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# Anatomophysiological relationships and clinical considerations of tasting and smelling loss in patients with COVID-19

Anatomophysiological relationships of tasting and smelling loss in COVID-19

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**Abstract**

BACKGROUND

There are numerous conflicting discussions about the outbreak of the new coronavirus (COVID-19).

AIM

To present some anatomical and physiological considerations about two of the symptoms reported by patients: the loss or reduction of smell and taste.

METHODS

Since, these symptoms are presented in a peculiar way, with some cases of persistence even after COVID-19. For this, it was searched in three databases, PubMed/MEDLINE, Web of Science and Scopus, using the following keywords: "Smell", "Taste", "Smell AND COVID-19", "Taste AND COVID-19", no publication time restriction, only in English with full text available, excluding also brief communications, letters to the editor, editorials, reviews, comments and conference abstracts.

RESULTS

The search found 776 articles in the database Pubmed/MEDLINE, 1018 in the Web of Science database and 552 in the Scopus database, from which duplicates were removed (104 articles) 17 studies were selected, as they met the eligibility criteria, presenting titles and abstracts lesions in regions of the central nervous system responsible for these senses. This review suggests that viral mechanisms of action may be related to lesions both at the local level and at the level of the central nervous system, lasting up to 3 to 4 wk, considered persistent if it exceeds this period, as reported in one case in this review. There are still few studies about the treatment, among those addressed in this review, only two studies report possible treatments and emphasize the scarcity of data, with the best option being treatments that do not cause harm, such as gustatory and olfactory physiotherapy

CONCLUSION

Given the scarcity of data, this review emphasizes the importance of prevention, through the correct use of personal protective equipment (PPE) by health professionals and respect for local behavioral indications. It is also emphasized, through 5 studies, that there is a predominance of this symptom in patients with COVID-19, which can be a tool to control dissemination, through the early isolation of patients until the results are ready.

**Key Words:** SARS-CoV-2; COVID-19; Coronavirus; Olfactory nerve; Smell; Taste

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**Core Tip:** We discuss the anatomical and physiological considerations about two of the symptoms reported by patients: the loss or reduction of smell and taste. There are still few studies about the treatment, among those addressed in this review, only two studies report possible treatments and emphasize the scarcity of data, with the best option being treatments that do not cause harm, such as gustatory and olfactory physiotherapy. Given the scarcity of data, this review emphasizes the importance of prevention, through the correct use of personal protective equipment (PPE) by health professionals and respect for local behavioral indications. It is also emphasized, through 5 studies, that there is a predominance of this symptom in patients with COVID-19, which can be a tool to control dissemination, through the early isolation of patients until the results are ready.

## INTRODUCTION

In December 2019, in Wuhan (China), the emergence of an acute respiratory syndrome, SARS-CoV-2, caused by the new Coronavirus, with a peculiar and highly contagious behavior, was reported[1]. Thus, the World Health Organization decreed on March 11, 2020, a state of pandemic, considering the condition of community transmission of human infection by the virus[2]. In the current world scenario, there are already approximately 493 million infected and 6.1 million dead. In Brazil, there are approximately 30.1 million infected and 661 thousand dead[2]. Such global and national data are alarming and may be related to the high speed of dissemination, high mortality rate in people with comorbidity and the coping strategies of each country, as well as socioeconomic and health conditions[3,4].

The clinical manifestations of COVID-19 are very varied, the most common symptoms being fever (74%), cough (79%), fatigue (75%), headache (78%), gastrointestinal disorders (57%), loss of smell (63%) and taste (65%). These symptoms, when present, lead to the diagnostic suspicion of COVID-19, until confirmed by exams[5,6]. The sensory pathway of smell is initially given by the nerve endings of the olfactory nerve, the primary olfactory neuron, located in the upper third of the nasal cavity and nasal septum, stimulated by chemical substances from the air that are transformed into action potential[7-9]. This stimulus travels through the primary neuron crossing the cribriform plate of the ethmoid bone through its foramina[8]. Upon accessing the anterior cavity of the skull, they synapse with the secondary neuron. The olfactory nerve impulses terminate in the primary cortical projection area and travel to the thalamus, which proceeds to the orbitofrontal and rectus olfactory gyrus. There is also an association of some odors with the limbic system, causing reactions of pleasure or aversion[8-11] (Figures 1-2).

Taste is provided by the specialized sensitivity of the tongue, *via* the glossopharyngeal nerve (IX cranial nerve) in the posterior third, vagus nerve (X cranial nerve) with few branches at the base of the tongue and epiglottis, and chorda tympani nerve (branch of the VII cranial nerve, the facial-intermediate nerve) in the anterior two thirds of the tongue[7,8]. They receive the stimulus through taste buds that are made up

of epithelial cells that have different receptors for each type of flavor, distributed throughout the tongue[12]. From there, the stimuli travel through the primary afferent fibers of the respective gustatory sensory nerves to the solitary tract in the medulla, then to the thalamus, passing to the cortex[8] (Figures 3-4).

Given this context, research has sought strategies in order to clarify the sensory alterations of loss of smell and taste, the possible mechanism of action of the virus in these nerves and its treatment. Thus, the present study aims to review the anatomy and physiology of the olfactory and gustatory pathways, and their relationship with symptomatology in patients with COVID-19.

## MATERIALS AND METHODS

For this study, 3 databases were searched, PubMed/MEDLINE, Web of Science and Scopus, using the following terms as keywords: "Smell", "Taste", "Smell AND COVID-19", "Taste AND COVID -19", without publication time restriction and only in the English language. Works that present titles and abstracts related to the topic of the initial research were verified, using the variables taste and/or smell and COVID-19. Subsequently, the text was evaluated of the articles previously selected by the abstract. The methodology, results and relevance were considered to list the choice of articles. For inclusion in the research, the articles must necessarily be accessed in their full content. Analysis and synthesis of reflective texts and consistent on the subject (Figure 5).

- Eligibility criteria:

The inclusion criteria were:

Description of changes in smell and taste due to COVID-19;

Human studies;

Publications in English only;

Publications that allow full access to the text.

- The exclusion criteria were:

Articles that have been duplicated;

Animal studies;

When the title was not related to the objective;

There was no loss of taste;

There was no loss of smell;

Other languages (except English);

When access to the full text has not been obtained;

Brief communications, letters to the editor, editorials, reviews, comments and conference abstracts.

## RESULTS

The search found 776 articles in the Pubmed/MEDLINE database, 1018 in the Web of Science database and 552 in the Scopus database, from which duplicates were removed (104 articles), then editorials, review articles were excluded, brief communications, letters to the editor, comments, conference abstracts, articles without full text available or not produced in English, as they are outside the eligibility criteria. Seventeen studies that met the eligibility criteria were selected (Table 1).

## DISCUSSION

The present study aimed to select and evaluate articles that elucidate the anatomophysiological relationships of the olfactory and gustatory pathways with the loss of smell and taste present in the main symptoms in patients with COVID-19[13,14]. This knowledge can help in the therapeutic approach during infection and in persistent post-infection cases, in addition, by giving due relevance to this symptomatology, since there is a high incidence in patients with COVID-19, isolation is possible of patients with this symptomatology, even before the test results, thus decreasing the transmissibility of SARS-CoV-2[13,14].

Among all the articles selected, through the methodology used, the presence of a very variable number of patient samples was found, in addition, there was a variability

in the anatomical structure placed as the focus of the discussion, which were studied and evaluated by different parameters. Six articles[15,18,20,22,23,28] focused on the olfactory and gustatory epithelium as the main responsible for the loss of smell and taste, due to the fact that they have ACE2 receptors, which at the time of the entry of SARS-CoV-2 alter and damage this mucosa, which is unable to act as local chemoreceptors. Eleven articles[13,14,16,17,19,21,24-27,29] in addition to highlighting ACE2 receptors as a gateway, indicate the olfactory pathways as the access pathways to the central nervous system by SARS-CoV-2, due to its neurotropic properties, which intracranially, are capable of injuring regions responsible for these senses.

Some studies conclude that there is a high prevalence of loss of smell and taste in patients with COVID-19, there was a variation in the ages studied and the degree of severity of the patient's disease[13-17], but due to the strong correlation of the symptomatology with the COVID-19 is considered a specific symptom of the disease[13,14]. These symptoms usually resolve in approximately 1 mo[17], however there are cases of persistent loss of smell and taste[18], which was observed by Vaira *et al.*[18], after biopsy of the nasal mucosa, alteration of the olfactory epithelium, which in some places, instead of forming normal tissues, formed metaplastic tissue, which is a possible explanation for the persistence in some cases.

Most articles[13,14,16,17,19,21,24-27,29] highlighted the neurotropic activity of SARS-CoV-2, allowing access and changes in the central nervous system. In the study carried out by Aragão *et al.*[19], a microvascular lesion in the olfactory bulb in a patient with COVID-19 and loss of smell and taste was documented through neuroimaging obtained through Magnetic Resonance Imaging (MRI), demonstrating a possible mechanism of action of the virus in addition to its action on the olfactory epithelium.

The study by Izquierdo-Dominguez *et al.*[30] not included in this study because it is a systematic review, confirms the change in smell and taste due to the presence of ACE2 receptors in the respective mucosa and the fact that SARS-CoV-2 has affinity for these receptors. In addition to these sites, ACE2 can be found in various types of tissues, such as those of the central nervous system, which may also represent one of the causes

of loss of smell and taste, if damaged. Studies that performed the autopsy of patients with COVID-19 and found hyperemic, swollen brain tissue and some sites with degenerated neurons were also discussed in this article, and also detected the presence of SARS-CoV-2 nucleic acid in the cerebrospinal fluid[30].

Among the main questions on the subject, in addition to the cause, as well as its anatomophysiological relationships, of the loss of smell and taste, there are also whether there are possible preventions and what therapeutic measures can be carried out in the treatment in cases of persistent losses. Among the selected articles, there were no reports of possible preventive measures for loss of smell and taste, but Xu *et al*.[31] raise the hypothesis that the use of vitamin D, as it has several independent neuroprotective mechanisms, can generate protection of central and peripheral nervous tissues, through neurotrophins. The authors hypothesize that the neuroprotective potential could prevent the neurological complications of COVID-19[31].

Regarding therapeutic measures, we selected the study by Vaira *et al*.[18] who cites the existence of evidence of the use of steroid rinses and a pilot study with submucosal injection of platelet-rich plasma into the epithelium, obtaining relevant improvement, but studies would still be necessary to reach more significant conclusions and be indicated as a treatment in the future[18]. Kanjanaumpor *et al*.[32], not addressed in our study because it is a systematic review, argues that there is still no significant evidence to recommend any type of pharmacological treatment, however, an interesting therapy for not presenting contraindications, low cost and evidence of improvement, would be olfactory training in cases of patients with persistent loss of smell and taste with COVID-19[32].

About prognosis, Kanjanaumpor *et al*.[32] reveals that between about 32-66% of patients there is spontaneous recovery and that a US study reported improvement in the loss of smell and taste in 74% of infected patients correlating with the overall resolution of clinical symptoms. Jalessi *et al*.[22] mentions recovery of smell in 44.0% of patients in the short term (2 wk) and Vaira *et al*[18] reported that about 66% of patients achieved complete recovery in an average of 19.3 days from the onset of symptoms.

Regarding preventive measures against COVID-19 and its symptoms, such as loss of smell and taste, the importance of using PPE (personal protective equipment) is found in the literature, as in the study by Kim *et al.*[34], that limited access to this equipment (mask, lab coat, new gloves and face shield) was significantly associated with a higher risk of developing symptoms of COVID-19, in addition to being associated with more severe disease, with moderate or severe symptoms[34].

Adequate access to PPE by health professionals, especially those on the front line, is associated with a lower chance of contracting the disease, and even if PPE fails, there is an association with less severe and shorter forms[34].

There are numerous studies in progress, including a study by da Fonseca Orcina *et al.*[36] proposes the therapeutic use of a phthalocyanine-derived mouthwash, as being able to reduce the severity of the disease locally, reducing the viral load in the oral cavity, consequently the clinical symptoms, such as sore throat, cough and mouth ulcers. It can thus also reduce the severity of the general disease, since the oral cavity and oropharynx are important means of dissemination of SARS-CoV-2, thus, reducing the viral load, the dissemination is reduced[35,36]. The authors emphasize the need for more randomized clinical trials for further conclusions[36].

Likewise therapeutic measures in the loss of smell and taste, there are ongoing research testing several drugs, among them, the therapy with sprays and topical rinses based on corticosteroids has obtained good results, in addition to presenting a high safety profile, being appropriate indication for post-infection patients with persistent loss of these senses[37]. However, smell and taste training is the only specific therapy with proven efficacy, although the exact mechanism of action is not known, it is believed that through repeated stimulation there is an increase in the neuroplastic and regenerative capacity of the brain, being an important therapy to be used indicated at first to the patient with a persistent condition[37-39].

There are difficulties in quantifying the prevalence and incidence of gustatory and olfactory dysfunction in the general population, due to causes such as analysis and evaluation methods, sample size and area, and the correct definitions of

dysfunctions[40]. Multicentric research from Europe, in the year 2020, showed interesting data such as that 85.6% of patients with COVID-19 reported olfactory loss. It was also one of the pioneering studies in the identification of taste loss, which at the time was 88.0% in patients with COVID-19. In addition, the manuscript described that infected patients could experience this loss without the presence of other significant symptoms[40].

With the emergence of coronavirus variants, infections caused by Omicron can currently be highlighted, which resulted in mild disease, mainly due to the discovery and use of vaccines. Compared to other strains such as Delta, Omicron infections were more often associated with symptomatology and upper respiratory tract infections, have lower viral loads, less dysregulated immune cell profiles, and lower levels of pro-inflammatory cytokines[41].

A study, through questionnaires, evaluated the clinical profile of patients who developed COVID-19 after full vaccination, in symptomatic patients. The most frequent symptoms were: asthenia (82.4%), chemosensory dysfunction (63.4%), headache (59.5%), coryza (58.2%), muscle pain (54.9%), loss of appetite (54.3%) and nasal obstruction (51.6%). However, 62.3% and 53.6% of survey participants reported olfactory and gustatory dysfunction, respectively. Symptom severity was mild or moderate in almost all cases. Chemosensory dysfunction is still a frequent symptom, even in people who contracted the infection after full vaccination. In this way, the sudden loss of smell and taste may continue to represent a useful and specific diagnostic aid in suspected COVID-19, even in vaccinated individuals[42].

As limitations of this study, one can consider the rapid change in the literature on COVID-19, as well as the emergence of new variants, with different symptoms from the initial versions.

## CONCLUSION

Most of the articles studied pointed as possible anatomophysiological mechanisms, related to the loss of smell and taste, the olfactory and gustatory tissue injured locally

because they have ACE-2 receptors, being the gateway of SARS-CoV-2, as well as tissues of the Central Nervous System related to these senses also injured by the neurotropic capacity of SARS-CoV-2. The duration, in most cases, can extend from 3 to 4 wk, considered persistent after 1 mo.

Therapeutic conducts in persistent cases with better initial results, which could be indicated by the doctor, are the use of steroid-based sprays and rinses and, mainly, the training of the senses of smell and taste. Likewise, the best measure to be taken is prevention, with the correct use of PPE by health professionals, and respect for local health recommendations determined in order to reduce viral spread.

## ARTICLE HIGHLIGHTS

### *Research background*

There are numerous conflicting discussions about the outbreak of the new coronavirus (COVID-19).

### *Research motivation*

Describe the anatomy and physiology relationships of taste and smell losses due to COVID-19

### *Research objectives*

The aim of this review was to present some anatomical and physiological considerations about two of the symptoms reported by patients: the loss or reduction of smell and taste.

### *Research methods*

Since, these symptoms are presented in a peculiar way, with some cases of persistence even after COVID-19. For this, it was searched in three databases, PubMed/MEDLINE, Web of Science and Scopus, using the following keywords: "Smell", "Taste", "Smell AND COVID-19", "Taste AND COVID-19", no publication time restriction, only in

English with full text available, excluding also brief communications, letters to the editor, editorials, reviews, comments and conference abstracts.

***Research results***

The search found 776 articles in the database Pubmed/MEDLINE, 1018 in the Web of Science database and 552 in the Scopus database, from which duplicates were removed (104 articles) 17 studies were selected, as they met the eligibility criteria, presenting titles and abstracts lesions in regions of the central nervous system responsible for these senses. This review suggests that viral mechanisms of action may be related to lesions both at the local level and at the level of the central nervous system, lasting up to 3 to 4 wk, considered persistent if it exceeds this period, as reported in one case in this review. There are still few studies about the treatment, among those addressed in this review, only two studies report possible treatments and emphasize the scarcity of data, with the best option being treatments that do not cause harm, such as gustatory and olfactory physiotherapy

***Research conclusions***

Most of the articles studied pointed as possible anatomophysiological mechanisms, related to the loss of smell and taste, the olfactory and gustatory tissue injured locally because they have ACE-2 receptors, being the gateway of SARS-CoV-2, as well as tissues of the Central Nervous System related to these senses also injured by the neurotropic capacity of SARS-CoV-2. The duration, in most cases, can extend from 3 to 4 wk, considered persistent after 1 mo.

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*Research perspectives*

To be a reference for describing the relationships between the anatomy and physiology of taste and smell losses due to COVID-19

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