Bosnian Journal of Basic Medical Sciences
ISSN: 1512-8601 (Print) | ISSN: 1840-4812 (Online) | OPEN ACCESS
Journal Impact Factor® (2021): 3.75
CiteScore® (2021): 5.2
www.bjbms.org | blog.bjbms.org

RESEARCH ARTICLE

NEW AND EMERGING MEDICAL ENTITIES

Cazzolla et al.: Taste dysfunctions in COVID-19

Evaluation of qualitative and quantitative taste alterations in COVID-19

Angela Pia Cazzolla[1], Roberto Lovero[2], Francesca Spirito[1], Michele Di Cosola[1], Luigi Santacroce[3], Eleonora Lo Muzio[4], Domenico Ciavarella[1], Mario Dioguardi[1], Vito Crincoli[5], Maria Pepe[6], Lucia Varraso[2], Renato Contino[2], Francesca Di Serio[2], Lorenzo Lo Muzio[1,7]*

[1]Department of Clinical and Experimental Medicine, Università degli Studi di Foggia, Foggia, Italy

[2]Clinical Pathology Unit, AOU Policlinico Consorziale di Bari - Ospedale Giovanni XXIII, , Bari, Italy

[3]Ionian Department (DJSGEM), Microbiology and Virology Lab, Università Degli Studi di Bari, Bari, Italy

[4]Department of Translational Medicine and for Romagna, School of Orthodontics, University of Ferrara, Ferrara, Italy

[5]Department of Basic Medical Sciences, Neurosciences and Sensory Organs, "Aldo Moro" University of Bari, Bari, Italy

[6]Transfusional Medicine Unit, University-Policlinico, Bari, Italy

[7]Consorzio Interuniversitario Nazionale per la Bio-Oncologia (C.I.N.B.O), Chieti, Italy

***Corresponding author:** Lorenzo Lo Muzio, Department of Clinical and Experimental Medicine, Università degli Studi di Foggia, Foggia 71122, Italy; E-mail: lorenzo.lomuzio@unifg.it

DOI: https://doi.org/10.17305/bjbms.2022.6973

Submitted: 23 January 2022/**Accepted:** 25 February 2022/ **Published online**: 07 July 2022

Conflicts of interest: Authors declare no conflicts of interest.

Funding: Authors received no specific funding for this work.

ABSTRACT

Taste dysfunctions occur in a large proportion of COVID-19 patients. This observational study compared interleukin-6 (IL-6) levels in mild and moderate COVID-19 patients with the type (quantitative or qualitative) of taste disorders. The 208 COVID-19 patients (118 men and 90 women) showing only taste dysfunctions as prodromic symptoms were classified as mild and moderate patients. The evaluation of the taste disorder was carried out using a survey. The IL-6 levels were measured with a chemiluminescence assay. Statistical analysis was performed using the Wilcoxon rank, Welch's, and Mann-Whitney tests ($p < 0.05$). The results showed that there were no statistically significant differences in the perception of sour and salty, nor in the presence of dysgeusia and phantogeusia in moderate versus mild patients ($p > 0.05$). However, there were statistically significant differences in the perception of umami, bitter, sweet, and the presence of parageusia in moderate versus mild patients ($p < 0.05$). There was an impairment of multiple tastes up to ageusia in patients with high IL-6 levels. The results showed that dysfunctions in the perception of sweet, bitter, umami, and the presence of parageusia can be considered as signs of more severe forms of COVID-19.

KEYWORDS: COVID-19; taste dysfunction; dysgeusia.

INTRODUCTION

Taste dysfunctions occur in a large proportion of COVID-19 patients and self-reported loss of taste may have a more important prognostic significance than other symptoms of COVID-19 (fatigue, fever or cough) [1]. Some studies reported prevalence ranging from 71% to 88.8% for taste disturbances (78.9% for hypogeusia/ageusia and 21.1 % for parageusia) in mild-to-moderate forms of coronavirus disease 2019 (COVID-19) [2-4] while two meta-analyses showed a pooled gustatory dysfunction of 38.2–49.0% [5]

Taste disturbances are divided into qualitative and quantitative categories. Qualitative disturbances include dysgeusia (a distortion of taste perception evoked by previously approved foods that become unpleasant), parageusia (an altered taste perception, more often unpleasant with external stimulus) and phantogeusia (the perception of metallic or salty taste without external stimulus). Quantitative disturbances include ageusia (total deficit), hypogeusia (loss of certain taste) and hypergeusia (the increase of gustatory sensitivity)[6].

The perception of taste is closely related to the sense of smell and can be considered optimal when there is an adequate salivation, a good neuronal network, and a correct stimulation of taste buds. Taste buds are chemoreceptors present in the fungiform, foliate, and circumvallate papillae of the dorsal mucosa of the tongue ENREF 10 but also in the palate, pharynx, and larynx. Filiform papillae contain trigeminal nerve endings that transmit information on the temperature, texture and pain. [7]

The average turnover of taste cells was estimated to be about 8–12 days and it is important that progenitor cells in the surrounding tissues continuously differentiate into the specific types of taste cells for taste bud homeostasis and intact taste function.[8]

Each taste buds is composed of 150 to 300 epithelial cylindrical cells and contains 5 types of cells: type 1, 2, 3 cells (specialized epithelial cells for recognizing taste), type 4 cells, and supporting cells and neuronal processes[.9] The type 1 cells are glial-like cells with several long microvilli and are thought to mediate salty taste. The type 2 cells contain the G-protein-coupled receptors (GPCR) and are thought to transduce sweet, umami and bitter tastes. The type 3 cells are presynaptic cells that transduce sour and salty[10] taste, mediate communication from the type 2 cells via P2Y adenosine receptors, and mediate signals to the afferent neurons via release of serotonin. The type 4 cells are basal precursor cells and differentiate into type 1, 2 and 3 taste cells during rapid cell turnover in taste buds[8].

To date, the mechanisms of taste reception are not well understood. In fact, receptor system for salty taste has yet to be identified even though is suggested that an amiloride-sensitive ion channels ENAC (epithelial Na channel) and ASIC (add sensing ion channel) are involved in the perception of salty in rodents [11]. Sour taste is mediated by two members of the TRP superfamily of ion channel polycystic kidney disease protein 1-like 3 (PKD1L3), PKD2L1 and by ASIC channels which are present on different populations of papillae. Receptors belonging to the C class receptors, GPRC, are involved in the perception of other tastes. [12]

In particular, artificial sweeteners and sugars bind to sweet taste receptors T1R2/3 and activate downstream pathways (sugars activate a phospholipase C–dependent pathway, while artificial sweeteners activate adenylyl cyclase pathway). Monosodium glutamate binds to the umami receptor, T1R1/3 and activates a phospholipase C pathway Bitter taste activates 25 T2R receptors, potassium channel and subsequently phospholipase C and adenylyl cyclase pathways. [8, 12]

After the bond between gustatory stimuli molecules and the specific receptor, the transfer of information to the central nervous system (CNS) occurs via three nerves: the chorda tympani (CN-VII), the glossopharyngeal nerve (CN-IX), and the trigeminal (CN-V) [12]. Information reach the gustatory cortex, where is a gustotopic map.[13]

The entry of the Sars-CoV-2 into cells is mediated by ACE receptors [14-18] and TMPRSS2 proteases [19]. TMPRSS2 proteases are expressed in the epithelium and mesenchyme of the soft palate and in the tongue epithelium in mice. They showed a progressive increase over developmental stages (mice and humans share similar gene expression patterns for ACE receptor and TMPRSS2 proteases) [20]. ACE2 receptors are expressed in salivary glands, in oral tissues in higher numbers in keratinocytes of the oral tongue than in other buccal and gingival tissues, and in lymphocytes within oral mucosa. [15] In particular, ACE2 receptors are not expressed in the specialized cells of the taste buds, in the progenitor cells surrounding taste buds, nor in the epithelial cells of the taste buds. ACE receptors are present in a subpopulation of epithelial cells in the basal region of filiform non-taste buds and in a small percentage of type 3 taste cells. Therefore, the loss of taste is not caused by direct infection of SARS-CoV-2 of taste cells but by a involvement of the epithelial cells of the non-gustatory papilla.[20]

Further, SARS-CoV-2 has been demonstrated to be neuroinvasive and neurotropic through signal interactions between the spike protein and the ACE2 receptor on olfactory mucosal cells[21]. This particular tropism leads to CNS infection with concomitant neuronal loss[21].

The potential causes of taste loss are not clear. It may result from different causes, such as neurologic damage[22], tissue hypoxia[23], binding of SARS-CoV-2 to sialic acid receptors with interference with glycoprotein-mediated transport of taste substances before they can be detected [24], changes in cellular zinc homeostasis of gustatory cells [25], local and/or systemic

immune responses [26, 27], inflammatory reaction [28] with cellular changes that could alter taste [29]. During SARS-CoV 2 infection there is an inflammatory storm with the release of 150 different inflammatory cytokines and chemical mediators secreted by immune and non-immune cells (cytokine release syndrome-CRS). [30, 31]

The main role in CRS is played by interleukin 6 (IL-6) which induces the release of several acute-phase proteins (CRP fibrinogen, C3, C4, etc.,) and it is recognized as a negative prognostic factor in SARS-CoV 2 infection. Elevated levels of IL-6 were significantly related to severe clinic manifestations affecting the respiratory tract, heart, kidneys, liver, gastrointestinal tract with microbiota dysbiosis [32], spleen, central nervous system, lymph nodes, and skin. [33]

The aim of this observational study was to compare IL-6 levels in mild and moderate COVID-19 patients with the type (quantitative or qualitative) of taste disorders. Furthermore, the levels of IL 6 were compared, in the context of quantitative disorders, with the number of the flavors of foods normally present at the home (household tastes) in order to define which taste disorders is most compromised in mild and moderate COVID-19 patients and if the alteration of a particular taste is indicative of a more severe clinical manifestations

MATERIALS AND METHODS

This study was conducted from March 15, 2020, to April 15, 2021. Mild to moderate COVID-19 patients were included in the study. Inclusion and exclusion criteria are indicated in Table 1.

The patients were divided into mild and moderate categories based on clinical manifestations (Table 2) and the presence of qualitative (dysgeusia, parageusia, and phantogeusia) and quantitative (ageusia, hypogeusia, hypergeusia) taste disturbances was assessed using a survey.

On admission to the hospital, the venous sample was taken for each patient. The venous samples were collected in 5 ml Vacutainer tubes without anticoagulants, then centrifuged (1000 × g, 15 min, 4 ° C) and stored at - 80 ° C until analysis. The IL-6 levels (v.n. 0 – 7 pg/ml) have been measured with a chemiluminescence assay using Cobas e801 (Roche Instrumentation).

The survey that was given to each patient consisted of two parts. The first part was for health care professionals and it included general questions (age, sex, residence, work activity, smoking habit, previous institutionalization or acute hospitalization), the presence of systemic diseased (hypertension, diabetes, gastrointestinal, thyroid, heart, kidney, liver pathologies, upper respiratory infection, and head trauma), and local diseases (oral cavity infections, candidiasis, poor oral hygiene, and Burning Mouth Syndrome). The second part of the survey was for the patients. It investigated time of onset of taste disorder and the type of the taste alteration. Taste and Smell Questionnaire Section (CSQ) of the US NHANES 2011–2014 protocol (CDC 2013b) was used as a reference to evaluate gustatory function. [33]

The survey investigated the type of taste disturbance (salty, bitter, sour, umami, sweet) evaluating the perception of the flavors of foods normally present at the home (household tastes). The number of household unperceived tastes was determinded by assigning a score to each household taste not perceived. The score was obtained by attributing the value 0 when all tastes were perceived and 5 when they were not perceived. In addition, it was asked if the saltiness of the table salt dissolved in the water was perceived (salty), if the taste of sugar dissolved in the water was perceived (sweet), if the lemon juice was perceived (sour), if the taste of bitter coffee was perceived (bitter), if the taste of parmesan, a food that contains glutamate, was perceived (umami). To evaluate the presence of qualitative disturbances, it was asked whether the patients experienced unpleasant tastes (metallic or salty) with or without food.

Ethical statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics committee of Bari (Italy) N. 6388 COVID19 DOM protocol number 0034687/12-05-2020. Informed consent was obtained from all subjects involved in the study.

Statistical analysis

All analyses were performed using MedCalc software. Age, sex, symptoms associated, and taste disorders are reported in numerals and percentages of the total. The mean ± SD are given using descriptive statistics for quantitative variables. Normality distribution of variables was assessed by the Kolmogorov-Smirnov test and Shapiro-Wilk test. Both tests proved a non-normal distribution of variables.

The Wilcoxon rank test and Welch's t-test or unequal variance t-test were used to evaluate IL-6 values in both mild and moderate patients with taste dysfunction and IL-6 values in relation to the type of taste disorder reported (quantitative or qualitative disorders). Mann-Whitney test was used to evaluate the differences between independent groups of mild and moderate patients and the different alterations of taste.

A 5% p-value threshold was adopted for all tests used.

RESULTS

208 COVID-19 patients with taste disturbance, (118 (57%) men aged 59 ± 13 and 90 (43%) women (age 56 ± 12)) were selected.

Of 1155 COVID 19 patients, 821 (71%) presented chemosensitive dysfunctions. Of them, 208 (25%) patients (118 men aged 59±13 and 90 women aged 56±12) showed only taste dysfunctions as prodromic symptoms, 286 (35%) showed only smell dysfunctions as prodromic symptoms, and 180 (22%) presented smell and taste disorders. 147 (18%) patients were excluded because 37 (25%) refused to answer, 35 (24%) required intensive care admission (critical patients), 13 (9%) presented allergic rhinitis, 4 (3%) finished chemotherapy, and 2 (1%) radiotherapy for oral and oropharyngeal cancer recently, 15 (10%) presented diabetes, 15 (10%) were affected by liver diseases, 10 (7%) affected by kidney diseases, 9 (6%) affected by hypothyroidism, and 7 (5%) affected by neurologic and psychiatric diseases.

The distribution of IL-6 in moderate versus mild patients showed an increase in IL-6 values in patients with a severe clinical course (Figure 1).

The Wilcoxon Rank test showed a statistically significant difference in IL-6 levels in moderate versus mild patients with ageusia, hypogeusia (score) and parageusia ($p < 0.05$). In the context of hypogeusia the patients were divided into: patients that reported a deficit in the perception of acid and/or salty, mediated by ion receptors and patients that reported a deficit in the perception of sweet and/or of bitter and/or umami, mediated by GPCRs.

There were statistically significant differences ($p<0.05$) in IL-6 values between moderate versus mild patients for quantitative umami, bitter, and sweet taste disturbances (GPCRs). There were no significant differences ($p> 0.05$) in IL-6 values between moderate versus mild patients for quantitative sour and salty taste disturbance (ion receptors) (Table 3).

There was no significant difference in IL-6 values between moderate and mild patients with dysgeusia and phantogeusia ($p> 0.05$) (Table 3).

Welch’s t-test showed a statistically significant difference between the mean values of IL-6 in moderate (67.8 pg/ml) versus mild (22.9 pg/ml) patients and between patients affected by hypogeusia and parageusia ($p < 0.05$) and in patients with altered perception of umami, bitter and sweet ($p<0.05$). There were no significant differences in IL-6 mean values between moderate versus mild patients with dysgeusia, phantogeusia, and in the perception of sour and salty ($p>0.05$). (Table 4).

Wilcoxon Rank test and Welch’s test demonstrated that IL-6 could play an important role in the onset of quantitative (ageusia and hypogeusia) and qualitative (parageusia) taste disorders in COVID-19 patients.

Mann-Whitney's test was used to compare moderate versus mild patients affected by taste disorders. There were significant differences for the presence of ageusia, hypogeusia (score), parageusia, and the perception of umami, bitter and sweet ($p < 0.05$). There were no statistically significant differences for the perception of dysgeusia, phantogeusia, and sour and salty ($p>0.05$). Mann Whitney's test showed that tastes perceived through GPCRs (umami, bitter and sweet) are more impaired in moderate COVID-19 patients with taste alterations than in mild ones (Table 4).

DISCUSSION

Taste alterations in association with smell disorders are prodromic symptoms in COVID-19 patients and they are an important factor in the early diagnosis of the disease. [34-36]

This is the first observational study that investigated IL-6 levels in COVID-19 patients with only taste dysfunction.

The results of the present study confirmed the literature data demonstrating a statistically significant correlation between the increased levels of IL-6 in moderate versus mild COVID-19 patients and taste disorders.[27]

They showed that in moderate patients with high IL-6 levels an impairment of multiple tastes up to ageusia ($p < 0.05$) was present. They also showed that in mild patients with milder inflammatory clinical manifestations sour and salty tastes mediated by ion receptors were impaired ($p > 0.05$), while umami, bitter and sweet tastes perceived through GPCRs were present in patients with more severe clinical manifestations ($p < 0.05$),. In the context of qualitative disorders parageusia was present in moderate patients ($p < 0.05$) while phantogeusia and dysgeusia were present in mild patients ($p > 0.05$).

These data suggested that following the entry of SARS-CoV-2 into the cells of the non-gustatory filiform papillae where there are ACE receptors, an inflammatory process is generated with the release of cytokines that act on taste cells. In fact, Tapas et al. have shown that the link between the Spike protein and the ACE receptors activates a series of molecular mechanisms in the infected cells with the production of IL-6 and other pro-inflammatory cytokines.[37]

Choudhury et al.[38] suggested that the inflammatory response could be due to interaction between Toll-like receptors (TLRs), particularly TLR4, present on type 2 cells that express gustducin [28] and virus with tissue damage.[39] Stimulation of TLR4 by viral pathogens in the oral cavity can activate the production of inflammatory cytokines in taste buds that could influence both normal taste transduction and the cell turn-over of taste buds resulting in taste dysfunction.

The inflammatory response could first damage the cells responsible for the sour and salty taste and then the cells responsible for sweet, umami, and bitter taste. If the inflammatory process persists, it could lead to a condition of ageusia.

In mild patients, there was a prevalent impairment of the amiloride-sensitive ion channels ENAC and ASIC for the salty and of ion channel PKD1L3, PKD2L1, ASIC channels for the sour while in moderate patients there was an impairment of both ionic channels and GPCR receptors.

The ion channels can be influenced by cytokines, chemokines, and other inflammatory mediators. Different researches demonstrated the link between inflammation and ion transport: inflammatory mediators may cause changes in epithelial ion transport with impaired cell permeability and may influence cell proliferation with the appearance of less differentiated cells with a reduced number of ion channels. These alterations could induce a modification in the transmission of sour and salty tastes to the CNS. [40]

Futhermore, role of cytokines has been demonstrated in alterated transmission of sweet, umami, and bitter tastes to the CNS through determining dysfunction and desensitization of C class receptors (GPCR). [41]

In the context of qualitative disorders, both dysgeusia and phantogeusia are present in mild and moderate forms while parageusia is present in moderate forms. To date, the pathophysiological basis of the onset of these disorders is not clear and there is a lack of studies on the matter. The results obtained would suggest that dysgeusia and phantogeusia could probably be linked to an impairment of ion receptors [42] while parageusia could be linked to a greater involvement of GPCRs (Figure.2).

Further, until now, no specific treatment has been approved for the improvement of taste alterations in patients with COVID-19. The use of corticosteroids has been proposed as local therapy in the form of steroid nasal spray or steroid paste to improve the symptoms of anosmia and dysgeusia[34]. Indeed, a zinc deficiency is often reported in COVID-19 patients and, given its role in taste function, oral zinc administration could improve dysgeusia symptoms by favoring the information transmission from taste cells to gustatory nerve fibers[35].

The limitations of the present study include the limited number of patients included in studied sample and absence of cooperation of the interviewed patients due to the clinical manifestations. Also, the assessment of taste disorders was carried out only using a questionnaire with a subjective and non-objective evaluation. Another limitation is that this is an observational study, which aim is to generate hypotheses that may or may not be confirmed by subsequent, appropriately designed experimental studies.

CONCLUSION

This study evidenced that tastes perceived through GPCRs (umami, bitter and sweet) are more impaired in moderate patients than in mild ones. It also showed that taste dysfunctions of sweet, bitter and umami associated with parageusia can be considered signs of more severe forms of COVID-19. In conclusion, our study therefore shows how the type of taste alteration,

being correlated to the levels of inflammatory mediators such as IL-6, could be considered a prognostic index of the course of COVID-19 disease.

Also, it suggested new research perspectives in the physiopathology of taste disorders. Further experimental studies on broader statistic data are needed in order to confirm obtained data.

ACKNOWLEDGMENTS

The authors express their gratitude to Alessandro Gaetano Mastrorillo for his contribution to the drafting the paper; to Rosa Genco, Carmela Petrelli, Angela Calamita, Vito Masellis for contribution to dosage of the IL-6 in different samples. Without their contribution it would not have been possible to do this work.

REFERENCES

1. Cirillo N, Bizzoca ME, Lo Muzio E, Cazzolla AP, Lo Muzio L. Gustatory dysfunction in COVID-19 patients: A rapid systematic review on 27,687 cases. Acta odontologica Scandinavica. 2021:1-8.

2. 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. European Archives of Oto-Rhino-Laryngology. 2020;277(8):2251-61.

3. Santacroce L, Charitos IA, Del Prete R. COVID-19 in Italy: An overview from the first case to date. Electronic Journal of General Medicine. 2020;17(6).

4. Santacroce L, Bottalico L, Charitos IA. The impact of COVID-19 on Italy: a lesson for the future. The international journal of occupational and environmental medicine. 2020;11(3):151.

5. Tong JY, Wong A, Zhu D, Fastenberg JH, Tham T. The prevalence of olfactory and gustatory dysfunction in COVID-19 patients: a systematic review and meta-analysis. Otolaryngology–Head and Neck Surgery. 2020;163(1):3-11.

6. Rademacher WMH, Aziz Y, Hielema A, Cheung KC, de Lange J, Vissink A, et al. Oral adverse effects of drugs: Taste disorders. Oral diseases. 2020;26(1):213-23.

7. Triantafyllou A, Coulter P. Structural organization of subgemmal neurogenous plaques in foliate papillae of tongue. Human pathology. 2004;35(8):991-9.

8. Feng P, Huang L, Wang H. Taste bud homeostasis in health, disease, and aging. Chemical senses. 2014;39(1):3-16.

9. Roper SD, Chaudhari N. Taste buds: cells, signals and synapses. Nature Reviews Neuroscience. 2017;18(8):485-97.

10. Roper SD. The taste of table salt. Pflügers Archiv-European Journal of Physiology. 2015;467(3):457-63.

11. Bigiani A. Does ENaC work as sodium taste receptor in humans? Nutrients. 2020;12(4):1195.

12. Gravina SA, Yep GL, Khan M. Human biology of taste. Annals of Saudi medicine. 2013;33(3):217-22.

13. Chen X, Gabitto M, Peng Y, Ryba NJ, Zuker CS. A gustotopic map of taste qualities in the mammalian brain. Science. 2011;333(6047):1262-6.

14. Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science. 2020;367(6485):1444-8.

15. 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. International journal of oral science. 2020;12(1):1-5.

16. Guzzi PH, Mercatelli D, Ceraolo C, Giorgi FM. Master regulator analysis of the SARS-CoV-2/human interactome. Journal of clinical medicine. 2020;9(4):982.

17. Santacroce L, Charitos IA, Carretta DM, De Nitto E, Lovero R. The human coronaviruses (HCoVs) and the molecular mechanisms of SARS-CoV-2 infection. Journal of Molecular Medicine. 2020:1-14.

18. Charitos IA, Del Prete R, Inchingolo F, Mosca A, Carretta D, Ballini A, et al. What we have learned for the future about COVID-19 and healthcare management of it? Acta Bio Medica: Atenei Parmensis. 2020;91(4).

19. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271-80. e8.

20. Wang Z, Zhou J, Marshall B, Rekaya R, Ye K, Liu H-X. SARS-CoV-2 receptor ACE2 is enriched in a subpopulation of mouse tongue epithelial cells in nongustatory papillae but not in taste buds or embryonic oral epithelium. ACS pharmacology & translational science. 2020;3(4):749-58.

21. Freni F, Meduri A, Gazia F, Nicastro V, Galletti C, Aragona P, et al. Symptomatology in head and neck district in coronavirus disease (COVID-19): A possible neuroinvasive action of SARS-CoV-2. Am J Otolaryngol. 2020 Sep - Oct;41(5):102612.

22. Lahiri D, Ardila A. COVID-19 pandemic: a neurological perspective. Cureus. 2020;12(4).

23. Couzin-Frankel J. Why don’t some coronavirus patients sense their alarmingly low oxygen levels. Science. 2020;10.

24. Milanetti E, Miotto M, Di Rienzo L, Nagaraj M, Monti M, Golbek TW, et al. In-Silico evidence for a two receptor based strategy of SARS-CoV-2. Frontiers in molecular biosciences. 2021;8.

25. Lozada-Nur F, Chainani-Wu N, Fortuna G, Sroussi H. Dysgeusia in COVID-19: possible mechanisms and implications. Oral surgery, oral medicine, oral pathology and oral radiology. 2020;130(3):344.

26. Schirinzi A, Cazzolla AP, Lovero R, Lo Muzio L, Testa NF, Ciavarella D, et al. New insights in laboratory testing for COVID-19 patients: looking for the role and predictive value of Human epididymis secretory protein 4 (HE4) and the innate immunity of the oral cavity and respiratory tract. Microorganisms. 2020;8(11):1718.

27. Dioguardi M, Cazzolla AP, Arena C, Sovereto D, Caloro GA, Dioguardi A, et al. Innate Immunity in Children and the Role of ACE2 Expression in SARS-CoV-2 Infection. Pediatric Reports. 2021;13(3):363-82.

28. Cazzolla AP, Lovero R, Lo Muzio L, Testa NF, Schirinzi A, Palmieri G, et al. Taste and smell disorders in COVID-19 patients: role of interleukin-6. ACS Chemical Neuroscience. 2020;11(17):2774-81.

29. Wang H, Zhou M, Brand J, Huang L. Inflammation and taste disorders: mechanisms in taste buds. Annals of the New York Academy of Sciences. 2009;1170:596.

30. Moradian N, Gouravani M, Salehi MA, Heidari A, Shafeghat M, Hamblin MR, et al. Cytokine release syndrome: inhibition of pro-inflammatory cytokines as a solution for reducing COVID-19 mortality. European cytokine network. 2020;31(3):81-93.

31. Crincoli V, Ballini A, Fatone L, Di Bisceglie M, Nardi G, Grassi F. Cytokine genotype distribution in patients with periodontal disease and rheumatoid arthritis or diabetes mellitus. Journal of biological regulators and homeostatic agents. 2016;30(3):863-6.

32. Santacroce L, Inchingolo F, Topi S, Del Prete R, Di Cosola M, Charitos IA, et al. Potential beneficial role of probiotics on the outcome of COVID-19 patients: an evolving perspective. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2021.

33. Carretta DM, Silva AM, D'Agostino D, Topi S, Lovero R, Charitos IA, et al. Cardiac Involvement in COVID-19 Patients: A Contemporary Review. Infectious Disease Reports. 2021;13(2):494-517.

34. Singh CV, Jain S, Parveen S, Deshmukh P. The outcome of fluticasone nasal spray on anosmia and triamcinolone oral paste in taste dysgeusia in COVID-19 patients. Am J Otolaryngol. 2021 Jul-Aug;42(4):103009.

35. Santos HO. Therapeutic supplementation with zinc in the management of COVID-19-related diarrhea and ageusia/dysgeusia: mechanisms and clues for a personalized dosage regimen. Nutr Rev. 2021 Aug 2.

TABLES AND FIGURES WITH LEGENDS

TABLE 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
- age > 18 years - laboratory-confirmed COVID-19 infection (reverse transcription-polymerase chain reaction, RT-PCR) - patients with only taste disfunction like prodromic symptom	- patients without a laboratory-confirmed diagnosis of COVID-19 infection - patients with taste dysfunctions before the epidemic (congenital ageusia, side effects of drugs, previous surgery of ear and of wisdom teeth, radiotherapy of the oral and pharyngeal cavities, chemotherapy, diabetes mellitus, increasing age and institutionalization or acute hospitalization) - nutrient deficiency -insufficient hydration - head trauma - hypothyroidism - heart disease - liver diseases - kidney diseases - malignancies (oral and tongue carcinoma) - ear infection . - patients with neurodegenerative and psychiatric disorders (Parkinson's disease, major depression and Alzheimer disease) - upper respiratory infection - allergic rhinitis, asthma - oral cavity infections (related to the use of dental prostheses, candidiasis) - poor oral hygiene - Burning Mouth Syndrome - smoke

TABLE 2. General characteristics, associated symptoms, associated pathologies of 208 COVID-19 patients.

General characteristics	
Gender	Age (years)
Male 118 (57%)	59 ± 13
Female 90 (43%)	56 ± 16
Days from COVID-19 symptoms onset	4 ± 1
Clinical classification	
MILD 127 (61%)	54±13
Male 62 (4.9%)	53 ± 15
Female 65 (51%)	49 ± 14
MODERATE 81 (39%)	62± 12
Male 56 (69%)	69 ± 11
Female 25 (31%)	66 ± 12
Associated symptoms	
Cough	176 (85%)
Muscle or joint pains	194 (93%)
Stuffy nose	97(46%)
Chest pain	144 (69%)
Fever	196 (94%)
Felt tired	153 (73%)
Problems breathing	66 (80.4%)
Asthenia	185 (89%)
Rhinorrhea	78 (36%)
Headache	102 (49%)
Abdominal symptoms	29 (14%)
Sore throat	131 (63%)
Vomit	59 (28%%)
Nausea	91 (44%)
Diarrhea	31 (152%)
Loss of appetite	159 (76%)
Associated pathologies	
Gastroesophageal reflux disease	101 (48%)
Hypertension	99 (47%)
Thyroid diseases	52 (25%)
Respiratory insufficiency	29 (14%)

TABLE 3. Evaluation of IL-6 values in moderate vs mild patients with qualitative and quantitative taste disorders.

Parameters	**p value**
IL-6 value in moderate vs mild patients	<0.05
Taste quantitative disorders	
IL-6 value in moderate vs mild patients (ageusia)	<0.05
IL-6 value in moderate vs mild patients (hypogeusia-score)	<0.05
Taste quantitative disorders: hypogeusia	
IL-6 value in moderate vs mild patients (sour and salty)	>0.05
IL-6 value in moderate vs mild patients (umami, bitter and sweet)	<0.05
Taste qualitative disorders	
IL-6 value in moderate vs mild patients (parageusia)	<0.05
IL-6 value in moderate vs mild patients (dysgeusia)	>0.05
IL-6 value in moderate mild patienrs (phantogeusia)	>0.05

IL-6: interleukin 6

TABLE 4. Evaluation of mean values IL-6 in moderate vs mild patients with taste disorders (Welch's t-test) and evaluation in moderate vs mild patients with ageusia, parageusia, dysgeusia, phantogeusia, sour, salty, umami, bitter, and sweet disorders (Mann-Whitney's test)

Parameters	**p value**
IL-6 value in moderate vs mild patients	<0.05
Taste quantitative disorders	
IL-6 value in moderate vs mild patients (ageusia)	<0.05
IL-6 value in moderate vs mild patients (hypogeusia-score)	<0.05
Taste qualitative disorders	
IL-6 value in moderate vs mild patients (parageusia)	<0.05
IL-6 value in moderate vs mild patients (dysgeusia)	>0.05
IL-6 value in moderate vs mild patients (phantogeusia)	>0.05
Taste quantitative disorder (hypogeusia)	
IL-6 value in moderate vs mild patients with hypogeusia (sour and salty)	>0.05
IL-6 value in moderate vs mild patients with hypogeusia (umami, bitter and sweet)	<0.05
Mann Whithney test	
Parameters	**p value**
Taste quantitative disorders	
moderate vs mild patients (ageusia)	<0.05
moderate vs mild patients (hypogeusia-score)	<0.05
Taste qualitative disorders	
moderate vs mild patients (parageusia)	<0.05
moderate vs mild patients (dysgeusia)	>0.05
moderate vs mild patients (phantogeusia)	>0.05
Taste quantitative disorder (hypogeusia)	
severe vs mild patients (sour and salty)	<0.05
severe vs mild patients (umami, bitter and sweet)	>0.05

IL-6: interleukin 6

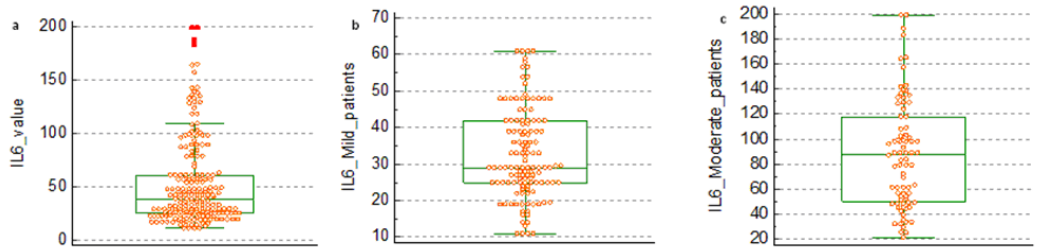

FIGURE 1. Distribution of IL-6: **A**) throughout the selected sample, **B**) in mild patients, **C**) in moderate patients; IL-6: interleukin 6

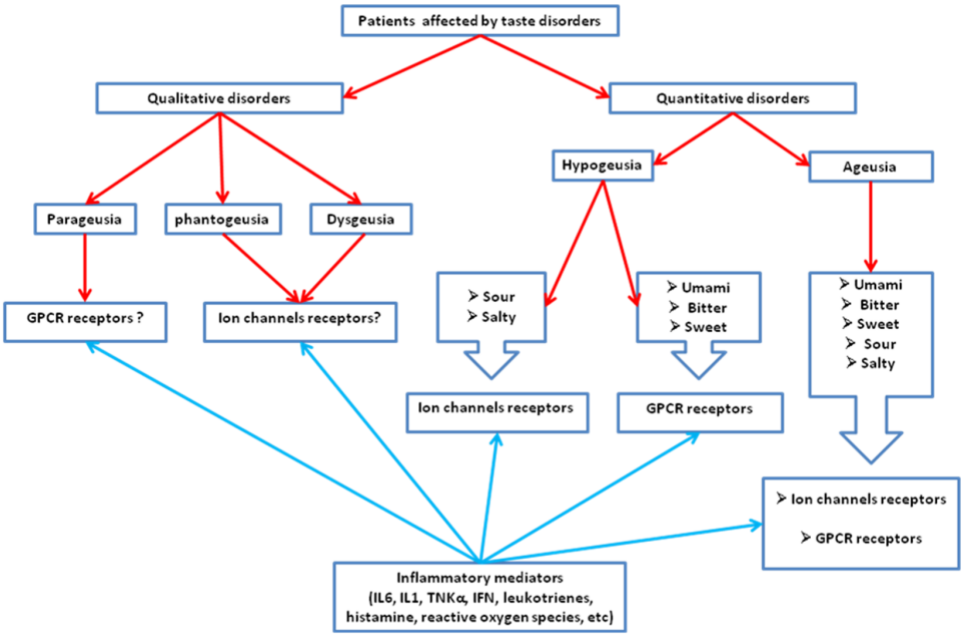

FIGURE 2. Summary scheme of the probable mechanisms of onset of tests disorders (qualitative and quantitative)