 665 Egyptian patients who were confirmed COVID-19-positive based on the polymerase chain reaction (PCR) test. After applying the exclusion criteria, cases with mild-to-moderate symptoms were included in the study. The questionnaire consisted of 4 sections. The 1st section included demographic data, smoking, alcohol consumption, and general health status. The 2nd section contained questions regarding the oral hygiene status of the patients, and additionally a question about the hygienic measures they took while being infected with COVID-19. The 3rd section included questions about the most commonly reported COVID-19 symptoms the patients suffered from. The 4th section included questions that referred to the oral manifestations the patients complained of while being infected with COVID-19.

Results. A total of 573 patients were included in this survey. It was reported that 71.7% of COVID-19 patients presented with some oral manifestations at a level of significance, with variable incidence – oral or dental pain (23%), pain in jaw bones or joint (12.0%), halitosis (10.5%), ulcerations (20.4%), and xerostomia (47.6%). Some patients (28.3%) showed 2 or 3 manifestations simultaneously.

Conclusions. It was proven that mild-to-moderate cases of COVID-19 infection are associated with oral symptoms, and thus the significance of dental examination of patients with communicable diseases should be emphasized.

Key words: xerostomia, oral hygiene, halitosis, coronavirus, COVID-19

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Introduction

Coronavirus disease 2019 (COVID-19) is a serious worldwide threat caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).¹ In COVID-19, initially lungs are infected, and patients can present with a broad range of symptoms, from mild flu to severe pneumonia and possibly fatal respiratory illness.²

In COVID-19 infection, the most commonly reported symptoms are a headache, a sore throat, diarrhea, the loss of taste and smell, and shortness of breath.³ Dermatological manifestations have also been observed, and few authors have reported oral signs and symptoms.⁴ It is not strange that COVID-19 can manifest itself through oral symptoms, since various pulmonary diseases and systemic disorders with pulmonary involvement are associated with oral manifestations.⁵

Meticulous checkups of the oral cavity in respiratory medicine can help in clinical diagnosis, and in providing advice and guidance to patients. In addition, dentists who detect atypical oral lesions should seek appropriate guidance and professional medical advice.⁵

Objectives

The main objective of this study was to highlight the oral manifestations which could be reported in mild-to-moderate cases of COVID-19. Moreover, our goal was to spread awareness among physicians, general and dental practitioners, about these oral symptoms so that early diagnosis could be achieved, thus maintaining patient's ultimate health and welfare.

Subjects and methods

Study design

An online questionnaire was designed for this investigation, because nearly all available questionnaires did not address the various possible oral manifestations of COVID-19 infection. A total of 665 Egyptian patients who recovered from COVID-19 were recruited from several Ministry of Health and university hospitals, including recovered dentists, nurses and physicians, who voluntarily participated in answering the questionnaire. A sharable link on Google Drive was sent to each patient via a WhatsApp message. A digital consent to participate in this study was obtained before completing the questionnaire. A web-based survey tool (Google Forms) was used to design the questionnaire.

Ethical statement

The current study protocol was approved by the ethics committee of the Faculty of Dentistry at Cairo University in Egypt (approval No. 21/6/20).

Exclusion criteria

The following exclusion criteria were adopted: failure to complete the whole questionnaire; patients with poor oral hygiene or suffering from any of the oral symptoms investigated before the pandemic; patients with chronic illnesses; smokers; alcoholics; patients with serious COVID-19 infection, who experienced severe respiratory failure (severe pneumonia, severe dyspnea, an increased respiratory rate of >30 breaths/min, and a decreased oxygen saturation of <93%) or patients who required hospitalization.

Inclusion criteria

The inclusion criteria were as follows: Egyptians; adults, 18–50 years old; laboratory-confirmed COVID-19 infection (the polymerase chain reaction (PCR) test); non-smokers; non-alcoholics; medically free patients; patients with mild-to-moderate symptoms; patients with good oral hygiene and not suffering from any oral manifestations before the pandemic.

Questionnaire tool

The questionnaire consisted of 4 sections and a total of 38 questions (Table 1). The 1st section included demographic data as well as smoking, alcohol consumption and general health status. The 2nd section contained questions regarding the oral hygiene status of the patients; it was designed in accordance with Kamel et al's questionnaire,⁶ in addition to the WHO oral health surveys.⁷ Furthermore, a question about the participants' hygienic measures taken while being infected with COVID-19 was added to the same section. The 3rd section included questions about the most commonly reported COVID-19 symptoms the patients suffered from. The 4th section included questions referring to the oral manifestations the patients complained of while being infected with COVID-19.

Assessment of the oral hygiene status

The oral hygiene of the patients was measured based on their answers from the 2nd section of the questionnaire, where the best answer for each question was given score '1', while '0' was given to other choices. The full score was 12; the participant's oral hygiene was considered good when at least 75% of this score was obtained.^{6,7}

Table 1. Questionnaire for investigating the oral manifestations of coronavirus disease 19 (COVID-19)

Questions	Answers	
Do you agree to participate in this study?	yes	no
1 st section: Demographic data		
Gender	male	female
Age		
Nationality	Egyptian	other
Level of education		
Chronic illnesses	yes	no
Smoking	yes	no
Alcohol consumption	yes	no
2 nd section: Oral hygiene status and the estimation of the rate of applying hygiene measures		
1. How many times during the day do you brush your teeth?	twice a day or more frequently	once a day or less frequently
2. How do you clean your teeth?	a toothbrush, fluoride toothpaste and dental floss	a toothbrush only
3. How often do you change your toothbrush?	once in 3 months	once in 6 months or less frequently
4. Do you use mouthwashes containing fluoride?	often	rarely or never
5. Do you complain of bleeding on brushing or gingival bleeding?	rarely or never	at every brushing or almost at every brushing
6. Do you suffer from tooth sensitivity?	rarely or never	often
7. How often do you visit a dental clinic for a checkup?	once a year or more frequently	once every few years or in case of pain
8. Do you have calculus regularly removed?	once every few years, once a year or more frequently	rarely or never
9. Are there any cavities in your teeth?	no cavities at all / don't know / / 1–2 cavities	3 cavities or more
10. Do you have teeth that are mobile?	no / I don't know	yes
11. Did you suffer from any of the following before the epidemic? bad smell / ulcerations / dry mouth / oral or dental pain / pain in jaw bones or joint	yes	no
12. What were your oral hygiene measures while being infected with COVID-19?	increased	the same / decreased
3 rd section: COVID-19 symptoms		
1. Was your PCR test result for COVID-19 positive?	yes	no
2. Did you complain of fever?	yes	no
3. Did you complain of cough?	yes	no
4. Did you complain of a sore throat?	yes	no
5. Did you complain of malaise?	yes	no
6. Did you complain of a headache?	yes	no
7. Did you complain of diarrhea?	yes	no
8. Did you complain of the loss of smell sensation?	yes	no
9. Did you complain of the loss of taste sensation?	yes	no
10. Did you complain of muscle pain?	yes	no
11. Did you experience dyspnea or shortness of breath?	yes	no
12. Did you need hospitalization?	yes	no
4 th section: Oral manifestations		
1. Did you complain of any oral manifestations while being infected with COVID-19?	yes	no
2. If yes, which of the following did you complain of?		
Halitosis (bad smell)	yes	no
Xerostomia (dry mouth)	yes	no
Ulcerations	yes	no
Oral or dental pain	yes	no
Pain in jaw bones or joint	yes	no

PCR – polymerase chain reaction.

Statistical analysis

Data was coded and entered using the statistical package IBM SPSS Statistics for Windows, v. 22.0 (IBM Corp., Armonk, USA). Categorical variables were summarized as frequency and percentage. Quantitative variables were summarized as mean (*M*) and standard deviation (*SD*). Comparisons between the groups, regarding the incidence of the studied parameters, were made using the χ^2 test. A *p*-value <0.05 was considered statistically significant.

Results

Survey respondents

A total of 665 patients agreed to take part in the questionnaire. Ninety-two patients were excluded from the analysis: 9 were under 18 years old; 11 did not have a confirmed positive PCR test result; 3 had Sjögren's syndrome; 13 were hospitalized; 6 did not complete the questionnaire; 7 were smokers; 21 had chronic illnesses; 9 were not Egyptians; and 13 had poor oral hygiene. Therefore, the final analysis was performed on 573 patients. Overall, the respondents submitted the questionnaires from May 1, 2020 to July 1, 2020.

Demographic data

The mean age of patients was 36.19 ± 9.11 years (range: 19–50 years). There were 408 females and 165 males. Regarding the educational level, patients were categorized into 3 levels: elementary education (*n* = 75); bachelor's degree (*n* = 444); and postgraduate education (*n* = 54).

Analysis of COVID-19 symptoms

In this study, we mainly included patients with mild-to-moderate symptoms, without severe respiratory failure, who were not hospitalized. As reported in Fig. 1, the percentage of the respondents who suffered from fever was 66.0%, cough – 55.5%, a sore throat – 52.4%, malaise – 72.8%, a headache – 70%, diarrhea – 50.3%, the loss of smell – 61.8%, the loss of taste – 55.5%, muscle pain – 76.4%, and dyspnea – 51.8%.

Analysis of the oral manifestations of COVID-19 in the respondents

It was found that 71.7% of the patients presented with some oral manifestations, with variable incidence, at *p* < 0.001. Regarding oral or dental pain, it was expressed as 23.0%, pain in jaw bones or joint – 12.0%, halitosis – 10.5%, ulcerations – 20.4%, and xerostomia – 47.6%. Some respondents (28.3%) showed 2 or 3 manifestations simultaneously.

There were statistically significant differences (*p* < 0.001) between the respondents' answers regarding each symptom except for xerostomia, where *p* = 0.5 (Table 2).

The assessment of the incidence of oral manifestations in relation to the 4 investigated parameters (gender, age, the educational level, and the rate of the oral hygiene measures taken by the patient while being infected with COVID-19) was performed as follows:

- the assessment of the incidence of oral manifestations in relation to the patient's gender – the statistical analysis identified a significantly increased number of ulcerations in male patients as compared to females (*p* = 0.02); however, pain in jaw bones or joint was significantly increased in female patients as compared to males (*p* = 0.006) (Fig. 2);

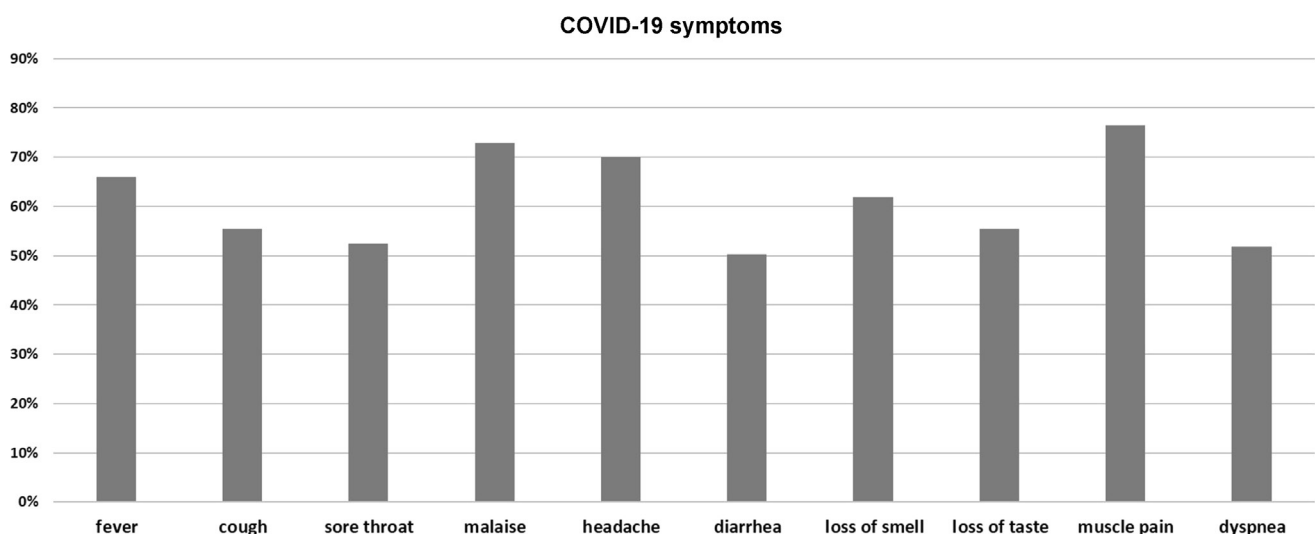
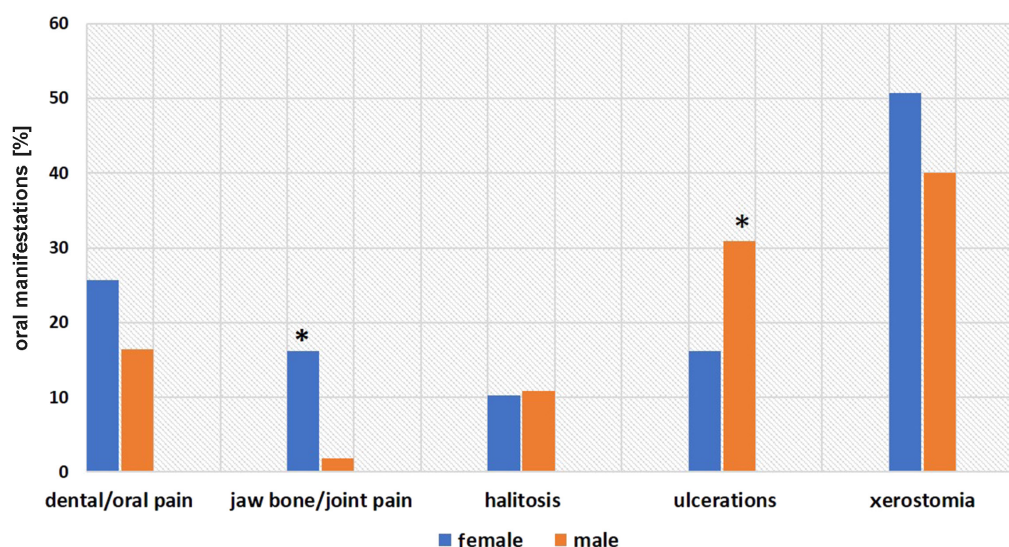


Fig. 1. Analysis of COVID-19 symptoms in mild-to-moderate cases

Table 2. Data regarding the respondents' oral manifestations while being infected with COVID-19

Oral manifestations	Answer	Number <i>n</i>	Percentage [%]	χ^2	<i>p</i> -value
Occurrence of oral manifestations	yes	411	71.7	6.00	<0.001*
	no	162	28.3		
Pain in jaw bones or joint	yes	69	12.0	110.00	<0.001*
	no	504	88.0		
Halitosis	yes	60	10.5	119.37	<0.001*
	no	513	89.5		
Ulcerations	yes	117	20.4	66.85	<0.001*
	no	456	79.6		
Xerostomia	yes	273	47.6	0.40	0.500
	no	300	52.4		
Oral or dental pain	yes	132	23.0	55.50	<0.001*
	no	441	77.0		
Combined manifestations	yes	162	28.3	36.00	<0.001*
	no	411	71.7		

* statistically significant differences between the answers ($p < 0.001$).

**Fig. 2.** Incidence of oral manifestations in relation to gender

* statistically significant differences between males and females ($p < 0.05$).

- the assessment of the incidence of oral manifestations in relation to the mean age of the respondents – the statistical analysis showed a non-significant difference in the mean age between the patients who complained of oral manifestations and those who did not ($p > 0.05$) (Fig. 3);
- the assessment of the incidence of oral manifestations in relation to the educational level of the respondents – the statistical analysis showed non-significant differences in the incidence of the oral symptoms associated with COVID-19 infection between the participants with a higher educational level and those with a lower level of education ($p > 0.05$) (Fig. 4);

Regarding the frequency of the oral hygiene measures taken while being infected with COVID-19, the patients were grouped according to their answers

into 3 categories: 1 – those whose oral hygiene measures decreased while being infected (17.8%); 2 – those whose oral hygiene measures did not change (63.4%); and 3 – those whose oral hygiene measures increased while being infected (18.8%).

- the assessment of the incidence of oral manifestations in relation to the patient's oral hygiene measures taken while being infected with COVID-19 – there was a statistically significant difference between the 3 groups of patients in the incidence of oral/dental pain ($p < 0.05$) and ulcerations ($p < 0.001$), with the highest percentage of oral pain and ulcerations observed in the patients with decreased hygiene measures, and the lowest percentage of oral pain and ulcerations in the patients with increased hygiene measures (Fig. 5).

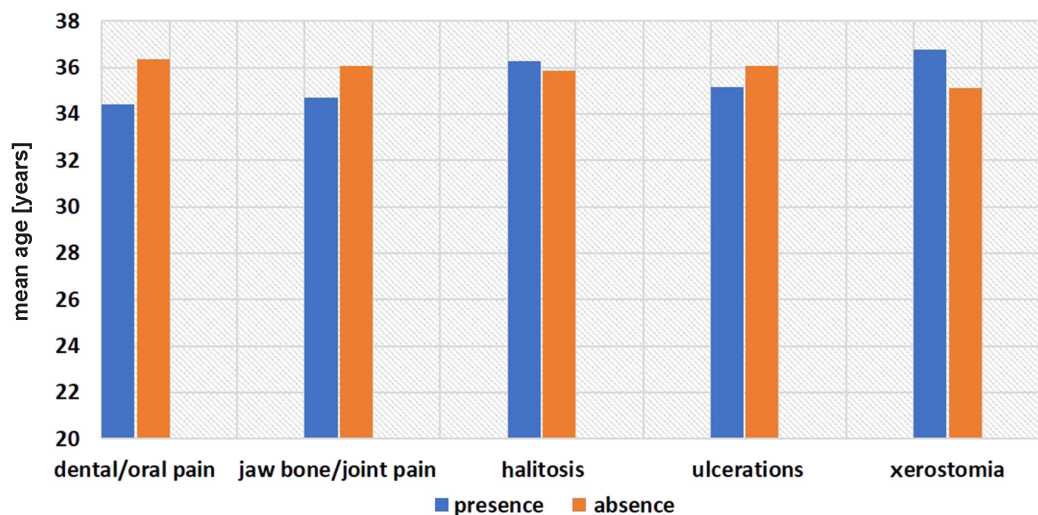


Fig. 3. Incidence of oral manifestations in relation to the mean age of the patients

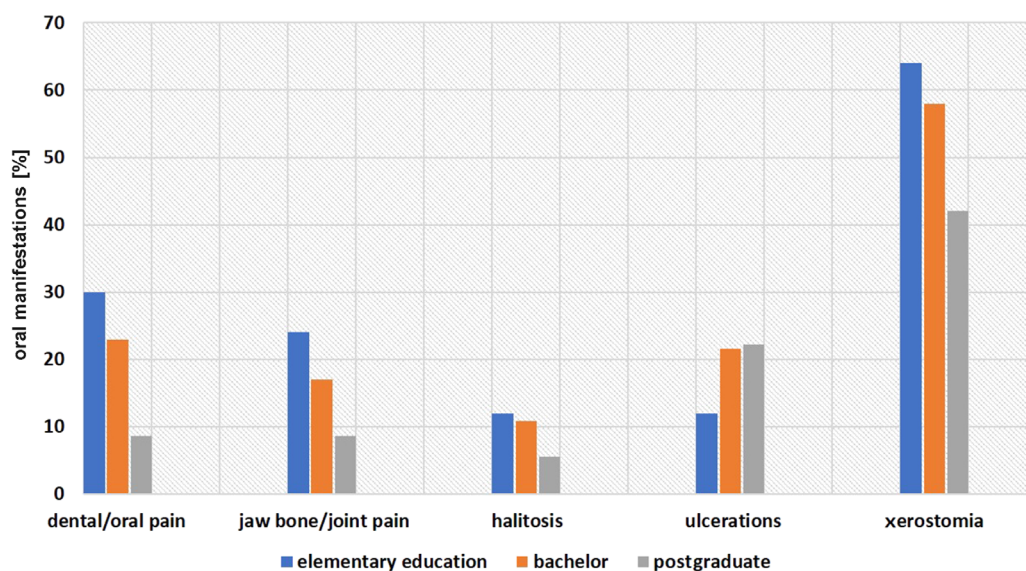


Fig. 4. Incidence of oral manifestations in relation to the educational level of the patients

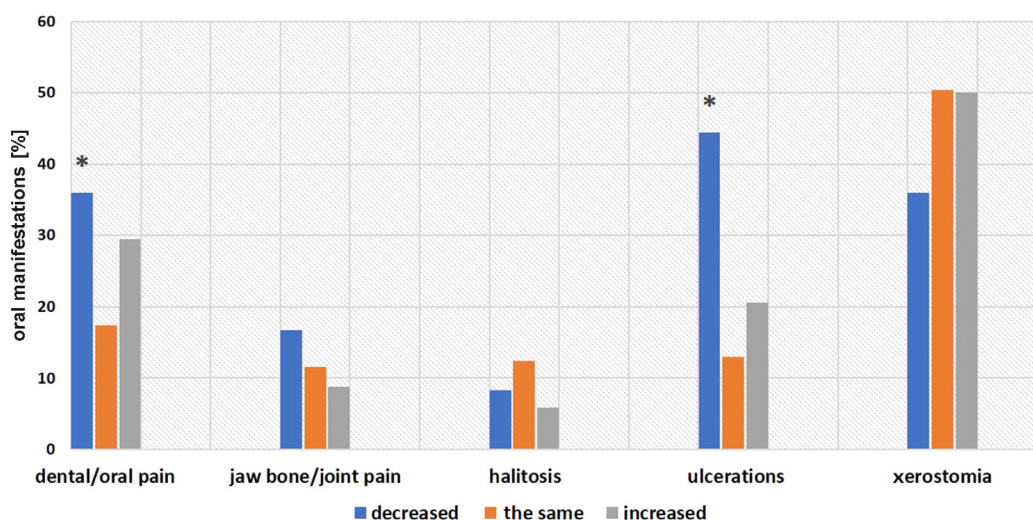


Fig. 5. Incidence of oral manifestations in relation to the rate of the hygienic measures taken by the patients while being infected with COVID-19

* statistically significant differences between groups ($p < 0.05$ for dental/oral pain and $p < 0.001$ for ulcerations).

Discussion

Clinical evidence shows that the oral mucosa is a primary site of entry for SARS-CoV-2, and is considered possibly at high risk of susceptibility to the 2019 novel coronavirus (2019-nCoV) infection. However, there is still uncertainty whether the above-mentioned oral manifestations result from direct viral infection or from systemic health deterioration and impaired immune system.⁸ The aim of the present work was to investigate the oral manifestations which could be associated with mild-to-moderate cases of COVID-19 infection.

In the present work, patients experienced the general signs and symptoms of COVID-19 infection, which are fever, cough, a sore throat, malaise, a headache, diarrhea, the loss of smell, the loss of taste, muscle pain, and dyspnea. This is in accordance with several clinical studies, which reported these symptoms as the most prevalent ones in mild and moderate cases of COVID-19 infection.⁹ In addition, hospitalized patients were excluded to avoid the variable of different drug usage. Moreover, a relatively narrow age range of participants was chosen, excluding subjects aged >50 years, who are considered by WHO more prone to experience severe COVID-19 symptoms.^{1,3}

In the current study, 47.6% of COVID-19 patients manifested xerostomia. This is in accordance with many cases, in which respiratory tract infections were reported as the main cause of xerostomia.¹⁰ In addition, a study involving 108 patients with confirmed COVID-19 in Wuhan reported that 46% of them complained of xerostomia.¹¹ In another study, 32% of patients reported dry mouth as one of their symptoms; xerostomia appeared before the onset of other general COVID-19 symptoms.¹²

It has been stated that the target of SARS-CoV-2 are angiotensin-converting enzyme 2 (ACE2)-positive cells. Angiotensin-converting enzyme 2 is detected in the duct epithelium of the salivary glands. Therefore, the salivary glands are a possible target for COVID-19 infection.¹³ It is speculated that SARS-CoV-2 can enter the epithelial cells of the salivary gland duct, multiply in them and be discharged into saliva. A study by To et al. demonstrated that SARS-CoV-2 nucleic acid was found in the saliva samples of 91.7% of patients.¹⁴ It is hypothesized that SARS-CoV-2 infection results in pathological inflammatory lesions in the salivary glands, causing their lysis at the early stages of infection; then, the salivary glands may be later destroyed by the immunopathological reactions. These findings suggest that all other oral manifestations in COVID-19 patients may develop due to a decreased salivary flow. It has also been reported that with the infection progression, amylase may enter peripheral blood after acinar cell damage.¹³

Moreover, xerostomia reported in COVID-19 patients may be triggered by stress, as dry mouth is usually found in psychiatric patients. It is commonly correlated with nutritional deficiencies, anxiety, tension, and distress, which

are often observed in the case of COVID-19 patients, who are stressed because of their fear of the disease, in addition to the stressful conditions of isolation.^{15,16}

In this survey, 23% of COVID-19 patients experienced oral or dental pain. This pain could be referred from muscles, as it was reported in the current study that 76.4% of COVID-19 patients experienced myalgia. It has been proven that in case of muscle pain, neurons become sensitive and the stimulus is transmitted to central nerves via neurotransmission. Subsequently, pain which originates in muscles can be felt in the upper and lower jaws.¹⁷ Moreover, also headaches can be referred to the teeth; it was reported in the present study that 70% of COVID-19 patients suffered from headaches. In headaches, neuropeptides are released from trigeminal nerve endings and dilate blood vessels; then, the subsequent inflammation is proven to cause pain.¹⁷ In addition, it has been reported that orofacial or dental pain sensation can be enhanced by psychological distress or emotional disturbances, which is the case in nearly all COVID-19 patients.^{15,16}

Furthermore, 20.4% of COVID-19 patients reported the appearance of ulcers in their oral cavities. This is in accordance with several cases, in which blisters and oral ulcers occurred during COVID-19 infection.⁸ It has been demonstrated that psychological upsets, such as anxiety and stress, contribute to the development and progression of oral lesions like recurrent aphthous ulcers, and this applies to COVID-19 patients.¹⁶ It has also been proven that psychological distress stimulates the immunoregulatory mechanism by elevating the leukocyte count at inflammatory sites.¹⁸ In addition, ACE2 is detected in the oral cavity and appears in high amounts in epithelial cells. It is elevated in the tongue, gingival and buccal mucosa. These findings demonstrate that the oral mucosa may be a target for COVID-19 infection.¹⁹

In the current study, 12% of patients complained of pain in jaw bones or joint. This is in agreement with several studies, where musculoskeletal pathologies, such as skeletal muscle, bone and joint disorders, were reported in COVID-19 patients and those with SARS-CoV-2 infection.^{20,21} It has been reported that in addition to potential direct viral infection, the cytokines and pro-inflammatory signaling molecules induced by the infection can impact skeletal muscles by reducing protein synthesis and stimulating muscle fiber proteolysis. The virus SARS-CoV-2 has been proven to infect type-II pneumocytes, which line the respiratory epithelium, and express ACE2 and transmembrane protease serine 2 (TMPRSS2).²¹ Angiotensin-converting enzyme 2 and TMPRSS2 are also expressed in numerous human skeletal muscle cells, several types of synovial cells, and different types of chondrocytes on articular surfaces and in the meniscus.²²

Moreover, joint pain in COVID-19 patients is most probably caused by emotional distress rather than mechanical and occlusal aspects. Stressed people usually grind and clench their teeth. They eventually suffer from

muscle fatigue and spasm. Patients experiencing joint pain usually complain of psychological symptoms, such as irritation, fear, worry, uneasiness, tension, malnutrition, and insomnia, which are the symptoms commonly experienced by COVID-19 patients.^{15,16}

In the present study, 10.5% of COVID-19 patients complained of halitosis. It has been reported that oral halitosis caused by respiratory tract infections may reach up to 10%.²³ This could be due to the passage of sinus or nasal secretions into the oropharynx.²⁴ The pungent gases produced by different respiratory pathogens are retained in the exhaled breath, stimulate olfactory receptors, and are released through the mouth or the nose, causing malodor.²⁵ In addition, halitosis is also among the symptoms related to *Helicobacter pylori* infection, which is the major pathogenic cause of ulcerative alterations in the gastric mucosa. Moreover, gastroesophageal reflux disease is usually associated with halitosis.²⁶

Additionally, 28.3% of COVID-19 patients in the current study showed 2 or 3 of the above-mentioned oral manifestations concurrently. This could be due to the interaction of several mechanisms in the oral cavity, where ACE2 plays the major role due to its presence in various oral tissues.¹⁹

The assessment of the incidence of oral manifestations in relation to the 4 investigated parameters showed that regarding gender, ulcerations were significantly more common in males than females. This is in accordance with a previous study, which showed the preponderance of ulcers among males.²⁷ However, this is opposite to the findings of other investigation, which reported female prevalence.²⁸ In the present study, it was probably hard to say what type of ulceration was present in the infected patients, since clinical examination was not applicable in those patients. However, we assumed that these ulcerations might be aphthous ulcers, as it has been reported that psychological stress plays an important role in the progression of recurrent aphthous ulcers, which is the case in nearly all COVID-19 patients, who experienced a very stressful situation.¹⁶ On the contrary, pain in jaw bones or joint was more common in females than males. This may be due to variations in estrogen levels between both sexes, as estrogen plays an essential role in bone health. Moreover, temporomandibular joint osteoarthritis is more prevalent in females, and can cause tenderness and pain in the joint region.²⁹

Regarding the mean age of the patients and their educational level, the statistical analysis showed non-significant differences in the incidence of oral symptoms in relation to these 2 measured parameters. It supports the hypothesis that these oral symptoms could result from direct viral infection and are not triggered by other variables.⁸

As for the rate of the oral hygiene measures taken by the patients while being infected with COVID-19, it was reported that in the patients with decreased oral hygiene measures, ulcerations and dental/oral pain were significantly increased. This can be attributed to plaque

and calculus accumulation around the teeth in case of poor oral hygiene, which will subsequently lead to the inflammation and ulceration of the gingiva, and eventually cause periodontitis, orofacial pain and tooth loss. This finding is confirmed by a study which investigated the complications of COVID-19 in patients with poor oral health.^{6,30} The authors proved that there was a link between elevated bacterial loads in the oral cavity and post-viral complications, and showed how improving oral hygiene measures could decrease the risk of COVID-19 complications.^{6,30}

In the current study, there were some limitations. Firstly, we were unable to include a control group, as the questionnaire was specifically designed for COVID-19 patients. To include a healthy population, it is required to design another version of the questionnaire, with different questions to suit healthy unaffected individuals, which could lead to contrasting answers, and thus inaccurate results.

Secondly, unfortunately, the number of female participants was greater than male participants. However, in our study, we did measure several parameters other than gender. Moreover, we were concerned with the presence of oral symptoms rather than the gender effect, as there is no exact proof in the literature that gender affects the presence or absence of oral manifestations associated with viral infections.

Finally, the clinical examination of patients was not applicable in the current work, as most of the dental and university clinics were closed at the time of the present investigation, treating only emergency cases.

Conclusions

It was proven that mild-to-moderate cases of COVID-19 infection were associated with oral manifestations, with variable incidence. The most frequent oral manifestation for the included participants was xerostomia, while the least expressed symptom was halitosis.


It was found that there was a significant increase in the expression of ulcerations in male patients. However, jaw bone/joint pain was significantly increased in female patients. Moreover, a statistically significant difference in the incidence of oral manifestations in relation to the oral hygiene measures taken by the patients while being infected with COVID-19 was noticed, with the highest percentage of ulcerations and oral pain observed in patients with decreased hygiene measures. Regarding the mean age of the participants and their educational level, there were non-significant differences between the patients who complained of oral manifestations and those who did not. Based on the above, the significance of dental examination of patients with communicable diseases should be highlighted and the role of a dentist as a member of a multidisciplinary team in assisting serious cases, such as COVID-19 patients, should be emphasized.


Recommendation

Further clinical studies are recommended to figure out whether oral manifestations in COVID-19 patients are due to direct viral infection or the emotional distress and stressful conditions experienced by the patients.

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