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Relationship between Post COVID-19 Conditions and Zinc

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Abstract

There are 200 or more different symptoms of post COVID-19 conditions (long COVID) that persist for at least two months after SARS-CoV-2 infection. No definitive treatment has been established, and symptomatic treatment and rehabilitation have been mainly conducted for treatment of the condition. Based on a lower serum zinc concentration in COVID-19 patients compared to unaffected individuals, along with hair loss, fatigue, and taste disorder that may be accompanied by symptoms related to zinc deficiency in some long COVID patients, it is suggested that such symptoms may be improved by zinc supplementation. Specifically, zinc may reportedly be effective for hair loss and neuropsychiatric manifestations such as sleep disturbance and fatigue. Although no consistent results for the efficacy of zinc against taste disorder have been shown, oral intake of zinc preparations has been recommended in patients with zinc deficiency. In this article, we introduce common symptoms between long COVID and zinc deficiency to describe the efficacy of treatment for symptoms of long COVID that can be expected to be improved by zinc supplementation based on hypotheses proposed and reports on the pathogenic mechanism of those symptoms.

Keywords: Zinc; Hypozincemia; Zinc deficiency; SARS-CoV-2; Post COVID-19 condition; Long COVID

Introduction

In patients infected with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), disorders that have developed within three months of the onset of coronavirus disease 2019 (COVID-19) and persisted for at least two months as those that cannot be explained by other diseases are defined as post COVID-19 conditions (long COVID) by the World Health Organization (WHO) [1]. As of January 2023 in the Unites States, the ratio of patients who have suffered from symptoms of long COVID at least once is 15% of the overall adult population, and the symptoms have still persisted in 6% of those patients [2].

In long COVID, there are at least 200 different symptoms including headache, fatigue, and taste and smell disorders, in addition to general symptoms such as fatigue, shortness of breath, and cognitive impairment [3,4], which have been reported to persist even one year or longer after onset in some patients [5]. However, the causes of persistence of those individual symptoms are unknown in general, and most guidelines for management of long COVID just recommend conducting adjunctive therapy and rehabilitation depending on the patient's symptoms [6-8]; the treatment methods are still being developed.

Zinc is one of the essential trace elements for survival of organisms, which has been shown to play a role in the functions of more than 300 different types of enzymes and at least 1,000 transcription factors [9], and in memory and recognition while existing at a higher concentration in brain cells [10]. Moreover, zinc deficiency may cause delayed wound healing, reproductive dysfunction, taste disorder, and compromised condition [11-13].

As for the relationship between COVID-19 and zinc, lower serum zinc concentration in COVID-19 patients compared to unaffected individuals, potential increase in SARS-CoV-2 infection with zinc deficiency, and zinc deficiency as a risk factor for death and severe conditions due to COVID-19 have been reported [14-21]. Therefore, the benefits of zinc supplementation are expected in COVID-19 patients with hypozincemia.

Abdallah, et al., reported that oral zinc administration decreased 30-day mortality, ICU admission rate, symptom duration, and length of hospital stay as compared to placebo in COVID-19 patients [22]. Gordon, et al., reported that zinc supplementation was effective for prevention of and decrease in COVID-19 in a case-control study [23]. On the other hand, a randomized controlled trial by Thomas, et al., was terminated early after zinc was considered not beneficial, showing no significant reduction in symptom duration [24]. Thus, no consistent opinions have been obtained by clinical assessments of zinc supplementation for COVID-19. In this review, we discuss the potential effects of zinc supplementation on long COVID.

Literature Review

Actual zinc intake and diagnostic criteria, treatment guide, and factors of zinc deficiency in Japanese population. Recommended amounts of zinc intake in Japanese population are 11 mg/day in adult men (10 mg/day in men aged 75 years or older) and 8 mg/day in adult

women (the amounts to be added for pregnant and lactating women are 2 mg/day and 3 mg/day, respectively) [25], while the actual amounts taken were lower than the recommended amounts in individuals other than women aged 60 to 79 years based on the National Health and Nutrition Examination Survey in 2019 [26]. In Japan, a condition with serum zinc concentration at less than 60 μg/dL is defined as zinc deficiency, and intake of zinc at 50 to 100 mg/day is recommended in patients with zinc deficiency [27].

Primary factors of zinc deficiency are inadequate intake, absorption defect, increased requirement, and enhanced excretion of zinc [27,28]. Additionally, patients with liver disease, diabetes mellitus, and kidney disease, as well as those on dialysis are more likely to develop zinc deficiency [27,29]. Elderly people tend to develop a chronic disease with higher long-term administration rate of an oral chelating drug. Pregnant women and low birth weight infants who require a higher amount of zinc are also at risk for zinc deficiency [27].

Major symptoms of hypozincemia

There are various symptoms of zinc deficiency. Zinc is associated with protein synthesis in the epidermis, and zinc deficiency may cause dermatitis due to decreased epidermal Langerhans' cells, and conditions such as hair loss related to skin disorders around the hair follicles [30]. Lower serum zinc concentration has also been reported in patients with hair loss as compared to healthy individuals. Kil, et al., reported that in patients with hair loss, mean serum zinc was 84.33± 22.88, significantly lower than the control group (97.94 ± 21.05 μg/dL) [31]. Furthermore, hypozincemia may induce taste disorder [13,32,33]. Since zinc is distributed in the epithelial cells of the tongue, and the taste buds and regions around the gustatory pores contain zinc-dependent enzymes such as alkaline phosphatase, zinc deficiency has been considered to cause taste disorder by a decrease in the number and size of the taste buds and its morphologic changes [34].

Meta-analyses by Swardfager, et al., showed lower serum zinc concentration in patients with depression, onset of depressive symptoms with serum zinc concentration at 1.8 M or lower [35], and various neurologic symptoms that may be caused by zinc deficiency [36,37]. Some reports showed that patients with refractory depression started to feel better after zinc supplementation [38,39].

Zinc deficiency may also cause imbalance between functions of the T helper 1 and 2 cells, leading to a decrease in the production of immune interferon-gamma and interleukin-2, and may increase inflammatory cytokine production and reduction in chemotaxis and phagocytosis of polymorphonuclear cells, resulting in compromised conditions by various routes [40-42]. Additionally, zinc deficiency is known to cause anemia, developmental disorders, gonadal failure, and gastrointestinal dysfunction with symptoms such as diarrhoea [27,43].

Similar and overlapped points of symptoms in long COVID and hypozincemia

Symptoms related to long COVID include fatigue, shortness of breath, cognitive impairment, and others that may affect daily living including headache, fatigue, and taste and smell disorders. Taste and smell disorders and hair loss that are observed by hypozincemia have also been reported in long COVID [44-46]. Although the pathogenesis of each symptom is unknown in COVID-19, a significantly lower serum zinc concentration has been reported in COVID-19 patients as compared to healthy individuals [16,47-50]. For example, Jothimani, et al., found a median serum zinc level of 74.5 (interquartile range 53.4-94.6) μg/dL in COVID-19 patients, which was significantly lower than the median level of 105.8 (interquartile range 95.65-120.90) μg/dL in healthy controls ($p<0.001$)[16]. Keleş, et al., also reported significantly lower median serum zinc levels in COVID-19 patients (88.5 μg/dL, IQR 77.2-100) compared to the control group (98 μg/dL, IQR 84-111) ($p=0.001$) [48]. Pvsn, et al., reported that serum zinc levels in COVID-19 patients were 8% lower than in the control group [50]. Overall, there is roughly an 8-31 μg/dL difference in zinc levels between healthy individuals and COVID-19 patients, although results varied depending on the study. In the meantime, the relationship between zinc and taste disorder has not yet been shown in COVID-19 patients.

Moreover, the most common symptom of long COVID accompanied by hypozincemia was reportedly general fatigue [51,52]. Al-Hakeim, et al., concluded that chronic fatigue was relate to inflammation and neuro-oxidative toxicity [51].

Discussion

Role of zinc for symptoms related to long COVID

Zinc supplementation is known to show efficacy for common sleep disorders [53,54]. Based on a narrative review by Pak, et al., zinc may be one of the essential trace elements to alleviate symptoms related to long COVID and improve inflammation and the quality of patient's sleep [55]. Moreover, zinc may be a trace element that strongly enhances hair follicle regeneration [56]. Hair loss related to COVID-19 is considered as Telogen Effluvium (TE) that may be associated with dysregulation of the hair growth cycle, being one of the causes of diffuse hair loss [57]. It is reported that serum zinc concentrations in patients with common TE were significantly lower than the values in non-TE patients [31], and zinc supplementation was effective for TE [58]. In addition, zinc supplementation is recommended in patients who developed hair loss after the onset of COVID-19 with a lower baseline serum zinc concentration [59]. A report showed that hair loss related to COVID was improved sooner in patients who received zinc supplementation as compared to those without a prescription of zinc [60]. The improvement rate of the group treated with zinc acetate hydrate was 73.3% after 4 weeks, 86.7% after 8 weeks, and 93.3% after 12 weeks, showing a significant difference from the non-administration group from an early stage. It was supporting the benefit of zinc supplementation for COVID-19.

Zinc supplementation was effective for taste disorder accompanied by hypozincemia in some reports [61-64], and others recommended zinc supplementation for taste disorder related to COVID-19 [8,65]. However, taste disorder was not improved in a study which examined the effects of zinc preparation administration on the improvement of individual symptoms in patients with long COVID [60]. Some studies suggested possibilities that the binding capacity of SARS-CoV-2 to Angiotensin Converting Enzyme-2 (ACE-2) receptors which are highly expressed on the surfaces of the tongue and the oral mucosa, may be associated with the pathogenesis of taste disorder related to COVID-19 and that the SARS-CoV-2 invading via the sialic acid receptors may inhibit the transport of taste substances via glycoproteins, leading to loss of taste [66-68]. It is also shown that infection and replication of the SARS-CoV-2 may occur in the taste cells [69], and that inflamed taste buds may be associated with taste disorder [70]. Taste disorder

may reportedly be correlated with Interleukin-6 (IL-6), an inflammatory cytokine [71], which may be indirectly responsible for damage to the gustatory receptors due to SARS-CoV-2 infection in the epithelial cells and subsequent local inflammation [72-74]. No definitive treatment method for taste disorder related to COVID-19 has been established. However, a rehabilitation method has been developed, and the efficacy of corticosteroid pastes has been reported [75,76].

Zinc supplementation has shown to decrease neuro-oxidative toxicity [77]. COVID-19 may affect the Central Nervous System (CNS) [78,79], and frequently cause neuropsychiatric symptoms such as depression [80]. It is said that the onset of depression related to COVID-19 may be associated with social factors including stress and financial problems, and pathological factors such as inflammation due to invasion of pro-inflammatory cytokines into the CNS [81], while zinc supplementation has been shown to be effective as an approach in the pathological aspect of neuropsychiatric manifestations related to COVID-19 [82].

Conclusion

Based on the above reports, zinc supplementation may be effective for sleep disorder, hair loss, neuropsychiatric symptoms, and taste disorder related to long COVID accompanied by hypozincemia. However, since the pathogenesis of long COVID is still unknown, we are not uncertain whether or not zinc supplementation can lead to a comprehensive solution, and may become just an adjunctive therapy eventually. A multidirectional approach is required for hypozincemia which symptoms were not improved even by zinc supplementation.

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