Persistent of Hyposalivation in patients with previous COVID-19 infection after resolution of the disease

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Abstract

Hyposalivation and/or dry mouth have been regarded as an oral symptom of COVID-19 in addition to taste changes, difficulty in swallowing, and burning mouth sensation. As the oral cavity considered the main route of infection, several published reports had given special attention to it.

The aim of this observational study was to evaluate the salivary flow rate of patients with previous COVID-19 infection.

A group of 35 patients met the inclusion criteria. A questionnaire of 16 questions regarding the oral and systemic health conditions was administered to these patients

observational study of 28 female & 7 males. Hyposalivation was appeared in 63% of cases (22 respondents) from total 35 respondents [19 females & 3 males]. Other oral symptoms that included in the questionnaire (that appear during active COVID-19 infection): Taste changes appear in 68%, burning mouth 8.5%, difficulty in swallowing 20%. While smell changes appear in 65.7% with different duration & severity of the disease. The study group was divided into two groups according to response of salivary flow rate (normal salivary flow rate ≥ 1.5, abnormal salivary flow rate < 1.5). A statistical difference in salivary flow rate P=0.001, duration of disease p=0.05, severity of the disease p=0.05, duration of the disease p=0.001 between normal & abnormal groups.

hyposalivation appeared in COVID-19 patients; this may persist even though after resolution of the disease, so these patients need supportive treatment to overcome oral complication.

Key words: Hyposalivation, COVID-19, Persistent symptoms. Patients, Clinical study

Introduction:

Coronavirus disease 2019 (COVID-19) is considered an infectious disease caused by a novel coronavirus. It is identified as the causative pathogen for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is the seventh type of the coronavirus family that affects humans (Zhu et al., 2020; Su et al., 2016). The first case of COVID-19 was registered in Wuhan city, China, caused by SARS-CoV-2 (Zhang and Holmes, 2020).

The World Health Organization (WHO) announced COVID-19 as a global pandemic on March 11, 2020. The transmission of the virus occurs from human to human via droplet and direct contact with nasal, oral, and eye mucous membranes (Lu et al., 2020). Studies have indicated that COVID-19 might become airborne through aerosols generated during clinical procedures (Wax and Christian, 2020). The incubation period is between 1 to 14 days, with most cases ranging from 3 to 7 days (Zhou et al., 2020). However, other studies have suggested an incubation period of approximately 5.2 days (Rothan and Byrareddy, 2020). According to the WHO, the most valid diagnostic clinical features of COVID-19 include acute respiratory infections, fever, and cough (Sohrabi et al., 2020).

Initially, the oral symptoms of COVID-19 were considered transient and could eventually disappear without specific treatment. However, there is increasing evidence that saliva secretory disorders and taste disorders persist in patients who have recovered from COVID-19, as well as other disorders such as dyspnea, fatigue, cough, headache, neurocognitive impairment (or brain fog), and hair loss. COVID-19 survivors followed up after recovery from the disease have reported persistent taste disorders (Tsuchiya, 2022; Barbara et al., 2022).

Dry mouth is a disorder that reflects insufficient salivary secretion or absolute dysfunction of the salivary gland. In many cases, it may reveal alterations in the quality of saliva, while the quantity of saliva does not change (Tanasiewicz et al., 2016; Glick, 2015). Diseases such as Type 1 diabetes, hyperthyroidism, renal failure, vitamin deficiencies, and some acute or chronic viral infections such as mumps, HIV, and CMV may cause dry mouth; these are some of the other causes of dry mouth. Following the outbreak of the new coronavirus pandemic, some cases of dry mouth related to COVID-19 have been reported, attracting the attention of researchers (Tanasiewicz et al., 2016).

As the oral cavity is considered the main route of infection, several published reports have given special attention to it (Al-Magsoosi et al., 2023), including the implications for dental practice (Amorim Dos Santos et al., 2021) and the potential use of saliva in the diagnosis of COVID-19 (To *et al*., 2020, . Sabino-Silva *etal,* 2020).

Materials & Methods:

35 patients were enrolled in this observational study in a period between (1August -6 Oct.2021) at seven health institutions in Baghdad/ Al- Karkh Directorate. The ethical committee of Al-Karkh Health Directorate approved the study protocol.

According to the Inclusion & exclusion criteria, 35 patients were selected with previous COVID-19 infections whom worked at health institutions in Baghdad/ Al- Karkh Directorate (medical-staff & sub-staff). Patients have history of previous COVID-19 infections (for 2 months and more) confirmed by polymerase chain reaction (PCR)& diagnosed according to diagnostic protocols of WHO. Each participant was signature on written informed consent before starting.

A questionnaire of 16 questions regarding the oral and systemic health conditions was administrated to these patients. Some of the answers were codified as dichotomous variables, namely as yes/No responses, absent or present. Appendix (1) A descriptive statistic was performed.

Statistical analysis: The obtained data were subjected to one-way analysis of variance (ANOVA) test to compare various groups with each other. Results were expressed as mean + standard errors (SE) and values of $p>0.05$ were considered statically non-significant while $p<0.05$ and $<0.01, 0.001, 0.000$ were considered significantly different, highly significantly different respectively. The relative risk (RR), its standard error and 95% confidence interval were calculated. The statistical analysis was carried out by SPSS (v 20).

The unstimulated salivary flow rate was measured using spitting methods: saliva was allowed to accumulate in the floor of the mouth, and the subject would then spit it into graduated test tubes (Hoseini et al., 2017). Hyposalivation was confirmed by measuring the unstimulated salivary flow rate at 9-11 PM, with a salivary flow rate of less than 1.5 ml/5 min (less than 0.3 ml/min). Other oral and extraoral symptoms were included in our study according to the case sheet (see Appendix 1). The severity of the disease was measured using a visual analogue scale (Malicka et al., 2014).

Statistical Analysis

The analysis likely uses measures ANOVA to compare the means of the two groups for each variable. This is suggested by the presence of P values indicating statistical significance.

Results and Discussion

Our study included 35 patients systematically healthy with previous COVID-19 infection (more than 2 months), consisting of 28 female & seven male average age (32.828 y.)

The study group divided into two groups according to response of salivary flow rate (Normal salivary flow rate ≥ 1.5, Abnormal salivary flow rate < 1.5). (18)

Table (1) description of normal & abnormal study groups

Tested groups	Female N (%)	Male N (%)	Total
Abnormal S.F.R	19(54.4)	3(8.6)	**22(63%)**
Normal S.F.R	9(25.6)	4(11.4)	**13(37%)**

Out of 35 responders, 22 (63%) had reduced salivary flow rate ranging from 0.1 – 0.25 ml/min & 13(37%) had normal salivary rate (equal or more than 1.5) as seen in figure (1).

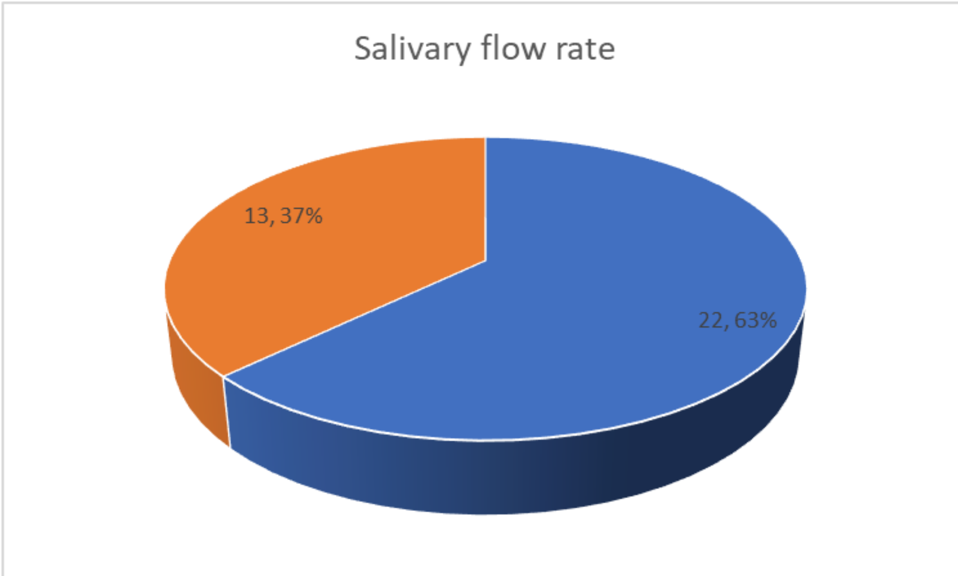

Figure (1): percentage of normal & abnormal salivary flow rate.

Severity of the disease was measured by visual analogue scale & represented as: mild less than 5, moderate equal to 5 & sever more than 5. The severity of the disease taken by patient own words.

Other oral & extra oral symptoms showed different frequency regarding normal & abnormal groups, as shown in table: (2) Among the symptoms, there is a significant difference in sleep disturbances between normal & abnormal groups. There is strong evidence that sleep disturbances are more likely to occur in individuals with abnormal salivary flow rate than those with Normal salivary flow rate. The relative risks and confidence intervals for other symptoms suggest varying degrees of association, but they do not reach statistical significance based on the provided P values.

Table (2): different frequency in normal & abnormal groups.

Symptoms N	Arrythmia	Headache	Sleep disturbances	Fatigue	Neurological manifestation	Smell changes	Taste changes	Burning mouth	Difficulty in swallowing
Abnormal 22	6	13	10	16	15	16	16	3	5
Normal 13	6	8	3	8	6	9	8	0	2
Relative risk	0.5	0.9	3.7	1.1	1.7	1	1.1	4.2	1.1
95% IC	0.24	0.2	5.9	0.7	0.7	0.6	0.7	0.2	0.27
P value	0.2	0.8	0.003	0.5	0.2	0.8	0.5	0.3	0.8

The result demonstrated that there is a significant difference in salivary flow rate also there were significant differences in duration of the disease, severity of the disease, and fever duration between normal & abnormal groups as shown in table (3)

Table 3: Mean Values for Normal &Abnormal group.

ABNORMAL S.F.R/ml Total No. 22	Age	S.F.R/ml	Duration of the disease/M	Severity of disease	Fever duration /d.
Mean	31.86	0.79	8.36	5.23	5.36
Std. Error of Mean	1.83	0.06	0.88	0.40	1.04
Median	26.50	0.73	9.50	5.00	3.00
Std. Deviation	8.57	0.28	4.14	1.88	4.88
Minimum	22.00	0.50	2.00	1.00	0.00
Maximum	50.00	1.50	18.00	8.00	14.00
Normal S.F.R/ml Total No.13	**Age**	**S.F.R/ml**	**Duration of the disease/M**	**Severity of disease**	**Fever duration /d.**
Mean	34.46	2.64	7.77	4.31	3.38
Std. Error of Mean	3.35	0.34	1.26	0.52	0.95
Median	32.00	2.35	6.00	4.00	3.00
Std. Deviation	12.09	1.24	4.53	1.89	3.43
Minimum	24.00	1.50	2.00	1.00	0.00
Maximum	59.00	6.00	15.00	7.00	12.00
P value	NS	0.001	0.05	0.05	0.001

The effects of COVID-19 infection appeared in multiple organs and sites, including the oral cavity (Amorim dos Santos et al., 2021). Oral manifestations caused by COVID-19 infection remain underestimated and unclear, despite many efforts and numerous studies aimed at investigating its general impacts (Fisher et al., 2021). Therefore, the rationale for the current observational study was to evaluate the persistence of hyposalivation in COVID-19 patients after the resolution of the disease. Several studies have correlated the presence of hyposalivation or xerostomia with SARS-CoV-2 infection (Sinjari et al., 2020).

In spite of this, numerous studies have focused on the oral cavity as the initial route of infection (Pedrosa et al., 2020). To date, the exact mechanism by which the SARS-CoV-2 virus affects the oral cavity is not fully understood. The current study revealed that there was a persistence of hyposalivation in patients with a previous COVID-19 infection, despite the resolution of the disease. These results indicated a potential relationship between sleep disturbances (during the acute stage of the disease) and the persistence of hyposalivation in an abnormal group. Infectious and inflammatory processes may also contribute to hyposalivation (Pedrosa et al., 2020).

Furthermore, there were differences in the duration of the disease, severity of the disease, and fever duration between the normal and abnormal groups; this may reinforce studies suggesting that medications and different types of pharmacological treatments are other reasons for xerostomia in COVID-19 patients. The most common medications in patients with COVID-19 include antiviral agents (such as remdesivir), hydroxychloroquine, anti-HIV medications (like ritonavir and lopinavir), and interferons (Dziedzic and Wojtyczka, 2020). Therefore, if there is an increase in the severity of the disease, this may correlate with increased medication consumption and pharmacological treatment, as well as an increase in disease duration.

Conclusion

One of the oral manifestations in COVID-19 patients is hyposalivation. In spite of diverse reasons have been noted for hyposalivation \ xerostomia in these cases, it seems that taking medicines & different types of pharmacological group considered other reasons suggested for xerostomia in COVID-19 patients.

In addition to that, there might be a relationship between sleep disturbances & persistence of hyposalivation in an abnormal group.

Furthermore, it is also established that dentists should have a role in the COVID-19 therapy team so as to improve the rehabilitation and the quality of life for the affected patients. So that dentists should have a major role in preventive measure to prevent oral complications results from hyposalivation.

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Conflicts of interest
The authors reported no potential conflict of interest.

References:

Al-Magsoosi M.J.N, Al-Asadi O.K.B, Al-Quraine N.T, Sami S.M, Haider J. (2023). Oral manifestations associated with COVID-19 infection: A cross-sectional study of recovered Iraqi patients. Int. J. Dent. 2023, 2023, 4288182. [CrossRef] [PubMed]

Amorim Dos Santos J, Normando A.G.C, Carvalho da Silva R.L, Acevedo A.C, De Luca Canto G, Sugaya N, Santos-Silva A.R, Guerra E.N.S. (2021). Oral manifestations in patients with COVID-19: A living systematic review. J. Dent. Res. 2021, 100, 141–154. [CrossRef]

Amorim dos Santos J, Normando A.G.C, Carvalho da Silva R.L, et al. (2021). Oral manifestations in patients with COVID-19: a living systematic review. Journal of Dental Research, vol. 100, no. 2, pp. 141–154.

Barbara J.M., Gatt J., Xuereb R.A., Tabone Adami N., Darmanin J., Erasmi R., Xuereb R.G., Barbara C., Stephen F., Jane Magri C. (2022). Clinical outcomes at medium-term follow-up of COVID-19. J. R. Coll. Physicians Edinb. 2022, 52, 220–227. [CrossRef] [PubMed]

Dziedzic A, Wojtyczka R. (2020). The impact of coronavirus infectious disease 19 (COVID-19) on oral health. Oral Dis. 27(S3), 703–706.

Fisher J, Monette D.L, Patel K.R, Kelley B.P, Kennedy M. (2021). COVID-19 associated parotitis. The American Journal of Emergency Medicine, vol. 39, pp. 254.e1–254.e3.

Glick M. (2015). Burket's Oral Medicine. PMPH, Buffalo, NY, USA.

Hoseini A, Mirzapour A, Bijani A, Shirzad A. (2017). Salivary flow rate and xerostomia in patients with type I and II diabetes mellitus. Electronic Physician. 2017 Sep;9(9):5244.

Lu C-W, Liu X-F, Jia Z-F. (2020). 2019-nCoV transmission through the ocular surface must not be ignored. Lancet. 2020;395(10224):e39.

Malicka B, Kaczmarek U, Skośkiewicz-Malinowska K. (2014). Prevalence of xerostomia and the salivary flow rate in diabetic patients. Adv Clin Exp Med. 2014; 23(2):225-33. PMID: 24913113.

Pedrosa M, Sipert C.R, Nogueira F.N. (2020). Salivary Glands, Saliva and Oral Presentations in COVID-19 infection. SciELO.

Pedrosa MD, Sipert CR, Nogueira FN. (2020). Salivary glands, saliva and oral findings in COVID-19 infection. Pesquisa Brasileira em Odontopediatria e Clínica Integrada. 2020 Jul 29;20(suppl 1):e0104.

Rothan HA, Byrareddy SN. (2020). The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun. 2020;109:102433.

Sabino-Silva R, Jardim ACG, Siqueira WL. (2020). Coronavirus COVID-19 impacts to dentistry and potential salivary diagnosis. Clin Oral Investig 2020; 24(4):1619-21. https://doi.org/10.1007/s00784-020-03248-x

Sinjari B, D'Ardes D, Santilli M, Rexhepi I, D'Addazio G, Di Carlo P, Chiacchiaretta P, Caputi S, Cipollone F. (2020). SARS-CoV-2 and oral manifestation: an observational, human study. Journal of Clinical Medicine. 2020 Oct 7;9(10):3218.

Sohrabi C, Alsafi Z, O'Neill N, et al. (2020). World Health Organization declares global emergency: a review of the 2019 novel coronavirus (COVID-19). Int J Surg. 2020;76:71-76.

Su S, Wong G, Shi W, et al. (2016). Epidemiology, genetic recombination, and pathogenesis of coronaviruses. Trends Microbiol. 2016;24(6):490-502.

Tanasiewicz M, Hildebrandt T, Obersztyn I. (2016). Xerostomia of various etiologies: a review of the literature. Adv. Clin. Exp. Med. 25(1), 199–206.

To KK-W, Tsang OT-Y, Yip CC-Y, Chan K-H, Wu T-C, Chan JM-C, et al. (2020). Consistent detection of 2019 novel coronavirus in saliva. Clin Infect Dis 2020; ciaa149. https://doi.org/10.1093/cid/ciaa149

Tsuchiya H. (2022). Gustatory and saliva secretory dysfunctions in COVID-19 patients with zinc deficiency. Life 2022, 12, 353. [CrossRef] [PubMed]

Wax RS, Christian MD. (2020). Practical recommendations for critical care and anesthesiology teams caring for novel coronavirus (2019-nCoV) patients. Can J Anaesth. 2020;(67):568-576.

Zhang Y-Z, Holmes EC. (2020). A genomic perspective on the origin and emergence of SARS-CoV-2. Cell 2020; 181(2):223-227. https://doi.org/10.1016/j.cell.2020.03.035

Zhou M, Zhang X, Qu J. (2020). Coronavirus disease 2019 (COVID-19): a clinical update. Front Med. 2020;14(2):126-135.

Zhu N, Zhang D, Wang W, et al. (2020). A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020; 382(8):727-733.