

## CONSIDERATIONS ON THE EFFECTS OF TASTE CHANGES CAUSED BY LONG-COVID ON NUTRITION AND ORAL HEALTH

Sorina Mihaela Solomon<sup>1</sup>, Liliana Pasarin<sup>1\*</sup>, Irina Georgeta Sufaru<sup>1 †</sup>, Antonela Maria Beldiman<sup>2 \*</sup>, Monica Mihaela Scutariu<sup>2 †</sup>, Costea Claudia Florida<sup>4 †</sup>, Georgiana Macovei<sup>2 †</sup>

<sup>1</sup> "Grigore T. Popa" U.M.Ph. - Iași, Romania, Faculty of Dentistry, Department 2

<sup>2</sup> "Grigore T. Popa" U.M.Ph. - Iași, Romania, Faculty of Dentistry, Department 3

<sup>3</sup> "Grigore T. Popa" U.M.Ph. - Iași, Romania, Faculty of Dentistry, Department 1

<sup>4</sup> "Grigore T. Popa" U.M.Ph. - Iași, Romania, Faculty of Medicine, Department 7

All authors have the same scientific contribution with the first author and equal rights

Corresponding author; Liliana Pasarin *e-mail*: liliana.pasarin@umfiasi.ro,

Antonela Maria Beldiman *e-mail*: maria.beldiman@umfiasi.ro

Georgiana Macovei

### ABSTRACT

Long-COVID, alternatively referred to as post-COVID syndrome, has garnered significant attention among individuals affected by SARS-CoV-2 as well as healthcare practitioners. The phenomenon began to be perceived as a secondary epidemic that is impacting an increasing number of individuals on a global scale. A notable proportion of individuals who have contracted SARS-CoV-2, including those with mild or moderate symptoms, have reported alterations in their sense of taste subsequent to the resolution of the acute stage of the disease. Patients sometimes report a frequent occurrence of an inability to interpret food tastes in a typical manner or an encounter with distorted taste perceptions. The present state of literature related to oral manifestations associated with long-term COVID-19 is still in the context of ongoing study. The nutritional imbalance observed in individuals with long-COVID syndrome may be attributed to changes in taste and smell, which affect both the quality and quantity of food intake. The changes in taste perception observed in persons suffering with long-COVID involve a complex and significant immune response that has implications for the nutritional and oral health of these patients.

**Key words:** long-Covid, taste changes, nutrition, oral health, ageusia

### INTRODUCTION

Long-COVID is a subject of current significance among individuals who have experienced infection with the SARS-CoV-2 virus, as well as healthcare practitioners. It is currently regarded as a prominent secondary pandemic, affecting a substantial and increasing number of individuals worldwide. [1,2] This syndrome is characterized by the persistence or appearance of symptoms weeks or even months after the initial apparent recovery of patients from acute infection.

Among the varied and persistent symptoms of long-COVID are post-exertional malaise, fatigue, brain fog, dizziness, gastrointestinal symptoms, heart palpitations, thirst, chronic cough, chest pain, postural orthostatic tachycardia syndrome, loss or modifications of smell or taste, [3,4], the last ones having a significant impact on patients' nutrition and oral health.

A considerable proportion of individuals who have contracted SARS-CoV-2, including those with mild or moderate manifestations of

the illness, have reported alterations in their sense of taste. Frequently, patients commonly express an inability to perceive food tastes in a regular manner or an experience of distorted taste perceptions. The occurrence referred to as ageusia has the potential to impact both the enjoyment derived from eating and the choices made in relation to food. Furthermore, the enduring nature of these alterations in taste might result in diminished hunger and modifications in dietary preferences, hence potentially contributing to deficits in essential nutrients and subsequent weight loss. The impact of taste and olfactory changes on oral health and implicitly on general status is considerable. [5]

The sense of taste plays an important part in the discernment of food preferences and the assessment of scents. Alterations in taste perception might lead individuals to avoid certain foods, especially those that are seen as unappetizing or repulsive, so influencing their taste preferences. The presence of taste distortions can potentially affect both the amount of food consumed and the frequency of meals. Individuals who experience the condition may demonstrate a proclivity towards consuming diminished amounts of food or displaying a predisposition for meals that possess intensified sensory characteristics, such as heightened sweetness or saltiness, potentially accompanied by elevated levels of sugar or salt content. The imposition of restrictions has the potential to result in a decrease in the diversity of food choices, consequently affecting an individual's consumption of vital nutrients, such as vitamins and minerals. The modified preferences possess the capacity to increase the vulnerability to dental caries and periodontal conditions, hence affecting the total oral health in the future.

Within the context of this specific framework, it is conceivable that the well-being of patients may be harmed, as the

satisfaction obtained from the act of consuming food is often intricately linked to social relationships and cultural experiences. The potential loss or modification of this specific experience has the potential to contribute to the emergence of emotions such as isolation, anxiety, and depression. Consequently, this may exacerbate the psychological consequences associated with long-COVID as previous studies have identified an increase in symptoms related to anxiety and depression within the initial six months following infection. [6,7,8]

The occurrence of Long-COVID and its association with changes in gustatory perception are significant aspects of the COVID-19 pandemic, with considerable implications for overall health and oral health. Conducting ongoing research is vital for comprehending the fundamental systems accountable for these adjustments and formulating tactics to efficiently manage them. Medical and dental professionals must acquire a comprehensive understanding of the implications associated with prolonged COVID-19 and provide specific suggestions to promote proper nutrition and attain optimal oral health in affected individuals.

The wide range of post-COVID symptoms and the complex profiles of patients who exhibit these symptoms, often requiring multiple treatments for concurrent clinical issues, underscore the necessity of a comprehensive and integrated approach to provide meaningful guidelines for the management and overall well-being of individuals with long-COVID. [9]

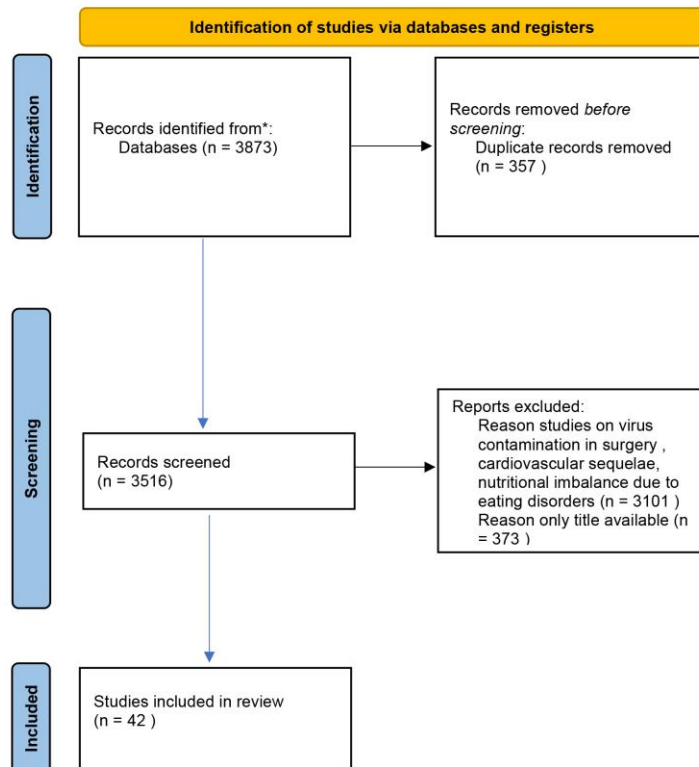
## **MATERIAL AND METHODS**

The review was conducted by searching Pubmed, Science Direct, Google scholar databases for the following keywords: long COVID; long COVID taste modifications on nutritional impact; long COVID and oral health relationship; ageusia and anosmia in long-Covid. We identified a total of 3873

results, in the end 43 studies were part of the study according to guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. [10] Due to low evidence about taste modification and oral implications of nutritional status in Long COVID, we didn't

apply restrictions during literature search regarding date, language of the publications; type of study. Exclusion criteria were studies about virus contamination in surgery, cardiovascular sequelae, nutritional imbalance due to eating disorders.

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71

**Figure 1. PRISMA diagram flow chart**

## RESULTS AND DISCUSSIONS

In the end we arrived at 43 studies regarding our review objective after the elimination of 357 duplicate studies, 3101 studies which matched the exclusion criteria, 373 studies only with the title available and the authors couldn't be contacted due to lack of contact information. The study-selection flowchart is illustrated in Figure 1.

### Discussions

Due to the complex aspects of long-

COVID, taste changes and oral health we considered it necessary to discuss oral symptoms in the context of long-COVID, taste perception, retro nasal olfaction and long-COVID in the context of oral health, nutritional imbalance in long-Covid due to changes in taste and oral health, strategies patients can adopt to cope with taste changes and maintain adequate nutritional status oral health and a good quality of life.

### Oral symptoms in long-Covid

The infectious disease known as Coronavirus disease (COVID-19) is mostly caused by the SARS-CoV-2 virus. In the context of infection, the prevailing symptoms typically include fever, tiredness, and a dry cough. In addition to more prevalent symptoms, there are several less frequently observed manifestations of the condition, including the production of sputum, headache, hemoptysis, diarrhea, anorexia, sore throat, chest discomfort, chills, as well as nausea and vomiting, olfactory and taste loss or modifications. There is a subset of the population who have contracted COVID-19 and, regardless of their hospitalization status, persist in experiencing symptoms. The previously mentioned enduring consequences are commonly referred to as long COVID. [11,12]

The syndrome referred to as long COVID initially attracted considerable interest within online support communities before subsequently getting recognition within scientific and medical communities. The underlying causes of this syndrome are not fully understood, as it occurs in individuals who had previously recovered from COVID-19 over a range of disease severity as a multi organ syndrome. [13]

The phenomenon commonly referred to as long COVID lacks a definitive and accurate characterization. However, a multitude of studies consistently report fatigue and dyspnea as the prevailing symptoms that linger for an extended duration after the acute phase of COVID-19. These symptoms have been seen to persist for several months. Furthermore, there are persistent symptoms that continue to manifest, such as cognitive and mental impairments, thoracic and joint discomfort, palpitations, muscle pain, disturbances in the sense of smell and taste, coughing, headaches, as well as gastrointestinal and cardiac issues. Multiple descriptions of long COVID have been

previously proposed, with the prevailing definition indicating the continuation of symptoms for a period more three months after the initial manifestation of symptoms. [14,15]

The prevalence of extended COVID in a substantial number of individuals presents a significant global health challenge for society. [16, 17]

According to research findings, those with mild-to-moderate cases of COVID-19, including younger patients who did not require respiratory support, hospitalization, or intensive care, are also susceptible to the disease's long-term effects. Long-COVID can also affect individuals who have been discharged from the hospital and no longer test positive for SARS-CoV-2, as well as those receiving outpatient care. [18,19,20] Moreover, it is worth noting that long-COVID affects children as well, even those who experienced asymptomatic COVID-19. This condition manifests in several symptoms, including dyspnea, fatigue, myalgia, cognitive impairments, headache, palpitations, and chest discomfort, which last for a minimum duration starting of 3 months and more than 6 months. [14, 2, 21]

The existing knowledge regarding oral symptoms linked to COVID-19 is still inadequate and lacks uniformity. Common types of oral lesions encompass erosions, ulcers, maculae, petechiae, as well as modifications in the tongue, lips, and gingiva. [22,23,24] The oral cavity has been shown to exhibit primary indicators and manifestations of Covid-19. These include a potential association with oral pathologies, as well as the possible underlying mechanisms of hyperinflammation that indicate an interaction between Covid-19 and oral illnesses. It is observed that the appearance of lesions aligns with simultaneous impairment of taste and smell. [25] Covid-19 can cause loss of taste (ageusia), diminished taste

sensitivity (hypogeusia), and confused taste perception (dysgeusia). Other oral manifestations include glossitis, white-coated tongue, mucositis, erythema, mucosal plaques, and desquamation, petechiae, pustules, blisters, vesicles, macula, hyperpigmentation, aphthous stomatitis, gingivitis, necrotizing periodontal disease, parotitis or sialadenitis, hyposalivation, xerostomia, trigeminal neuralgia, facial tingling, temporomandibular joint abnormalities, candidiasis, burning mouth, or pruritus may also occur. [26]

Hyposalivation has been observed to worsen many pre-existing oral cavity disorders in individuals who have previously contracted COVID-19. The affinity of SARS-CoV-2 for nerve cells has been noted, and there exists a theoretical hypothesis positing that the recurrence of anosmia and ageusia may be attributed to sensory neuron destruction. [27] The patient's inflammatory response may result in impaired secretory function of the salivary glands and reduced facial muscle tone, which can be related to neuronal damage. [28]

Interestingly, ageusia during the acute phase is associated with sex, myalgia and arthralgia, while ageusia in the post-acute phase is associated with sex, females being more affected. [29]

All these manifestations mentioned above can lead to changes in nutritional status due to associated phenomena that limit an optimal nutrition of the patient.

#### **Taste perception, retronasal olfaction and long-COVID in the context of oral health**

The taste changes associated with long-COVID are a complex and still poorly understood phenomenon involving multiple biochemical and neurological mechanisms. A decrease in taste sensitivity to a total loss of flavour may occur after SARS-CoV-2 infection. Although the specific mechanisms

are still being studied, viral attack on taste and olfactory receptors and central nervous system effect are thought to cause these changes. [30,31]

One mechanism of the major ways SARS-CoV-2 can affect the sense of taste is by binding to the angiotensin-converting enzyme 2 receptor, which is present on the surface of epithelial cells in the oral and nasal cavity. This allows the virus to enter cells and trigger inflammatory reactions. These inflammations can affect taste receptors located on taste buds on the tongue as well as olfactory cells in the nasal mucosa. This can disrupt signals sent to the brain, leading to changes in taste perception. The biochemical mechanisms involved in these changes include excessive production of inflammatory cytokines, which can directly affect taste cells. Inflammation can also lead to destruction or degradation of support cells around taste receptors, disrupting their normal functioning. In addition, damage to blood vessels and blood flow in the head and neck area can influence cell signalling within taste and olfactory receptors. [32]

In addition to these factors, the central nervous system plays an essential part in taste perception. The signals generated by taste buds and olfactory cells are transmitted through the cranial nerves to the brain, more precisely to the taste and olfactory nuclei in the cerebral cortex. SARS-CoV-2 infection can interfere with these signals, altering how the brain interprets tastes and aromas. Also, the impact of the virus on neurons and neural connections can disrupt the integration and processing of taste and olfactory signals in the brain.

Another way the virus can affect taste perception is by involving the immune system. The exaggerated immune response to infection can contribute to chronic inflammation and imbalances in the local environment of taste receptors, interfering

with how they detect and transmit taste signals to the brain. [33]

However, there are studies that assert that the aetiology of anosmia is not primarily attributed to neurological factors, despite its classification as a neurological condition. It has been observed that the sensory neurons responsible for detecting and transmitting olfactory signals to the brain are not susceptible to SARS-CoV-2. Rather, the gene associated with this function is expressed in the epithelial cells of the nasal cavity. Consequently, it has been postulated that this factor is the primary aetiology of anosmia in individuals afflicted with COVID-19. In relation to symptoms of ageusia, there has been a proposition that the gene expressed by the epithelium of the nasal cavity, which acts as a cellular receptor for SARS-CoV-2, is also widely expressed in the mucous membrane of the oral cavity, namely on the tongue. SARS-CoV-2 chemosensitivity is linked to the salivary mucin's sialic acid receptor, which protects taste buds' glycoproteins that transmit gustatory chemicals. Consequently, this interaction results in an elevated gustatory threshold, ultimately leading to the manifestation of ageusia. [34 -37]

Retronasal olfaction refers to the physiological mechanism via which smells are detected via inhalation, afterwards reaching the nasal cavity and so impacting the perception of taste. The transportation of flavours from food occurs during the processes of mastication and deglutition, wherein they are subsequently conveyed to the olfactory mucosa located at the upper region of the nasal cavity via the retronasal pathway. The interplay between flavours and tastes is of utmost importance in shaping individual food preferences and crafting the overall gastronomic encounter. Within the framework of the COVID-19 pandemic, it has been observed that the SARS-CoV-2 virus

has the capacity to impact the senses of smell and taste, hence exerting notable implications on the overall state of oral health. Anosmia, which refers to the loss of the sense of smell, and ageusia, which refers to the loss of the sense of taste, are characteristic symptoms associated with infection. [38] How frequent complications of long covid also occur mentally symptoms [39], the underlying symptoms have a greater impact on food preferences and the consumption of vital nutrients for dental and overall health.

Alterations in gustatory and olfactory perception have the potential to influence dietary choices, resulting in a preference for foods that are rich in sugar and sodium content. This inclination towards such food items might have adverse consequences for oral health. There might also be a proclivity to abstain from consuming meals that were previously deemed unappetizing as a result of taste distortions. These modifications have the potential to impact the nutritional value and elevate the susceptibility to dental caries and periodontal diseases. Furthermore, the deprivation or modification of the gustatory and olfactory senses might have an impact on interpersonal relationships and the overall satisfaction derived from the act of consuming food. This particular factor has the potential to influence the mental well-being of the individual, leading to the development of stress, anxiety, and depression. Consequently, these psychological conditions can subsequently damage oral health by causing a decrease in or inconsistent compliance to oral hygiene practices.

#### **Nutritional imbalance in long-Covid due to changes in taste and oral health**

In current literature, there are not many references about nutritional status in long-Covid, further research is needed, but there is proof of a high prevalence of malnutrition post-Covid especially in severe forms of the

disease

The potential causes of inadequate nutritional status among individuals with COVID-19 may stem from various variables, including inflammation, and increased respiratory muscle effort, [40] taste and smell modifications.

The nutritional imbalance in long-COVID syndrome could result also from alterations in taste and smell, encompasses both qualitative and quantitative aspects. This multifaceted matter carries substantial implications for the overall health of affected individuals. Alterations in gustatory and olfactory perception have the potential to elicit modified food choices or the avoidance of specific food items, hence leading to disturbances in the consumption of vital nutrients.

The qualitative imbalance is evidenced by the tendency to select processed foods that are high in sugar or salt content, as a means to compensate for alterations in taste perception. Insufficient consumption of vital nutrients may result in inadequate intake and heighten the susceptibility to metabolic diseases. Simultaneously, the act of abstaining from the consumption of nutritious foods, such as fruits and vegetables, can result in the development of deficits in essential nutrients.

The quantitative imbalance manifests itself through a reduction in food consumption as a result of diminished appetite caused by alterations in taste and smell perception. This phenomenon can lead to a reduction in calorie intake and subsequent weight loss, so exerting a direct influence on the immune system. The body's capacity to mount an efficient response to inflammation and infection may be compromised as a result of nutritional abnormalities.

This condition has the potential to exert significant effects on both general health and dental health. The use of processed and sugar-rich meals in large quantities has the potential

to negatively impact oral health, hence elevating the susceptibility to dental problems such as cavities. Furthermore, it should be noted that the immunological state can be impacted by dietary imbalance, specifically due to insufficiency in vital nutrients such as vitamins C, D, zinc. This shortage can have significant implications on the immune response and the body's capacity to combat inflammation and infections.

The presence of a nutritional imbalance has the potential to sustain the symptoms associated with long-COVID in conjunction with response already triggered by the former contact with virus itself, the immune response may cause these enduring symptoms by supporting an ongoing inflammatory process [41] and facilitate the reactivation of pre-existing diseases via its anti-inflammatory function. Chronic inflammation may arise due to insufficient consumption of antioxidants and natural anti-inflammatory compounds. This phenomenon has the potential to impede the process of recuperation and sustain the manifestation of symptoms such as fatigue and weakness.

When considering this intricate matter, seeking guidance from qualified nutrition experts and formulating individualized dietary strategies can significantly contribute. The adoption of a well-balanced diet that guarantees sufficient nutrient intake has the potential to contribute to the maintenance of overall health and oral well-being, while also enhancing the resilience of the immune system. Therefore, it has the potential to enhance the recuperation of individuals suffering from long-COVID and mitigate the adverse effects of taste and olfactory alterations on their well-being.

The Long-COVID condition, along with its associated comorbidities, namely MIS-A and MIS-C, poses a significant issue within the medical profession. The presence of pre-existing medical conditions can increase the

vulnerability of both adult and paediatric patients with COVID-19 to adverse consequences, not only during the acute phase of SARS-CoV-2 infection but also in the subsequent period. The aforementioned factors has the potential to exert a substantial influence on the well-being and overall quality of life of individuals suffering from long-COVID, in addition to imposing a considerable economic strain. [2,42,43]

**What can be done? Strategies patients can adopt to cope with taste changes and maintain adequate nutritional status**

Despite the existence of several guidelines pertaining to the management of long-COVID, a significant practical gap persists, with a lack of comprehensive assessment on specific therapeutic options. Optimizing therapeutic results necessitates the consideration of patient safety as well as the enhancement of advanced diagnosis and holistic assessment. [44]

From our point of view, we may suggest that patients experiencing taste alterations due long-COVID, have the option to employ specific measures aimed at enhancing nutritional quality and ensuring adequate nutrient consumption, but it is important to approach these modifications in a knowledgeable manner and embrace adaptable strategies in order to uphold optimal well-being and mitigate the risk of additional difficulties.

One strategy could be food diversity. The act of engaging in the exploration of novel flavours, textures, and combinations of food has the potential to assist individuals in mitigating the effects of partial taste loss. The incorporation of natural spices the potential to enhance the perception of flavour sensations. Moreover, the incorporation of aromatic plants and citrus fruits in culinary practices can effectively enhance the taste and visual appeal of dishes.

An additional approach involves

meticulous observation of the visual aesthetics of food. The aesthetically pleasing arrangement of culinary preparations has the potential to elicit an inclination to partake in food consumption, even in instances when the flavours have been modified. Incorporating a diverse range of hues and employing creative techniques in the presentation of culinary creations can serve as a means to engage and captivate individuals' attention towards gastronomy.

The adaptation of food texture is also an important aspect. Foods exhibiting diverse textures, such as those characterized by crispness or smoothness, possess the ability to elicit both tactile and gustatory experiences, so partially mitigating the diminished sensitivity to taste. Furthermore, the act of avoiding foods that possess excessive dryness or hardness can effectively enhance the process of consuming, particularly in instances where there may be a potential decline in saliva production.

Regarding oral hygiene, the consistent practice of an impeccable oral hygiene contributes to the preservation of oral well-being. When individuals experience changes in their taste perceptions, the utilization of toothpastes with fragrances that are both refreshing and agreeable might help diminish the discomfort associated with maintaining dental hygiene. Additionally, it is crucial to consider the promotion of saliva production, since it serves a vital function in the detection and transmission of olfactory and gustatory stimuli.

Specialized counselling, in addition to seeking advice from a registered nutritionist or dental professional, can offer individualized support in effectively addressing alterations in taste perception. Developing a well-rounded dietary regimen that prioritizes the consumption of nutrient-dense foods, including those abundant in key nutrients such as protein, vitamins, and

minerals, can effectively facilitate adequate nutritional intake in the face of altered taste

perceptions.

## CONCLUSIONS

1. Consequently, the alterations in gustatory perception witnessed in individuals affected by long-COVID encompass a multifaceted and noteworthy immunological expression that carries ramifications for the nutritional and dental well-being of these patients. The alterations in gustatory perception have the potential to impact dietary preferences and decisions related to nutrition, often resulting in a decrease in the consumption of vital nutrients. The potential consequences of this situation may have adverse impacts on both the immune system's functionality and the body's ability to heal, while also potentially leading to the development or worsening of nutritional deficiencies.
2. Alterations in taste perception have the potential to indirectly impact the dental health of individuals suffering with long COVID. Taste problems have the potential to induce alterations in food choices, leading to heightened consumption of processed or sugar-laden meals. Consequently, this heightened consumption may contribute to an elevated susceptibility to oral diseases, such as dental caries. It is important to note that nutritional deficiencies have the potential to impact the state of oral tissues and the process of wound healing, thereby playing a role in the emergence of periodontal disorders and other oral conditions.
3. Therefore, while managing individuals suffering with long COVID, it is imperative to adopt a multidisciplinary and holistic approach that involves the evaluation of taste alterations, nutritional

state, and dental health. The establishment of a collaborative relationship between medical and dental health specialists is necessary in order to effectively recognize and tackle these interrelated concerns. The implementation of a well-balanced dietary regimen, according to the individual's health condition, together the maintenance of proper oral hygiene, are crucial elements in enhancing the overall well-being and facilitating the recuperation process in instances of long COVID.

4. As research advances, a holistic methodology that integrates information from the disciplines of biochemistry, neurology, immunology, and genetics has the potential to offer enhanced understanding of these intricate mechanisms. This finding has the potential to facilitate the advancement of individualized treatment and intervention approaches aimed at mitigating taste alterations in individuals suffering from long COVID. Therefore, a more profound comprehension of these pathways can facilitate the development of efficacious therapies and enhance the quality of life for patients impacted by these notable alterations in taste perception.
5. Future therapeutic and research prospects for long-COVID taste changes in oral health is an area of potential for development, given the magnitude of the impact of these changes on the quality of life and health of affected patients.

## REFERENCES

- 1 Perumal R, Shunmugam L, Naidoo K, Abdool Karim SS, Wilkins D, Garzino-Demo A, Brechot C, Parthasarathy S, Vahlne A, Nikolich JŽ. Long COVID: a review and proposed visualization of the complexity of long COVID. *Front Immunol.* 2023 Apr 20;14:1117464. doi: 10.3389/fimmu.2023.1117464. PMID: 37153597; PMCID: PMC10157068.
- 2 Stafie CS, Solomon SM, Sufaru IG, Manaila M, Stafie II, Melinte G, Simionescu B, Leustean L. Pathogenic Connections in Post-COVID Conditions: What Do We Know in the Large Unknown? A Narrative Review. *Viruses.* 2022 Jul 30;14(8):1686. doi: 10.3390/v14081686. PMID: 36016309; PMCID: PMC9413998.
- 3 Yelin D, Moschopoulos CD, Margalit I, Gkrania-Klotsas E, Landi F, Stahl JP, Yahav D. ESCMID rapid guidelines for assessment and management of long COVID. *Clin Microbiol Infect.* 2022 Jul;28(7):955-972. doi: 10.1016/j.cmi.2022.02.018. Epub 2022 Feb 17. PMID: 35182760; PMCID: PMC8849856
- 4 Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol.* 2023 Mar;21(3):133-146. doi: 10.1038/s41579-022-00846-2. Epub 2023 Jan 13. Erratum in: *Nat Rev Microbiol.* 2023 Jun;21(6):408. PMID: 36639608; PMCID: PMC9839201
- 5 Alenazy MF, Aljohar HI, Alruwaili AR, Daghestani MH, Alonazi MA, Labban RS, El-Ansary AK, Balto HA. Gut Microbiota Dynamics in Relation to Long-COVID-19 Syndrome: Role of Probiotics to Combat Psychiatric Complications. *Metabolites.* 2022 Sep 27;12(10):912. doi: 10.3390/metabo12100912. PMID: 36295814; PMCID: PMC9611210.
- 6 Dugan C, Popescu BO, Părlătescu I, Dobre M, Milanese E, Popa C. Clinical And Psychological Impact Of Sars-Cov-2 Infection In Burning-Mouth Syndrome Patients: A Comparative Study, *Romanian Journal of Oral Rehabilitation* ,Vol. 14, No.2 April-June 2022,p 15-25,
- 7 Zawilska JB, Kuczyńska K. Psychiatric and neurological complications of long COVID. *J Psychiatr Res.* 2022 Dec;156:349-360. doi: 10.1016/j.jpsychires.2022.10.045. Epub 2022 Oct 20. PMID: 36326545; PMCID: PMC9582925.
- 8 Kubota T, Kuroda N, Sone D. Neuropsychiatric aspects of long COVID: A comprehensive review. *Psychiatry Clin Neurosci.* 2023 Feb;77(2):84-93. doi: 10.1111/pcn.13508. Epub 2022 Dec 12. PMID: 36385449; PMCID: PMC10108156.]
- 9 Conti V, Corbi G, Sabbatino F, De Pascale D, Sellitto C, Stefanelli B, Bertini N, De Simone M, Liguori L, Di Paola I, De Bernardo M, Tesse A, Rosa N, Pagliano P, Filippelli A. Long COVID: Clinical Framing, Biomarkers, and Therapeutic Approaches. *J Pers Med.* 2023 Feb 15;13(2):334. doi: 10.3390/jpm13020334. PMID: 36836568; PMCID: PMC9959656.]
- 10 Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* 2021, 372, n71.
- 11 Hu B, Guo H, Zhou P, Shi ZL. Characteristics of SARS-CoV-2 and COVID-19. *Nat Rev Microbiol* 2021; 19: 141-154 doi: 10.1038/s41579-020-00459-7]
- 12 World Health Organization. Coronavirus disease (COVID-19). URL: [https://www.who.int/health-topics/coronavirus#tab=tab\\_1](https://www.who.int/health-topics/coronavirus#tab=tab_1) [data accesării, iunie 2023]],
- 13 Stefanou MI, Palaiodimou L, Bakola E, Smyrnis N, Papadopoulou M, Paraskevas GP, Rizos E, Boutati E, Grigoriadis N, Krogias C, Giannopoulos S, Tsiodras S, Gaga M, Tsiygoulis G. Neurological manifestations of long-COVID syndrome: a narrative review. *Ther Adv Chronic Dis.* 2022 Feb 17;13:20406223221076890. doi: 10.1177/20406223221076890. PMID: 35198136; PMCID: PMC8859684.
- 14 Yong SJ. Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments. *Infect Dis (Lond).* 2021 Oct;53(10):737-754. doi: 10.1080/23744235.2021.1924397. Epub 2021 May 22. PMID: 34024217; PMCID: PMC8146298.
- 15 Carfi A, Bernabei R, Landi F; Gemelli against COVID-19 Post-Acute Care Study Group . Persistent symptoms in patients after acute COVID-19. *JAMA.* 2020;324(6):603-605.

- 16 Briggs A, Vassall A. Count the cost of disability caused by COVID-19. *Nature*. 2021;593:502–5.
- 17 Koc HC, Xiao J, Liu W, Li Y, Chen G. Long COVID and its Management. *Int J Biol Sci*. 2022 Jul 11;18(12):4768-4780. doi: 10.7150/ijbs.75056. PMID: 35874958; PMCID: PMC9305273.
- 18 Dennis A, Wamil M, Alberts J, et al.. Multiorgan impairment in low-risk individuals with post-COVID-19 syndrome: a prospective, community-based study. *BMJ Open*. 2021;11(3):e048391, Miyazato Y, Morioka S, Tsuzuki S, et al.. Prolonged and late-onset symptoms of coronavirus disease 2019. *Open Forum Infect Dis*. 2020;7(11):ofaa507.
- 19 van den Borst B, et al.. Comprehensive health assessment three months after recovery from acute COVID-19. *Clin Infect Dis*. 2020;ciaa1750.
- 20 Townsend L, Dowds J, O'Brien K, et al.. Persistent poor health post-COVID-19 is not associated with respiratory complications or initial disease severity. *Ann Am Thorac Soc*. 2021. DOI: 10.1513/AnnalsATS.202009-1175OC.
- 21 Suárez-Robles M, Iguaran-Bermúdez MDR, García-Klepizg JL, Lorenzo-Villalba N, Méndez-Bailón M. Ninety days post-hospitalization evaluation of residual COVID-19 symptoms through a phone call check list. *Pan Afr Med J*. 2020;37:289.
- 22 Temneanu OR, Popescu MR,\*, Otilia Novac O, Barbacariu L, Pohaci-Antonesei LS, Șerban R, Simionescu B, Manole LM. Oral Mucosa Lesions In Children With Sars-Cov-2, *Romanian Journal of Oral Rehabilitation*, Vol. 15, No.2 April-June 2023, p 379-387
- 23 Di Spirito F, Iandolo A, Amato A, Caggiano M, Raimondo A, Lembo S, Martina S. Prevalence, Features and Degree of Association of Oral Lesions in COVID-19: A Systematic Review of Systematic Reviews. *Int J Environ Res Public Health*. 2022 Jun 18;19(12):7486. doi: 10.3390/ijerph19127486. PMID: 35742735; PMCID: PMC9224460.
- 24 Martu MA, Maftai GA, Sufaru IG, Jelihovschi I, Luchian I, Hurjui L, Martu I, Pasarin L. COVID-19 and periodontal disease – ethiopathogenic and clinical implications, *Romanian Journal of Oral Rehabilitation* Vol. 12, No. 4, October - December 2020, 116-124
- 25 Brandini DA, Takamiya AS, Thakkar P, Schaller S, Rahat R, Naqvi AR. Covid-19 and oral diseases: Crosstalk, synergy or association? *Rev Med Virol*. 2021 Nov;31(6):e2226. doi: 10.1002/rmv.2226. Epub 2021 Mar 1. PMID: 33646645; PMCID: PMC8014590.
- 26 Marchesan JT, Warner BM, Byrd KM. The "oral" history of COVID-19: Primary infection, salivary transmission, and post-acute implications. *J Periodontol*. 2021 Oct;92(10):1357-1367. doi: 10.1002/JPER.21-0277. Epub 2021 Sep 7. PMID: 34390597; PMCID: PMC9374061.
- 27 Vaira L.A., Salzano G., Deiana G., de Riu G. Anosmia and Ageusia: Common Findings in COVID-19 Patients. *Laryngoscope*. 2020;130:1787. doi: 10.1002/lary.28692
- 28 Alenazy MF, Aljohar HI, Alruwaili AR, Daghestani MH, Alonazi MA, Labban RS, El-Ansary AK, Balto HA. Gut Microbiota Dynamics in Relation to Long-COVID-19 Syndrome: Role of Probiotics to Combat Psychiatric Complications. *Metabolites*. 2022 Sep 27;12(10):912. doi: 10.3390/metabo12100912. PMID: 36295814; PMCID: PMC9611210.
- 29 Algahtani SN, Alzarroug AF, Alghamdi HK, Algahtani HK, Alsawina NB, Bin Abdulrahman KA. Investigation on the Factors Associated with the Persistence of Anosmia and Ageusia in Saudi COVID-19 Patients. *Int J Environ Res Public Health*. 2022 Jan 18;19(3):1047. doi: 10.3390/ijerph19031047. PMID: 35162068; PMCID: PMC8834158.
- 30 Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, Cook JR, Nordvig AS, Shalev D, Sehrawat TS, Ahluwalia N, Bikdeli B, Dietz D, Der-Nigoghossian C, Liyanage-Don N, Rosner GF, Bernstein EJ, Mohan S, Beckley AA, Seres DS, Choueiri TK, Uriel N, Ausiello JC, Accili D, Freedberg DE, Baldwin M, Schwartz A, Brodie D, Garcia CK, Elkind MSV, Connors JM, Bilezikian JP, Landry DW, Wan EY. Post-acute COVID-19 syndrome. *Nat Med*. 2021 Apr;27(4):601-615. doi: 10.1038/s41591-021-01283-z. Epub 2021 Mar 22. PMID: 33753937; PMCID: PMC8893149.
- 31 Alkodaymi MS, Omrani OA, Fawzy NA, Shaar BA, Almamlouk R, Riaz M, Obeidat M, Obeidat Y, Gerberi D, Taha RM, Kashour Z, Kashour T, Berbari EF, Alkattan K, Tleyjeh IM. Prevalence of post-acute COVID-19 syndrome symptoms at different follow-up periods: a systematic review and meta-analysis. *Clin Microbiol Infect*. 2022 May;28(5):657-666. doi: 10.1016/j.cmi.2022.01.014.

- Epub 2022 Feb 3. PMID: 35124265; PMCID: PMC8812092.
- 32 Narayanan SN, Shivappa P, Padiyath S, Bhaskar A, Li YW, Merghani TH. The Prevalence and Pathophysiology of Chemical Sense Disorder Caused by the Novel Coronavirus. *Front Public Health*. 2022 Jun 6;10:839182. doi: 10.3389/fpubh.2022.839182. PMID: 35734755; PMCID: PMC9207763.
- 33 Javed N, Ijaz Z, Khair AH, Dar AA, Lopez ED, Abbas R, Sheikh AB. COVID-19 loss of taste and smell: potential psychological repercussions. *Pan Afr Med J*. 2022 Sep 21;43:38. doi: 10.11604/pamj.2022.43.38.31329. PMID: 36505013; PMCID: PMC9716963.
- 34 Brann D.H., Tsukahara T., Weinreb C., Lipovsek M., Van Den Berge K., Gong B., Chance R., Macaulay I.C., Chou H.-J., Fletcher R.B., et al. Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. *Sci Adv*. 2020;6:eabc5801. doi: 10.1126/sciadv.abc5801.
- 35 Okada Y., Yoshimura K., Toya S., Tsuchimochi M. Pathogenesis of Taste Impairment and Salivary Dysfunction in COVID-19 Patients. *Jpn. Dent. Sci. Rev*. 2021;57:111–122. doi: 10.1016/j.jdsr.2021.07.001.
- 36 Vaira L.A., Salzano G., Fois A.G., Piombino P., De Riu G. Potential Pathogenesis of Ageusia and Anosmia in COVID-19 Patients. *Int. Forum Allergy Rhinol*. 2020;10:1103–1104. doi: 10.1002/alr.22593.
- 37 Algahtani SN, Alzarroug AF, Alghamdi HK, Algahtani HK, Alsywina NB, Bin Abdulrahman KA. Investigation on the Factors Associated with the Persistence of Anosmia and Ageusia in Saudi COVID-19 Patients. *Int J Environ Res Public Health*. 2022 Jan 18;19(3):1047. doi: 10.3390/ijerph19031047. PMID: 35162068; PMCID: PMC8834158.
- 38 Boscolo-Rizzo P, Hummel T, Invitto S, Spinato G, Tomasoni M, Emanuelli E, Tofanelli M, Cavicchia A, Grill V, Vaira LA, Lechien JR, Borsetto D, Polesel J, Dibattista M, Menini A, Hopkins C, Tirelli G. Psychophysical assessment of olfactory and gustatory function in post-mild COVID-19 patients: A matched case-control study with 2-year follow-up. *Int Forum Allergy Rhinol*. 2023 Feb 28. doi: 10.1002/alr.23148. Epub ahead of print. PMID: 36852674.
- 39 Huerne K, Filion KB, Grad R, Ernst P, Gershon AS, Eisenberg MJ. Epidemiological and clinical perspectives of long COVID syndrome. *Am J Med Open*. 2023 Jun;9:100033. doi: 10.1016/j.ajmo.2023.100033. Epub 2023 Jan 18. PMID: 36685609; PMCID: PMC9846887
- 40 de Blasio F, Scalfi L, Castellucci B, Sacco AM, Berlingieri GM, Capitelli L, Alicante P, Sanduzzi A, Bocchino M. Poor Nutritional Status and Dynapenia Are Highly Prevalent in Post-Acute COVID-19. *Front Nutr*. 2022 Jun 3;9:888485. doi: 10.3389/fnut.2022.888485. PMID: 35719154; PMCID: PMC9205211
- 41 Ramakrishnan RK, Kashour T, Hamid Q, Halwani R, Tleyjeh IM. Unraveling the Mystery Surrounding Post-Acute Sequelae of COVID-19. *Front Immunol*. 2021 Jun 30;12:686029. doi: 10.3389/fimmu.2021.686029. PMID: 34276671; PMCID: PMC8278217
- 42 Akbarialiabad H, Taghrir MH, Abdollahi A, Ghahramani N, Kumar M, Paydar S, Razani B, Mwangi J, Asadi-Pooya AA, Malekmakan L, Bastani B. Long COVID, a comprehensive systematic scoping review. *Infection*. 2021 Dec;49(6):1163–1186. doi: 10.1007/s15010-021-01666-x. Epub 2021 Jul 28. PMID: 34319569; PMCID: PMC8317481
- 43 Solmi M, Estradé A, Thompson T, Agorastos A, Radua J, Cortese S, et al. Physical and mental health impact of COVID-19 on children, adolescents, and their families: The Collaborative Outcomes study on Health and Functioning during Infection Times - Children and Adolescents (COH-FIT-C&A). *J Affect Disord*. 2022 Feb 15;299:367–376. doi: 10.1016/j.jad.2021.09.090. Epub 2021 Oct 2. PMID: 34606810; PMCID: PMC8486586
- 44 Koc HC, Xiao J, Liu W, Li Y, Chen G. Long COVID and its Management. *Int J Biol Sci*. 2022 Jul 11;18(12):4768–4780. doi: 10.7150/ijbs.75056. PMID: 35874958; PMCID: PMC9305273.