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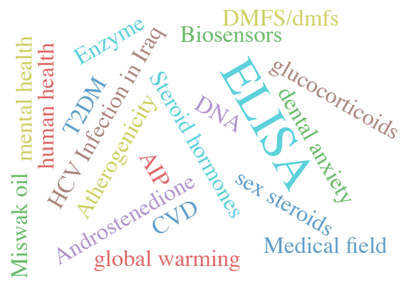

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Make a Submission

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Focus & Scope

Indexing

Author Guidelines

Peer Review Process

Author Fees

Publication Ethics

Open Access Statement

Plagiarism Policy

Special Issues

Archiving

Contact

Gmail

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Inbox 278

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39 of 906

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Dr. Muhannad Z. khalifa <ASJMS@alsalam.edu.iq>
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Sun, Sep 28, 2025, 5:11 PM

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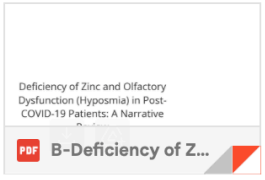

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to me, Velycia, Fauzan, Ibnu, Nany, Emad

Thu, Jan 15, 5:14 AM

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Our decision is to: Accept Submission

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Deficiency of Zinc and Olfactory Dysfunction (Hyposmia) in Post-COVID-19 Patients: A Narrative Review

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ABSTRACT: Olfactory dysfunction is among the most common and specific symptoms of COVID-19, persisting in a significant proportion of patients as part of post-acute sequelae of SARS-CoV-2 infection (PASC). Zinc (Zn), an essential micronutrient, has been implicated in immune modulation, neuroregeneration, and olfactory function. Zn deficiency may contribute to the persistence of hyposmia after COVID-19. This review evaluates the role of Zn deficiency in post-COVID-19 olfactory dysfunction and examines the evidence for Zn supplementation as a therapeutic option. The study is a sort of narrative review, wherein articles indexed on PubMed, Scopus, and Google Scholar between 2019 and 2025 are searched for any relation between zinc and changes in smell perception during COVID-19. A number of articles show that individuals with low blood zinc levels are at a high risk of developing anosmia and changes in taste perception. The molecular explanation for this could be the differential expression of zinc transporters in the olfactory mucosa. There are also clinical trials that show that taking zinc, with steroids or without, accelerates recovery of smell disturbances during COVID-19. However, the evidence is not uniform, with no consensus on the nature of the zinc supplement regimen. It appears that zinc deficiency is indeed a risk factor for post-COVID anosmia, but zinc treatment may show promise but requires further rigorous trials for its true efficacy.

Keywords: Olfactory dysfunction, COVID-19, zinc deficiency, hyposmia, anosmia

1. INTRODUCTION

Ever since the outbreak of SARS-CoV-2 in late 2019, it has been triggering COVID-19 infections, impacting millions of people across the world. Though for most people, it was an acute phase infection leading to symptoms of respiratory distress, another symptom that quickly emerged and remains most distinctive for COVID-19 infection has been that of an impaired sense of smell, leading to anosmia and hyposmia [1-3]. In fact, for many patients, this symptom has persisted into what has been termed “Long COVID” and has impaired these patients’ normal lives, leading to decreased appetite, changes in food tastes, and mental health issues like anxiety and depression. Yet, despite this dawning realization, much remains unclear regarding the underlying cause and ideal treatments for this particular symptom too [4]. Zinc, an important trace mineral, plays critical roles in boosted immunities, skin and mucosal repair, and nerve impulses transduction too [2].

Prior to this pandemic, an important underlying cause for chemosensory disorders, including those impacting a person’s sense of smell and taste, was already known for this mineral: zinc deficiency [5],[6]. Recent research suggests that changes in Zn balance during and after SARS-CoV-2 infection may lead to persistent olfactory loss [7]. Several clinical studies have shown that zinc supplementation, alone or in combination with corticosteroids, may accelerate recovery of olfactory function in post-COVID-19 patients [8], [9].

This article is a narrative review synthesizing current evidence on the association between Zn deficiency and olfactory dysfunction in post-COVID-19 patients. Literature searches were conducted in the PubMed, Scopus, and Google Scholar databases. The search strategy combined the keywords “COVID-19,” “post-COVID,” “long COVID,” “olfactory dysfunction,” “hyposmia,” “anosmia,” and “zinc.”

Articles published between 2019 and 2025 were considered. Eligible studies included observational studies, clinical trials, molecular and transcriptomic studies, and relevant English-language review articles. Studies on olfactory dysfunction unrelated to COVID-19 or that did not discuss Zn homeostasis were excluded.

A total of 89 articles were identified, and 10 studies were included in the final narrative synthesis based on relevance, methodological quality, and contribution to understanding Zn-related mechanisms or therapeutic implications for post-COVID-19 olfactory dysfunction.

2. DEFINITION AND CLASSIFICATION OF OLFACTORY DISORDERS

Olfactory disorders are conditions in which a person experiences a reduction or loss of the ability to detect, identify, or evaluate odors. Olfactory disorders can be categorized into several types based on their characteristics: anosmia, the complete loss of smell; hyposmia, a partial reduction in olfactory sensitivity; parosmia, the distorted perception of odors; and phantosmia, the perception of odors in the absence of an external stimulus [10].

Etiologically, olfactory disorders can be classified into two categories: conductive and sensorineural. Conductive disorders result from physical blockages of airflow that prevent odor molecules from reaching the olfactory epithelium, such as in rhinitis, sinusitis, or nasal polyps. Sensorineural olfactory disorders arise from injury to the olfactory epithelium, disruption of the olfactory nerve pathways, or abnormalities in the brain areas involved in odor perception. Within the context of the SARS-CoV-2 virus, the loss of the sense of smell, particularly when the nasal passages are not congested, emerged as one of the earliest as well as most prevalent symptoms. Olfactory dysfunction, in the sense of smelling, appears in about two-thirds to over four-fifths of the population who have been affected by the SARS-CoV-2 virus. However, while many patients recovered their sense of smell in a short while, many have been left grappling with the problem for weeks or months following their recovery [11].

Recently, experts have proposed a classification of the SARS-CoV-2-related loss of the sense of smell as transient versus persistent depending upon its duration. This classification may reflect the underlying molecular differences, including the regulation of the zinc quotient in the smell-sensing epithelium [12].

Genetic studies have indicated that UGT2A1 and UGT2A2 are genes that could influence a person’s susceptibility to smell loss related to COVID-19. Therefore, in the assessment of olfactory dysfunction following a case of COVID, it is important to not only consider the duration and intensity of the symptoms, but also genetic susceptibility and nutritional factors, such as zinc levels, among others [12].

3. EPIDEMIOLOGY OF OLFACTORY DYSFUNCTION IN POST-COVID-19 SYNDROME

ssues related to smell (and taste) are some of the most common symptoms experienced by patients with late sequelae of SARS-CoV-2 infections. The World Health Organization defined “post-COVID-19 syndrome” as conditions that occur within 3 months of initial detection, persist for 2 months or more, but do not result from another diagnosis. The prevalence of patients complaining of smell and taste disorders after contracting COVID-19 is great, ranging from 10% to more than 80% of patients, depending on variables such as study populations, types of COVID-19, time of follow-up, among others. In this regard, some of the observation rates by various researches include those by Badahdah et al. (2022), which showed a prevalence of 15.3% of patients suffering from anosmia or ageusia, which affects younger patients as well as those whose conditions are not severe.

Studies have found in long-term follow-ups that the loss of smell is one of the most prevalent and persistent symptoms exhibited by patients during long COVID. In a retrospective study conducted by Matsuoka et al. (2023), impaired olfactory perception was among the most frequently experienced problems at or beyond the 12th week, alongside exhaustion and taste disturbances. There was, however, some level of recovery; however, patients continue to experience a number of deficits.

A meta-analysis that pooled data from over 9,000 patients revealed one in four people experienced a lack of sense of smell, and 16% had persistent taste disturbance symptoms six months following the initial illness. While many patients experienced improvement in the first few weeks, a significant proportion persisted for six months or longer, with some patients extending past a year [13].

Factors that contributed to the long-term impairment of the sense of smell included female sex, young age, less severe illness, and less systemic inflammatory symptoms, indicating that the extent of illness does not solely influence the long-term recovery of the affected sense in patients.

4. PATHOPHYSIOLOGICAL MECHANISMS UNDERLYING OLFACTORY DYSFUNCTION IN COVID-19

Loss of olfaction associated with SARS-CoV-2 may present without the typical symptoms of the upper or lower respiratory tracts. Indeed, various mechanisms are at play here: direct damage to the olfactory epithelium due to the virus or the inflammatory response; the inflammatory process at the level of the entire organism; alterations at the biochemical level [14].

The pathogenic process begins when SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptor and the transmembrane serine protease TMPRSS2, both abundantly expressed in the sustentacular and basal cells of the olfactory epithelium. Although olfactory sensory neurons lack ACE2 expression, infection of these supporting cells disrupts the local microenvironment, altering mucus composition, inducing metabolic stress, and compromising the structural and trophic support required for normal odor transduction. In parallel, local and systemic immune activation stimulates macrophages, neutrophils, and central nervous system glial cells, including astrocytes and microglia. This immune activation promotes a cytokine-mediated inflammatory response characterized by the release of mediators such as IL-1, IL-2, IL-6, TNF-α, and IFN-γ, which further contribute to olfactory dysfunction [15].

. These cytokines have a damaging effect on tissue, inhibiting the regeneration of olfactory neurons, and can extend to the central nervous system, particularly to the olfactory bulb and brainstem, as illustrated in Figure 1, which provides a systematic explanation of this path mechanism [16].

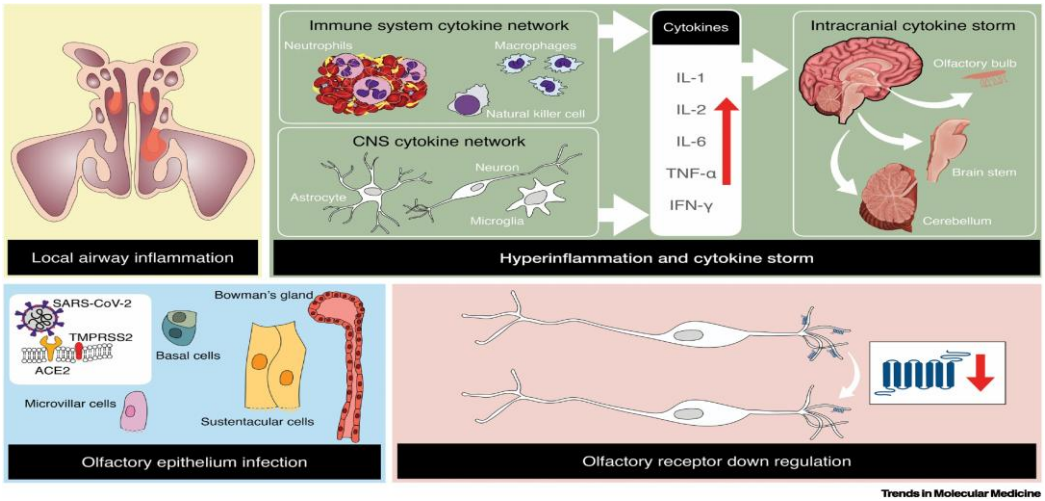

FIGURE 1. - Pathophysiological mechanisms underlying olfactory dysfunction in COVID-19 [16]

SARS-CoV-2 enters sustentacular and basal cells of the olfactory epithelium via ACE2 and transmembrane serine protease 2 (TMPRSS2) receptors, leading to epithelial injury and disruption of olfactory neuronal support. Subsequent local and systemic inflammation leads to the release of cytokines (IL-1, IL-6, TNF-α, IFN-γ), oxidative stress, and hinders neuronal regeneration. Disrupted zinc homeostasis worsens neuroinflammation and delays olfactory recovery, leading to persistent olfactory dysfunction in post-COVID-19 cases.

This reduction of olfactory protein further aggravates the condition, particularly during the recovery phase, along with epigenetics changes, which contributes to oxidative stress. If neglected, patients with post-COVID-19 may be left with chronic hyposmia or parosmia.

In conclusion, the issue of olfactory problems related to COVID-19 involves both peripheral pathologies and central neuroinflammation, such as olfactory receptor dysfunction and systemic immune reactions, and this is as complex as that can be!

5. ZINC (Zn) AND OLFACTORY FUNCTION

Zinc has several essential roles in our body, and these include enzymatic reactions, immune functions, maintenance of epithelial barriers, and neurotransmission. It comes second after iron regarding concentration in our bodies; however, it lacks a zinc pool; that is, we `require constant dietary intake.' Only a small percentage of this zinc concentration exists in our plasma.

The zinc level in the body is regulated by essentially two families of transporters, SLC30 (ZnT) that transports zinc from cells and SLC39 (ZIP) that imports zinc into cells. Imbalances in this well-regulated homeostasis appear as various disorders, including obesity, cardiovascular diseases, and even in some medications, ACE inhibitors and thiazide diuretics.

Immunologically, the roles of zinc include the development of the immune system, the proliferation of lymphocytes, and antiviral function. In additional roles, the regulation of zinc finger proteins, such as the ZCCHC3 protein, is involved in the recognition of viral RNA and the interferon alpha signaling pathway. There are some experimental reports indicating that zinc can inhibit the function of SARS-CoV RNA polymerase and modulate ACE2 expression. Moreover, beyond its immune functions, zinc also supports the integrity of the olfactory epithelium and the functioning of the sensory neurons. Even a temporary deficiency of zinc, which commonly occurs during certain systemic infections, has been correlated with decreased alkaline phosphatase expression in taste and olfactory neurons, changes in salivary zinc-binding proteins, and nervous damage [11-14].

New transcriptomic analyses also suggest an abnormal relationship between metallothioneins and the loss of smell post-COVID-19. Thus, an underlying mechanism for the relation between abnormal zinc homeostasis and slower recovery in the sense of smell becomes apparent. In conclusion, the recovery of function in COVID-19 also incorporates the essential role of zinc in the prevention of viral infections, as postulated by [11].

With this background, increasing understanding of the protective function of zinc against disruption of the olfactory epithelia and zinc's involvement in neural function can further suggest a trial of zinc supplement therapy for the odor impairment aftermath of COVID-19 infection. The following section will review human studies related to zinc treatments and their application in managing symptoms long term [14].

6. THERAPEUTIC ROLE OF ZINC SUPPLEMENTATION

There has been growing interest in the use of zinc supplementation as a possible therapy for those with olfactory dysfunction, including those with post-COVID-19 hyposmia, as more patients exhibit persistent sensory symptoms. A few studies have observed an association between low zinc concentrations and olfactory dysfunction. For example, Abdelmaksoud et al. (2021) observed that Egyptian COVID-19 patients with low serum zinc concentrations were significantly more likely to develop anosmia, suggesting that the symptom of smell loss is likely a result of a conditional zinc deficiency.

In a contrasting observation, Tsuchiya et al. (2022) failed to identify any significant difference between patients with associated changes in smell and taste patterns and those who were unaffected regarding their serum zinc concentrations, suggesting that the relationship may differ according to population or stage of illness. In further support of a biological relationship is a molecular biology observation by Lupi et al. (2023) that there were changes in the expression patterns for a series of genes associated with zinc within the olfactory epithelium for patients with persistent anosmia, suggesting a relationship with immune effector functions and local neuronal repair. [15].

Zinc supplements have been studied as an intervention for taste and smell disorders associated with infection. For example, in the clinical experiment, Chiang and Jiang (2024) demonstrated that taking 10 mg zinc gluconate three times daily, along with low-dose prednisone, resulted in significant improvement in smell sensation from one to four months, with more than 90% of patients experiencing an increase in their UPSIT-TC scores. Additionally, the review by Tsuchiya (2023) evaluated the efficacy of polaprezinc containing approximately 17 mg zinc daily, with positive outcomes regardless of the route, which could be oral or topical.

In Japan, among others, Kogure et al. (2025) have found polaprezinc and zinc-containing herbal medicines to be among those most often used to treat patients with chemosensory impairment due to Long-COVID. In addition, Finzi & Harrington (2021) propose, taking into account retrospective experiences, a possible shortening of mild symptoms of COVID-19, such as hyposmia, by sublingual zinc, which is not as yet proved by clinical tests [16, 17].

In addition, there is supporting data from descriptive and follow-up researches. Matsuda et al. (2023) and Matsuoka et al. (2023) found that the incidence of low zinc (hypozincemia) was higher in patients suffering persistent dysgeusia and hyposmia, and a tendency towards its relationship with longer disease courses was found. These trials did not examine the use of zinc treatment, but the relationship of zinc biochemical levels and the symptom of dysgeusia and/or hyposmia in the post-COVID scenario is strongly suggested [18].

Propper further proposed that any difficulties with smell and taste in COVID-19 patients might also indicate zinc deficiency, citing precedent from biological study. Taken in total, although not all of the evidence supports a causative relationship, the evidence suggests that zinc supplementation, particularly for those with hypozincemia, might alleviate recovery time for smell dysfunction following a COVID-19 infection [19], see table (1).

Table 1. - Overview of the previous study

No	Title	Author	Method	Subject	Zn Dose	Result
1	A study on SARS-CoV-2 infected patients with measured serum Zn levels during home care	Tsuchiya et al. (2022)	Observational, cross-sectional	102 COVID-19 patients in Japan	No supplementation was given; only Zn levels were checked.	Zn concentrations were lower in patients with pneumonia; however, no significant differences were observed between those with and without hyposmia or ageusia, or between younger and older patients [10].
2	Olfactory disturbances as presenting manifestation among Egyptian patients with COVID-19: possible role of Zn	Abdelmaksoud et al. (2021)	Cross-sectional	134 COVID-19 patients in Egypt	No supplementation was given, only correlation of serum Zn levels	A significant association exists between low serum Zn levels and olfactory disturbances, as patients with anosmia exhibit substantially lower Zn concentrations than those without anosmia ($p < 0.001$). [11].
3	Persistent and transient olfactory deficits in COVID-19 are associated to inflammation and Zn homeostasis	Lupi et al. (2023)	Observational + analysis RNA-seq + IHC	24 anosmic COVID-19 patients, compared to controls and patients with rapid recovery	No supplementation given; focus on Zn homeostasis analysis	Persistent anosmia group showed Zn gene dysregulation (SLC39A8, metallothionein); supporting a role for Zn in olfactory mucosal neuroregeneration [12].
4	Effect of oral Zn and steroids on long COVID hyposmia and hypogeusia	Chiang & Jiang (2024)	Retrospective, pre-post test	71 long COVID patients in Taiwan (Omicron), 2–4 months follow-up	Zn gluconate 10 mg TID + Prednisone 10 mg BID for 1–4 months	At the 10-month follow-up, 91.2% of patients demonstrated improved olfactory function, as evidenced by a significant increase in UPSIT-TC test scores. [14].
5	Symptomatic characteristics of hypozincemia detected in long COVID patients	Matsuda et al. (2023)	Observational descriptive	24 long COVID patients with hypoxemia	No supplementation given; focus on symptom evaluation	The main symptoms of hypozincemia include fatigue, dysgeusia, depression, and muscle pain; hyposmia is not predominant. Dysgeusia is a common symptom of Zn deficiency [15].

6	Symptom profile of patients with post-COVID-19 conditions and influencing factors for recovery	Matsuoka et al. (2023)	Six-month longitudinal survey	414 post-COVID-19 patients in Japan	No explicit Zn supplementation was given	Dysgeusia and hyposmia are more common in patients with hypozincemia. Low Zn levels are significantly associated with longer-lasting symptoms [13].
7	Treatment of Long Coronavirus Disease in Japan: A Nationwide Study of Symptom-Associated Drug Prescriptions	Kogure et al. (2025)	National data-based retrospective study	3,769 long COVID patients out of 652,016 cases	No dosage is specified; polaprezinc and kampo are most commonly prescribed for olfactory disorders.	Polaprezinc and Zn-rich herbal formulas are the most frequently prescribed medications for smell/taste disorders in long-term COVID-19. This reflects Zn's potential in the recovery of post-COVID-19 hyposmia [20].
8	Treatments of COVID-19-associated taste and saliva secretory disorders	Tsuchiya H. (2023)	Narrative review	-	Polaprezinc 75 mg/day (equivalent to 17 mg Zn) is used in practice	Zn supplementation, specifically polaprezinc, has been reported to be beneficial in accelerating the recovery of salivary and olfactory disorders following COVID-19. Topical and oral Zn use has been highlighted as an effective therapeutic approach [17].
9	Zn treatment of outpatient COVID-19: A retrospective review	Finzi E & Harrington A,	Retrospective, observational	28 outpatients with COVID-19. Sublingual Zn therapy of 23–150 mg/day was given during the infection.	Sublingual Zn 23–150 mg/day (dose varies between patients), given during the acute phase of infection.	80% of patients improved within 4 days. There was no significant worsening of symptoms. The placebo effect was not confirmed due to the lack of a control group. Sublingual Zn may help speed recovery in mild COVID-19. Randomized clinical trials are needed for validation [18].
10	Smell/Taste alteration in COVID-19 may reflect zinc deficiency. Journal of clinical biochemistry and nutrition	Propper (2021)	Review / Hypothesis	Hypothesis based on previous studies	Not available	Hyposmia/taste alteration can be due to Zn deficiency [19].

7. CONCLUSIONS

Olfactory disturbances, particularly hyposmia and anosmia, are among the most prevalent and clinically relevant manifestations of post-COVID-19 syndrome. Accumulating evidence suggests that insufficient zinc availability may contribute to the persistence of olfactory impairment by impairing epithelial repair, promoting inflammatory responses in neural tissue, and disrupting zinc-dependent molecular pathways in the olfactory mucosa.

From a clinical perspective, assessment of zinc level can provide valuable information regarding patients who are left with a decreased sense of smell despite COVID-19 infection, especially those with risk factors for zinc deficiency. Thus, zinc supplementation therapy can also be recommended as an adjunct therapy, along with proven therapies such as corticosteroids despite the lack of consistent support from available evidence.

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CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

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Deficiency of Zinc and Olfactory Dysfunction (Hyposmia) in Post-COVID-19 Patients: A Narrative Review

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ABSTRACT: Olfactory dysfunction is among the most common and specific symptoms of COVID-19, persisting in a significant proportion of patients as part of post-acute sequelae of SARS-CoV-2 infection (PASC). Zinc (Zn), an essential micronutrient, has been implicated in immune modulation, neuroregeneration, and olfactory function. Zn deficiency may contribute to the persistence of hyposmia after COVID-19. This review evaluates the role of Zn deficiency in post-COVID-19 olfactory dysfunction and examines the evidence for Zn supplementation as a therapeutic option. The study is a sort of narrative review, wherein articles indexed on PubMed, Scopus, and Google Scholar between 2019 and 2025 are searched for any relation between zinc and changes in smell perception during COVID-19. A number of articles show that individuals with low blood zinc levels are at a high risk of developing anosmia and changes in taste perception. The molecular explanation for this could be the differential expression of zinc transporters in the olfactory mucosa. There are also clinical trials that show that taking zinc, with steroids or without, accelerates recovery of smell disturbances during COVID-19. However, the evidence is not uniform, with no consensus on the nature of the zinc supplement regimen. It appears that zinc deficiency is indeed a risk factor for post-COVID anosmia, but zinc treatment may show promise but requires further rigorous trials for its true efficacy.

Keywords: Olfactory dysfunction, COVID-19, zinc deficiency, hyposmia, anosmia

1. INTRODUCTION

Ever since the outbreak of SARS-CoV-2 in late 2019, it has been triggering COVID-19 infections, impacting millions of people across the world. Though for most people, it was an acute phase infection leading to symptoms of respiratory distress, another symptom that quickly emerged and remains most distinctive for COVID-19 infection has been that of an impaired sense of smell, leading to anosmia and hyposmia [1-3]. In fact, for many patients, this symptom has persisted into what has been termed “Long COVID” and has impaired these patients’ normal lives, leading to decreased appetite, changes in food tastes, and mental health issues like anxiety and depression. Yet, despite this dawning realization, much remains unclear regarding the underlying cause and ideal treatments for this particular symptom too [4]. Zinc, an important trace mineral, plays critical roles in boosted immunities, skin and mucosal repair, and nerve impulses transduction too [2].

Prior to this pandemic, an important underlying cause for chemosensory disorders, including those impacting a person’s sense of smell and taste, was already known for this mineral: zinc deficiency [5],[6]. Recent research suggests that changes in Zn balance during and after SARS-CoV-2 infection may lead to persistent olfactory loss [7]. Several clinical studies have shown that zinc supplementation, alone or in combination with corticosteroids, may accelerate recovery of olfactory function in post-COVID-19 patients [8], [9].

This article is a narrative review synthesizing current evidence on the association between Zn deficiency and olfactory dysfunction in post-COVID-19 patients. Literature searches were conducted in the PubMed, Scopus, and Google Scholar databases. The search strategy combined the keywords “COVID-19,” “post-COVID,” “long COVID,” “olfactory dysfunction,” “hyposmia,” “anosmia,” and “zinc.”

Articles published between 2019 and 2025 were considered. Eligible studies included observational studies, clinical trials, molecular and transcriptomic studies, and relevant English-language review articles. Studies on olfactory dysfunction unrelated to COVID-19 or that did not discuss Zn homeostasis were excluded.

A total of 89 articles were identified, and 10 studies were included in the final narrative synthesis based on relevance, methodological quality, and contribution to understanding Zn-related mechanisms or therapeutic implications for post-COVID-19 olfactory dysfunction.

2. DEFINITION AND CLASSIFICATION OF OLFACTORY DISORDERS

Olfactory disorders are conditions in which a person experiences a reduction or loss of the ability to detect, identify, or evaluate odors. Olfactory disorders can be categorized into several types based on their characteristics: anosmia, the complete loss of smell; hyposmia, a partial reduction in olfactory sensitivity; parosmia, the distorted perception of odors; and phantosmia, the perception of odors in the absence of an external stimulus [10].

Etiologically, olfactory disorders can be classified into two categories: conductive and sensorineural. Conductive disorders result from physical blockages of airflow that prevent odor molecules from reaching the olfactory epithelium, such as in rhinitis, sinusitis, or nasal polyps. Sensorineural olfactory disorders arise from injury to the olfactory epithelium, disruption of the olfactory nerve pathways, or abnormalities in the brain areas involved in odor perception. Within the context of the SARS-CoV-2 virus, the loss of the sense of smell, particularly when the nasal passages are not congested, emerged as one of the earliest as well as most prevalent symptoms. Olfactory dysfunction, in the sense of smelling, appears in about two-thirds to over four-fifths of the population who have been affected by the SARS-CoV-2 virus. However, while many patients recovered their sense of smell in a short while, many have been left grappling with the problem for weeks or months following their recovery [11].

Recently, experts have proposed a classification of the SARS-CoV-2-related loss of the sense of smell as transient versus persistent depending upon its duration. This classification may reflect the underlying molecular differences, including the regulation of the zinc quotient in the smell-sensing epithelium [12].

Genetic studies have indicated that UGT2B7 and UGT2A2 are genes that could influence a person’s susceptibility to smell loss related to COVID-19. Therefore, in the assessment of olfactory dysfunction following a case of COVID, it is important to not only consider the duration and intensity of the symptoms, but also genetic susceptibility and nutritional factors, such as zinc levels, among others [12].

3. EPIDEMIOLOGY OF OLFACTORY DYSFUNCTION IN POST-COVID-19 SYNDROME

ssues related to smell (and taste) are some of the most common symptoms experienced by patients with late sequelae of SARS-CoV-2 infections. The World Health Organization defined “post-COVID-19 syndrome” as conditions that occur within 3 months of initial detection, persist for 2 months or more, but do not result from another diagnosis. The prevalence of patients complaining of smell and taste disorders after contracting COVID-19 is great, ranging from 10% to more than 80% of patients, depending on variables such as study populations, types of COVID-19, time of follow-up, among others. In this regard, some of the observation rates by various researches include those by Badahdah et al. (2022), which showed a prevalence of 15.3% of patients suffering from anosmia or ageusia, which affects younger patients as well as those whose conditions are not severe.

Studies have found in long-term follow-ups that the loss of smell is one of the most prevalent and persistent symptoms exhibited by patients during long COVID. In a retrospective study conducted by Matsuoka et al. (2023), impaired olfactory perception was among the most frequently experienced problems at or beyond the 12th week, alongside exhaustion and taste disturbances. There was, however, some level of recovery; however, patients continue to experience a number of deficits.

A meta-analysis that pooled data from over 9,000 patients revealed one in four people experienced a lack of sense of smell, and 16% had persistent taste disturbance symptoms six months following the initial illness. While many patients experienced improvement in the first few weeks, a significant proportion persisted for six months or longer, with some patients extending past a year [13].

Factors that contributed to the long-term impairment of the sense of smell included female sex, young age, less severe illness, and less systemic inflammatory symptoms, indicating that the extent of illness does not solely influence the long-term recovery of the affected sense in patients.

4. PATHOPHYSIOLOGICAL MECHANISMS UNDERLYING OLFACTORY DYSFUNCTION IN COVID-19

Loss of olfaction associated with SARS-CoV-2 may present without the typical symptoms of the upper or lower respiratory tracts. Indeed, various mechanisms are at play here: direct damage to the olfactory epithelium due to the virus or the inflammatory response; the inflammatory process at the level of the entire organism; alterations at the biochemical level [14].

The pathogenic process begins when SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptor and the transmembrane serine protease TMPRSS2, both abundantly expressed in the sustentacular and basal cells of the olfactory epithelium. Although olfactory sensory neurons lack ACE2 expression, infection of these supporting cells disrupts the local microenvironment, altering mucus composition, inducing metabolic stress, and compromising the structural and trophic support required for normal odor transduction. In parallel, local and systemic immune activation stimulates macrophages, neutrophils, and central nervous system glial cells, including astrocytes and microglia. This immune activation promotes a cytokine-mediated inflammatory response characterized by the release of mediators such as IL-1, IL-2, IL-6, TNF-α, and IFN-γ, which further contribute to olfactory dysfunction [15].

. These cytokines have a damaging effect on tissue, inhibiting the regeneration of olfactory neurons, and can extend to the central nervous system, particularly to the olfactory bulb and brainstem, as illustrated in Figure 1, which provides a systematic explanation of this path mechanism [16].

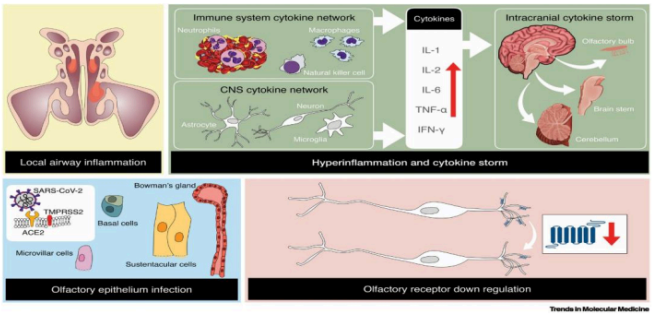

FIGURE 1. - Pathophysiological mechanisms underlying olfactory dysfunction in COVID-19 [16]

SARS-CoV-2 enters sustentacular and basal cells of the olfactory epithelium via ACE2 and transmembrane serine protease 2 (TMPRSS2) receptors, leading to epithelial injury and disruption of olfactory neuronal support. Subsequent local and systemic inflammation leads to the release of cytokines (IL-1, IL-6, TNF-α, IFN-γ), oxidative stress, and hinders neuronal regeneration. Disrupted zinc homeostasis worsens neuroinflammation and delays olfactory recovery, leading to persistent olfactory dysfunction in post-COVID-19 cases.

This reduction of olfactory protein further aggravates the condition, particularly during the recovery phase, along with epigenetics changes, which contributes to oxidative stress. If neglected, patients with post-COVID-19 may be left with chronic hyposmia or parosmia.

In conclusion, the issue of olfactory problems related to COVID-19 involves both peripheral pathologies and central neuroinflammation, such as olfactory receptor dysfunction and systemic immune reactions, and this is as complex as that can be!

5. ZINC (Zn) AND OLFACTORY FUNCTION

Zinc has several essential roles in our body, and these include enzymatic reactions, immune functions, maintenance of epithelial barriers, and neurotransmission. It comes second after iron regarding concentration in our bodies; however, it lacks a zinc pool; that is, we `require constant dietary intake.' Only a small percentage of this zinc concentration exists in our plasma.

The zinc level in the body is regulated by essentially two families of transporters, SLC30 (ZnT) that transports zinc from cells and SLC39 (ZIP) that imports zinc into cells. Imbalances in this well-regulated homeostasis appear as various disorders, including obesity, cardiovascular diseases, and even in some medications, ACE inhibitors and thiazide diuretics.

Immunologically, the roles of zinc include the development of the immune system, the proliferation of lymphocytes, and antiviral function. In additional roles, the regulation of zinc finger proteins, such as the ZCCHC3 protein, is involved in the recognition of viral RNA and the interferon alpha signaling pathway. There are some experimental reports indicating that zinc can inhibit the function of SARS-CoV RNA polymerase and modulate ACE2 expression. Moreover, beyond its immune functions, zinc also supports the integrity of the olfactory epithelium and the functioning of the sensory neurons. Even a temporary deficiency of zinc, which commonly occurs during certain systemic infections, has been correlated with decreased alkaline phosphatase expression in taste and olfactory neurons, changes in salivary zinc-binding proteins, and nervous damage [11-14].

New transcriptomic analyses also suggest an abnormal relationship between metallothioneins and the loss of smell post-COVID-19. Thus, an underlying mechanism for the relation between abnormal zinc homeostasis and slower recovery in the sense of smell becomes apparent. In conclusion, the recovery of function in COVID-19 also incorporates the essential role of zinc in the prevention of viral infections, as postulated by [11].

With this background, increasing understanding of the protective function of zinc against disruption of the olfactory epithelia and zinc's involvement in neural function can further suggest a trial of zinc supplement therapy for the odor impairment aftermath of COVID-19 infection. The following section will review human studies related to zinc treatments and their application in managing symptoms long term [14].

6. THERAPEUTIC ROLE OF ZINC SUPPLEMENTATION

There has been growing interest in the use of zinc supplementation as a possible therapy for those with olfactory dysfunction, including those with post-COVID-19 hyposmia, as more patients exhibit persistent sensory symptoms. A few studies have observed an association between low zinc concentrations and olfactory dysfunction. For example, Abdelmaksoud et al. (2021) observed that Egyptian COVID-19 patients with low serum zinc concentrations were significantly more likely to develop anosmia, suggesting that the symptom of smell loss is likely a result of a conditional zinc deficiency.

In a contrasting observation, Tsuchiya et al. (2022) failed to identify any significant difference between patients with associated changes in smell and taste patterns and those who were unaffected regarding their serum zinc concentrations, suggesting that the relationship may differ according to population or stage of illness. In further support of a biological relationship is a molecular biology observation by Lupi et al. (2023) that there were changes in the expression patterns for a series of genes associated with zinc within the olfactory epithelium for patients with persistent anosmia, suggesting a relationship with immune effector functions and local neuronal repair. [15].

Zinc supplements have been studied as an intervention for taste and smell disorders associated with infection. For example, in the clinical experiment, Chiang and Jiang (2024) demonstrated that taking 10 mg zinc gluconate three times daily, along with low-dose prednisone, resulted in significant improvement in smell sensation from one to four months, with more than 90% of patients experiencing an increase in their UPSIT-TC scores. Additionally, the review by Tsuchiya (2023) evaluated the efficacy of polaprezinc containing approximately 17 mg zinc daily, with positive outcomes regardless of the route, which could be oral or topical.

In Japan, among others, Kogure et al. (2025) have found polaprezinc and zinc-containing herbal medicines to be among those most often used to treat patients with chemosensory impairment due to Long-COVID. In addition, Finzi & Harrington (2021) propose, taking into account retrospective experiences, a possible shortening of mild symptoms of COVID-19, such as hyposmia, by sublingual zinc, which is not as yet proved by clinical tests [16, 17].

In addition, there is supporting data from descriptive and follow-up researches. Matsuda et al. (2023) and Matsuoka et al. (2023) found that the incidence of low zinc (hypozincemia) was higher in patients suffering persistent dysgeusia and hyposmia, and a tendency towards its relationship with longer disease courses was found. These trials did not examine the use of zinc treatment, but the relationship of zinc biochemical levels and the symptom of dysgeusia and/or hyposmia in the post-COVID scenario is strongly suggested [18].

Propper further proposed that any difficulties with smell and taste in COVID-19 patients might also indicate zinc deficiency, citing precedent from biological study. Taken in total, although not all of the evidence supports a causative relationship, the evidence suggests that zinc supplementation, particularly for those with hypozincemia, might alleviate recovery time for smell dysfunction following a COVID-19 infection [19], see table (1).

Table 1. - Overview of the previous study

No	Title	Author	Method	Subject	Zn Dose	Result
1	A study on SARS-CoV-2 infected patients with measured serum Zn levels during home care	Tsuchiya et al. (2022)	Observational, cross-sectional	102 COVID-19 patients in Japan	No supplementation was given; only Zn levels were checked.	Zn concentrations were lower in patients with pneumonia; however, no significant differences were observed between those with and without hyposmia or ageusia, or between younger and older patients [10].
2	Olfactory disturbances as presenting manifestation among Egyptian patients with COVID-19: possible role of Zn	Abdelmaksoud et al. (2021)	Cross-sectional	134 COVID-19 patients in Egypt	No supplementation was given, only correlation of serum Zn levels	A significant association exists between low serum Zn levels and olfactory disturbances, as patients with anosmia exhibit substantially lower Zn concentrations than those without anosmia ($p < 0.001$). [11].
3	Persistent and transient olfactory deficits in COVID-19 are associated to inflammation and Zn homeostasi	Lupi et al. (2023)	Observational + analysis RNA-seq + IHC	24 anosmic COVID-19 patients, compared to controls and patients with rapid recovery	No supplementation given; focus on Zn homeostasis analysis	Persistent anosmia group showed Zn gene dysregulation (SLC39A8, metallothionein); supporting a role for Zn in olfactory mucosal neuroregeneration [12].
4	Effect of oral Zn and steroids on long COVID hyposmia and hypogeusia	Chiang & Jiang (2024)	Retrospective, pre-post test	71 long COVID patients in Taiwan (Omicron), 2–4 months follow-up	Zn gluconate 10 mg TID + Prednisone 10 mg BID for 1–4 months	At the 10-month follow-up, 91.2% of patients demonstrated improved olfactory function, as evidenced by a significant increase in UPSIT-TC test scores. [14].
5	Symptomatic characteristics of hypozincemia detected in long COVID patients	Matsuda et al. (2023)	Observational descriptive	24 long COVID patients with hypoxemia	No supplementation given; focus on symptom evaluation	The main symptoms of hypozincemia include fatigue, dysgeusia, depression, and muscle pain; hyposmia is not predominant. Dysgeusia is a common symptom of Zn deficiency [15].

6	Symptom profile of patients with post-COVID-19 conditions and influencing factors for recovery	Matsuoka et al. (2023)	Six-month longitudinal survey	414 post-COVID-19 patients in Japan	No explicit Zn supplementation was given	Dysgeusia and hyposmia are more common in patients with hypozincemia. Low Zn levels are significantly associated with longer-lasting symptoms [13].
7	Treatment of Long Coronavirus Disease in Japan: A Nationwide Study of Symptom-Associated Drug Prescriptio	Kogure et al. (2025)	National data-based retrospective study	3,769 long COVID patients out of 652,016 cases	No dosage is specified; polaprezinc and kampo are most commonly prescribed for olfactory disorders.	Polaprezinc and Zn-rich herbal formulas are the most frequently prescribed medications for smell/taste disorders in long-term COVID-19. This reflects Zn's potential in the recovery of post-COVID-19 hyposmia [20].
8	Treatments of COVID-19-associated taste and saliva secretory disorders	Tsuchiya H. (2023)	Narrative review	-	Polaprezinc 75 mg/day (equivalent to 17 mg Zn) is used in practice	Zn supplementation, specifically polaprezinc, has been reported to be beneficial in accelerating the recovery of salivary and olfactory disorders following COVID-19. Topical and oral Zn use has been highlighted as an effective therapeutic approach [17].
9	Zn treatment of outpatient COVID-19: A retrospective review	Finzi E & Harrington A,	Retrospective, observational	28 outpatients with COVID-19. Sublingual Zn therapy of 23–150 mg/day was given during the infection.	Sublingual Zn 23–150 mg/day (dose varies between patients), given during the acute phase of infection.	80% of patients improved within 4 days. There was no significant worsening of symptoms. The placebo effect was not confirmed due to the lack of a control group. Sublingual Zn may help speed recovery in mild COVID-19. Randomized clinical trials are needed for validation [18].
10	Smell/Taste alteration in COVID-19 may reflect zinc deficiency. Journal of clinical biochemistry and nutrition	Propper (2021)	Review / Hypothesis	Hypothesis based on previous studies	Not available	Hyposmia/taste alteration can be due to Zn deficiency [19].

7. CONCLUSIONS

Olfactory disturbances, particularly hyposmia and anosmia, are among the most prevalent and clinically relevant manifestations of post-COVID-19 syndrome. Accumulating evidence suggests that insufficient zinc availability may contribute to the persistence of olfactory impairment by impairing epithelial repair, promoting inflammatory responses in neural tissue, and disrupting zinc-dependent molecular pathways in the olfactory mucosa.

From a clinical perspective, assessment of zinc level can provide valuable information regarding patients who are left with a decreased sense of smell despite COVID-19 infection, especially those with risk factors for zinc deficiency. Thus, zinc supplementation therapy can also be recommended as an adjunct therapy, along with proven therapies such as corticosteroids despite the lack of consistent support from available evidence.

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CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

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