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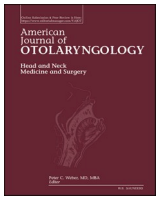

Eight-month follow-up of olfactory and gustatory dysfunctions in recovered COVID-19 patients

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ABSTRACT

Purpose: To investigate the recovery of loss of smell and taste among recovered COVID-19 patients.
Materials and methods: This cross-sectional follow-up study is a sequel to a study by Biadsee et al. Among the previous study population of 128 non-hospitalized patients, positive for COVID-19 by reverse transcription-polymerase chain reaction (RT-PCR), 97 patients participated in a survey designed for this study. Information and data regarding loss of smell and taste, rate of recovery, xerostomia, and additional symptoms; (Cough, Myalgia, Weakness, Rhinorrhea, Nasal congestion) were collected.
Results: A total of 43 men and 54 women were included. Mean age was 37.5 years (range 19–74). Mean follow-up was 229 days (range 191–253). Sixty-five patients reported gustatory dysfunction during the disease of which 61.5% reported full recovery, 38.5% partial recovery. Of 65 patients who reported olfactory impairment during the disease, 52% had full recovery and 48% reported partial recovery of olfactory function. Complete recovery of olfactory function was positively associated with full recovery of gustatory function ($p = 0.01$). Gender did not significantly affect the recovery of OD and GD ($p = 0.45$, $p = 0.90$, respectively). Patients who experienced olfactory dysfunction as an initial symptom had lower rates of olfactory complete recovery ($p = 0.043$).
Conclusion: After a mean follow-up of 229 days, complete recovery of smell and taste functions occurred in 52% and 61.5%, respectively. However, dysfunction persisted in 48%–38.5% of patients.

1. Introduction

According to recently published data, olfactory and gustatory chemosensory impairment are very prevalent in COVID-19 infection. In our previous study [1], we have reported initial symptoms and prevalence of olfactory and gustatory dysfunction among COVID-19 patients. We found that impaired sense of smell or taste as a presenting symptom can be as high as 38%. Similar to our results, Coelho et al. [2] found that 37.7% of their study group reported subjective olfactory or gustatory dysfunction (OD and GD, respectively) as a presenting symptom. Recovery rates of chemosensory impairment are being investigated, worldwide. Few studies have tracked outcomes at serial time points and have shown a gradual improvement in olfactory and gustatory functions over time [3,4]. Further analysis by Paderno et al. [4] found nasal congestion, gender, and grade of dysfunction, as risk-factors for late resolution from OD.

The emergence of the new COVID-19 vaccination and the possible opportunity for the elimination of the plague will prompt a shift of interest towards the long-term consequences of the COVID-19 virus. Currently, long-term information on recovery rates of OD and GD are lacking. This study reports the resolution rates of OD and GD in recovered COVID-19 patients.

2. Materials and methods

This study was conducted in the Department of Oral Rehabilitation, School of Dental Medicine of Tel Aviv University, in collaboration with the Otorhinolaryngology Department, Meir Medical Center, Kfar Saba, Israel (affiliated with Tel Aviv University).

This is a sequel to the previous study by Biadsee et al. [1] It was approved by the Tel Aviv University Ethics Committee (application number 0001623-2). Informed consent was obtained from all

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participants, by telephone.

2.1. Participants

2.1.1. Previous study

The previous study [1] was conducted from March 25, 2020 to April 15, 2020. One hundred twenty-eight ambulatory patients who tested positive for COVID-19 by reverse transcription-polymerase chain reaction (RT-PCR) were quarantined in a designated hotel and were recruited by an advertisement at the hotel and participated in a web-based questionnaire. The questionnaire assessed olfactory and gustatory functions using a non-validated 10-point scale. Pre-ailment scores were obtained retrospectively, and scores during the disease were obtained prospectively. Among 128 patients, 86 (67%) reported OD, 67 (52%) reported GD, 72 (56%) reported xerostomia and 25 patients reported anosmia, during the COVID-19 infection. (Fig. 1).

During the first few months of the pandemic in 2020, recovery from the disease was determined by 2 negative RT-PCR assay results, on sequential samples taken at least 24 h apart. Then, patients were discharged home.

2.1.2. Current study

The current study follow-up was conducted on December 5, 2020, using a 7-question telephone questionnaire. Of the previous study population of 128 non-hospitalized patients, 97 agreed to participate in the follow-up telephone survey and served as the new study group.

2.2. The survey

A 7-question telephone questionnaire was designed for this study, and was conducted on December 5, 2020 (Table 1).

The first section contained questions regarding the date of their second negative RT-PCR. The period of illness was defined as the number of days between the initial positive detection date by PCR (obtained from the previous study [1]) and the date of the second negative PCR test. The follow-up period was defined as the number of days between the second negative PCR test and the date of the survey. The second question addressed the patient's general symptoms at the time of the survey; (Cough, Myalgia, Weakness, Rhinorrhea, Nasal congestion).

Section 2 included a single dichotomous question regarding current feeling of xerostomia.

Table 1
Study questionnaire.

Section 1.
1. Date of second negative RT-PCR test:
2. Do you suffer one of these symptoms? (Cough/Myalgia/Weakness/Rhinorrhea/ Nasal congestion)
Section 2.
3. Do you still feel the need to drink more (dry mouth)? Yes/No
Section 3.
Taste:
4. Is your sense of smell normal? (Yes/No) comparing to your sense before the illness?
5. Rate your sense of taste to date, on a scale from 0 to 10
Section 4.
Smell:
6. Is your sense of smell normal? (Yes/No) comparing to your sense before the illness? Yes/NO
7. Rate your sense of smell to date, on a scale from 0 to 10

Sections 3 and 4 included two dichotomous questions about self-reported subjective recovery of smell and taste functions (Yes/No). Furthermore, responders rated their smell and taste function using a 10-point numerical scale from 0 to 10, with 0 representing anosmia and ageusia and 10 representing a very good sense of smell and taste, respectively.

Data obtained from the previous study [1] included: 1. Scores of olfactory and gustatory functions pre-ailment, 2. Scores of olfactory and gustatory during the disease, 3. Olfactory and/or gustatory dysfunction as a presenting symptom of the disease.

Study group patients who reported normal olfactory and/or gustatory functions in the previous study, were considered to have normal chemosensory functions.

Recovery of smell or taste sense was considered as full recovery when self-reported recovery was positive in sections 3 and 4 of the questionnaire and equal or higher scores of self-reported smell or taste functions at the time of the second survey compared to the pre-ailment scores obtained from the previous study data. Otherwise, it was considered as partial recovery only.

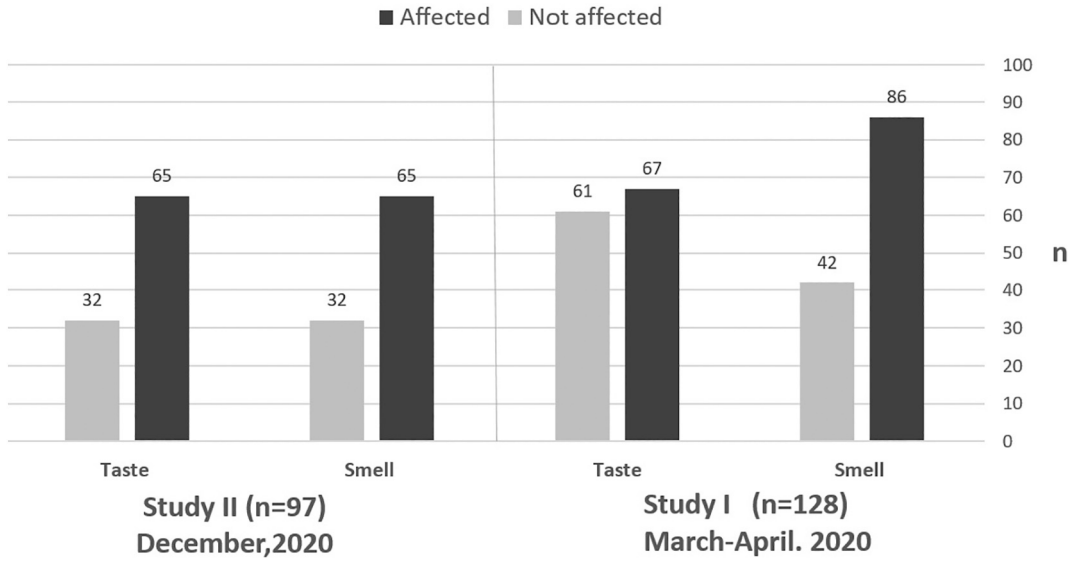

Fig. 1. A Comparison of prevalence rates of olfactory and gustatory dysfunctions among patients, between the previous study (Study I, conducted between March–April 2020) and the current follow-up study (Study II, conducted on 5, December 2020).

Improvement score was calculated and defined as the difference between the score obtained from the current study and the score obtained during the disease (previous study). Zero score in improvement, represents no improvement.

Information obtained from the questionnaires was tallied and summarized.

2.3. Statistical analysis

Statistical data was analyzed using the R Project for Statistical Computing, version 3.6.2.

Reported measures such as full-recovery endpoint and recovery scores were tested for the association with reported initial loss of smell \taste (yes\no). Patients were asked to score their senses before the infection, during and after they recover. A patient was said to reach sense-related full-recovery for each of the senses when the score showed decline during the infection and then revived at the day of the second survey. Otherwise, a patient was said to experience partial recovery if the scores indicated incline but not fully restored.

The tuples of three scores provided by each patient were fitted against their age, gender and initial experience of the loss of sense, using repeated-measures nested linear model.

The odds for reaching full recovery were tested against presenting of the symptom (yes\no), gender and their interaction using the logistic regression model.

Statistical significance of each covariate was tested using the likelihood ratio test. All tests and credible intervals are reported at a level of alpha = 0.05.

3. Results

A total of 43 men and 54 women were included in the study. Mean age was 37.5 years (range 19–74). Mean follow-up period was 7.6 months (range 6.3–8.4). Mean duration of illness from diagnosis to second PCR test was 26.2 days (range 5–58).

3.1. Taste

Sixty-five (67%) patients in the study group had gustatory impairment during COVID-19 disease. However, 32/97 patients (33%) did not report GD during the disease. (Fig. 1) Their mean age was 40.8 ± 17.4 years, 19 men and 13 women.

Forty of 65 patients (61.5%) suffering dysgeusia, reported full recovery of their taste function (mean age 30 ± 14.4 years, 15 men and 25 women). (Fig. 2).

Twenty-five (38.5%) of 65 patients (mean age 43.2 ± 17.4 years, 9 men and 16 women) reported only partial recovery of their taste function, with a taste scale average of 7.6 ± 1.1 points at the time of the second survey. (Fig. 2).

Among fully recovered patients, average improvement score was 5.38 ± 2.58 and 4.04 ± 2.73 points among partially recovered patients. However, 5 patients (2 men and 3 women) reported no improvement at the time of the second survey, with no ageusia reported. (Fig. 3).

Thirty-three (50.7%) of the patients who had GD, reported it as the presenting symptom of COVID-19 disease. Using logistic regression, GD as an initial symptom was not found statistically significant (OR = 0.804, $p = 0.87$), neither gender (OR = 0.677, $p = 0.902$) nor their interaction (OR = 1.76, $p = 0.622$).

3.2. Smell

Sixty-five (67%) of the study group patients had olfactory impairment during the disease. However, 32/97 (33%) did not report OD during the disease. (Fig. 1).

Their mean age 42.8 ± 17.3 years, 18 men and 14 women.

Thirty-four (52%) of 65 patients reported full recovery of their smell function (mean age 30.9 ± 14.2 years, 14 men and 20 women). (Fig. 2).

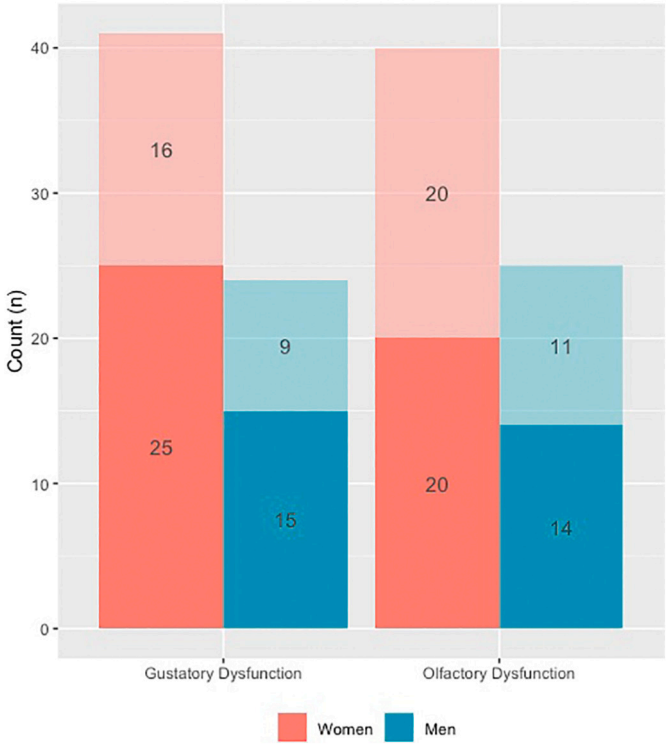

Fig. 2. Prevalence of partial or complete recovery of GD/OD among men and women. Opaque color represents full recovery, and translucent color represents partial recovery.

Thirty-one (48%) of 65 patients, mean age 37.7 ± 18.1 years, 11 men and 20 women, reported only partial recovery of olfaction, with an average smell score of 6.61 ± 2.0 at the time of the second survey. (Fig. 2).

Among fully recovered patients, average improvement scores were 6.38 ± 2.95 and 3.94 ± 2.63 among partially recovered patients. However, 5 patients (3 men and 2 women) reported no improvement at the time of second survey, with no anosmia reported (Fig. 3).

Thirty-six (55.3%, 16 men and 20 women) of the patients who suffered from olfactory dysfunction, reported OD as the presenting symptom of COVID-19 disease. The effect of presenting the symptom on the odds for complete recovery was found statistically significant (OR = 1.15, $p = 0.043$), unlike gender (OR = 1.88, $p = 0.45$) and their interaction ($p = 0.08$).

Complete recovery of olfactory function was positively associated with the complete recovery gustatory function. ($p = 0.01$, $r = 0.33$).

3.3. Dry mouth

Sixty patients (61.9%) reported xerostomia at the time of the first survey and 14 (14.4%) reported persistent xerostomia at the time of the current survey (6 men and 8 women), with no significant difference between the sexes ($p = 0.905$).

Persistent xerostomia was not significantly statistical correlated to gustatory function recovery ($p = 0.14$).

3.4. General symptoms

Ten patients reported persistent weakness and myalgia. 6 reported weakness only, and 5 myalgia.

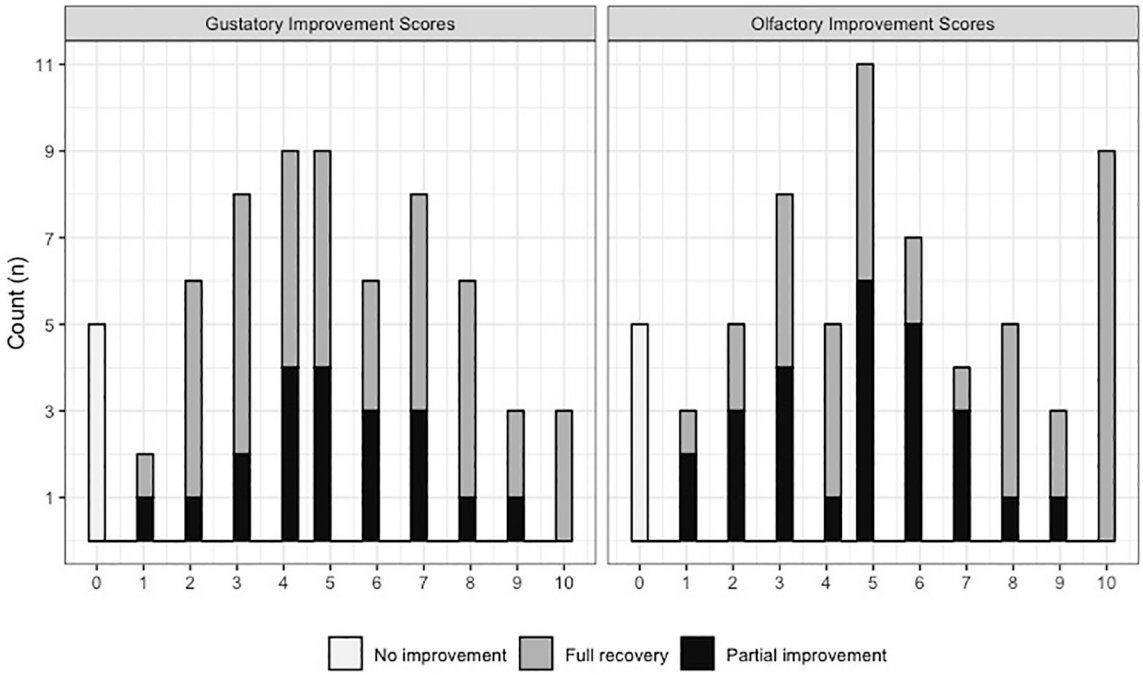

Fig. 3. Gustatory and olfactory improvement score distribution among partial and fully recovered patients.

4. Discussion

The current study investigated the recovery rates of olfactory and gustatory dysfunction among recovered COVID-19 patients who were not hospitalized while infected.

Smell and gustatory dysfunction are very prevalent in COVID-19 disease. In our previous cohort [1], we reported olfactory and gustatory dysfunction rates as high as 67% and 52%, respectively. Complete recovery of smell function after a mean follow up of 229 days was found in 52% of patients, while 48% reported only partial recovery. As reported by Chary et al. [5], we also found no significant difference between the sexes concerning recovery of smell function. However, Paderno et al. [4] found that later recovery of smell was more prevalent among women. This may be because women are more sensitive to minor smell alteration [6].

The oral cavity strongly expresses angiotensin-converting enzyme 2 (ACE II), particularly in the tongue [7]. A recent study demonstrated that ACE II inhibitors could engender loss of taste perception by alterations in the delicate mechanisms involving G-protein coupled proteins and sodium channels [8]. Moreover, another report suggested that ACE II receptors play a crucial role in cellular entry and are a potential cause of COVID-19 infection [9]. This can explain why dysgeusia is very prevalent in COVID-19 patients. We found a relatively low rate of complete gustatory recovery (61.5%) among the study group. Among patients with residual GD (38.5%), a mean improvement of 4.04 ± 2.73 points was reported. This improvement can be explained by the regenerative ability of chemosensory receptor cells in the oral cavity [10].

Olfactory and/or gustatory dysfunction have been widely reported as one of the sole initial manifestations of COVID-19 infection [1,4,11]. In our cohort, we found that patients who presented with OD as an initial symptom had significantly lower rates of complete recovery of olfactory ($p = 0.04$). Interestingly, GD as a presenting symptom of the disease did not affect the recovery of taste function.

To the best of our knowledge, no current study in the literature has reported a relation between OD as initial symptom and different chemosensory recovery rates.

In this analysis, which is a follow-up to the previous study by Biadsee et al. [1], we aimed to further understand the long term impact of the damage to the olfactory neuroepithelium caused by the COVID-19 virus, by using a 7-question telephone questionnaire. Chary et al. [5] found that 70% of COVID-19 patients reported OD without nasal obstruction. Furthermore, 64% of their cohort reported complete resolution of OD within 15 days after positive PCR diagnosis. D'Ascanio et al. [3] and Paderno et al. [4] found that OD was completely resolved for 84.3% and 88%, respectively, 30 days after diagnosis. Lechien et al. [12] reported complete resolution of OD among 72.6% of patients, within 8 days after the resolution of the disease. Xiong et al. [13] found 11% of their study group had residual OD 2–4 weeks after negative PCR. However, an analysis of 751 positive COVID-19 patients demonstrated lower resolution rate – 63% after a mean follow up time of 47 days from the first consultation [14].

During our follow-up of a mean of 7.6 months after the second negative PCR test, we found that OD had resolved completely in 52% of patients. Interestingly, 48% of the study group had residual OD. However, most reported a mean improvement of 3.94 ± 2.63 points in subjective olfactory scores.

Our analysis is characterized by a long follow-up period and a relatively high percentage of residual OD compared to other subjective reports in the literature [3,4,12,15–17] and provides a complementary data regarding the clinical course of OD and GD. Although, these variations in OD resolution rates could also be explained by the lack of an objective measurement method. Indeed, no correlation was found between objective test results and subjective reports of olfactory loss [18].

Post-viral olfactory loss is defined as the persistence or appearance of olfactory dysfunction after recovery from upper respiratory infection [19]. Suggested mechanisms for post-viral olfactory loss include the ability of viruses to penetrate the brain via the fovea ethmoidalis and elicit an immune response that can lead to neuroepithelial damage [20]. The relatively long follow-up period and high percentage of residual OD compared to reports in the literature may suggest that post-viral olfactory loss was more common among our cohort of patients.

The main limitations of this study are its relatively small size and the lack of objective measurements for diagnosis of OD and GD. As a follow up study on the same participates, there is a possibility of recall bias. We used two strategies to minimize the risk of recall bias. The first, during the follow-up telephone survey, patients did not know their previous

scores. Second, the long time that elapsed between the two surveys served as a "wash-out period".

Furthermore, in an effort to validate this report, full recovery of olfactory function was considered as a; positive answer in sections 3 and 4 of the questionnaire and equal or higher scores of self-reported smell or taste functions at the time of the second survey compared to the pre-ailment scores obtained from the previous study data. Another strength is the long follow-up (mean of 229 days after the second negative PCR test), which enabled good interpretation of patients' outcomes after long recovery period.

5. Conclusion

This analysis of olfactory and gustatory dysfunction in COVID-19 patients is characterized by a long follow-up period and a relatively high percentage of residual OD compared to other subjective reports in the literature. Complete resolution of OD was 52% and of GD 61.5%. Olfactory dysfunction that presented as an initial symptom of COVID-19 was a negative prognostic factor for complete recovery. Further objective and subjective studies are needed to explore the residual and persistent chemosensory dysfunction among these patients.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Ethics

The study was approved by the Tel Aviv University Ethics Committee (application number 0001623-2).

CRediT authorship contribution statement

Biadsee Ameen: Conceptualization; Data curation; Investigation; Methodology; Validation; Visualization; Writing - original draft; Writing - review & editing.

Or Dagan: Conceptualization, Data curation, Investigation, Writing - original draft.

Zeev Ormianer: Methodology, Supervision, Writing - review & editing.

Firas Kassem: Methodology, Writing - review & editing.

Shchada Masarwa: Data curation, Investigation, Formal analysis.

Ameer Biadsee: Conceptualization, Investigation, Supervision, Writing - original draft, Writing - review & editing.

Declaration of competing interest

None.

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References

[1] Biadsee A, Biadsee A, Kassem F, Dagan O, Masarwa S, Ormianer Z. Olfactory and oral manifestations of COVID-19: sex-related symptoms-a potential pathway to early diagnosis. Otolaryngol Head Neck Surg 2020;163:722–8. https://doi.org/10.1177/0194599820934380.

[2] Coelho DH, Kons ZA, Costanzo RM, Reiter ER. Subjective changes in smell and taste during the COVID-19 pandemic: a national survey-preliminary results. Otolaryngol Head Neck Surg 2020;163:302–6. https://doi.org/10.1177/0194599820929957.

[3] D'Ascanio L, Pandolfini M, Cingolani C, Latini G, Gradoni P, Capalbo M, et al. Olfactory dysfunction in COVID-19 patients: prevalence and prognosis for recovering sense of smell. Otolaryngol Head Neck Surg 2020. https://doi.org/10.1177/0194599820943530. 194599820943530.

[4] Paderno A, Mattavelli D, Rampinelli V, Grammatica A, Raffetti E, Tomasoni M, et al. Olfactory and gustatory outcomes in COVID-19: a prospective evaluation in nonhospitalized subjects. Otolaryngol Head Neck Surg 2020;194599820939538. https://doi.org/10.1177/0194599820939538.

[5] Chary E, Carsuzaa F, Trijolet J-P, Capitaine A-L, Roncato-Saberan M, Fouet K, et al. Prevalence and recovery from olfactory and gustatory dysfunctions in covid-19 infection: a prospective multicenter study. Am J Rhinol Allergy 2020;34:686–93. https://doi.org/10.1177/1945892420930954.

[6] Frasnelli J, Hummel T. Olfactory dysfunction and daily life. Eur Arch Otorhinolaryngol 2005;262:231–5. https://doi.org/10.1007/s00405-004-0796-y.

[7] Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci 2020; 12:8. https://doi.org/10.1038/s41368-020-0074-x.

[8] Tsuruoka S, Wakaumi M, Araki N, Ioka T, Sugimoto K, Fujimura A. Comparative study of taste disturbance by losartan and perindopril in healthy volunteers. J Clin Pharmacol 2005;45:1319–23. https://doi.org/10.1177/0091270005280445.

[9] Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020; 579:270–3. https://doi.org/10.1038/s41586-020-2012-7.

[10] Oakley B, Riddle DR. Receptor cell regeneration and connectivity in olfaction and taste. Exp Neurol 1992;115:50–4. https://doi.org/10.1016/0014-4886(92)90220-k.

[11] Kaye R, Chang CWD, Kazahaya K, Brereton J, Denneny JC. COVID-19 anosmia reporting tool: initial findings. Otolaryngol Head Neck Surg 2020;163:132–4. https://doi.org/10.1177/0194599820922992.

[12] Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Otorhinolaryngol 2020;277:2251–61. https://doi.org/10.1007/s00405-020-05965-1.

[13] Li J, Long X, Zhu C, Wang H, Wang T, Lin Z, et al. Olfactory dysfunction in recovered coronavirus disease 2019 (COVID-19) patients. Mov Disord 2020;35: 1100–1. https://doi.org/10.1002/mds.28172.

[14] Chiesa-Estomba CM, Lechien JR, Radulesco T, Michel J, Sowerby LJ, Hopkins C, et al. Patterns of smell recovery in 751 patients affected by the COVID-19 outbreak. Eur J Neurol 2020;27:2318–21. https://doi.org/10.1111/ene.14440.

[15] Lee Y, Min P, Lee S, Kim SW. Prevalence and duration of acute loss of smell or taste in COVID-19 patients. J Korean Med Sci 2020;35:e174. https://doi.org/10.3346/jkms.2020.35.e174.

[16] Hopkins C, Surda P, Whitehead E, Kumar BN. Early recovery following new onset anosmia during the COVID-19 pandemic - an observational cohort study. J Otolaryngol Head Neck Surg 2020;49:26. https://doi.org/10.1186/s40463-020-00423-8.

[17] Paderno A, Schreiber A, Grammatica A, Raffetti E, Tomasoni M, Gualtieri T, et al. Smell and taste alterations in COVID-19: a cross-sectional analysis of different cohorts. Int Forum Allergy Rhinol 2020. https://doi.org/10.1002/alr.22610.

[18] Lechien JR, Cabaraux P, Chiesa-Estomba CM, Khalife M, Hans S, Calvo-Henriquez C, et al. Objective olfactory evaluation of self-reported loss of smell in a case series of 86 COVID-19 patients. Head Neck 2020;42:1583–90. https://doi.org/10.1002/hed.26279.

[19] Seiden AM. Postviral olfactory loss. Otolaryngol Clin N Am 2004;37:1159–66. https://doi.org/10.1016/j.otc.2004.06.007.

[20] Baker H, Beth Genter M. The olfactory system and the nasal mucosa as portals of entry of viruses, drugs, and other exogenous agents into the brain. In: Doty R, editor. Handbook of olfaction and gustation. CRC Press; 2003. https://doi.org/10.1201/9780203911457.ch26.