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The association between salivary zinc levels and dysgeusia in COVID-19 patients

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Abstract. – OBJECTIVE: Zinc insufficiency has been proposed to play a role in taste and smell impairment in Coronavirus disease 2019 (COVID-19) patients. Therefore, this study aimed at comparing salivary zinc levels in COVID-19 patients with and without dysgeusia.

PATIENTS AND METHODS: A total of 127 participants were recruited for this study. The patients were divided into three groups based on their COVID-19 test results and taste impairment. Groups I and II were COVID-19 positive with and without taste loss, respectively. Group III included the negative control participants. Salivary zinc levels were measured at baseline in all groups and three months after baseline in groups I and II. Wilcoxon signed-rank test was used to compare the zinc levels between baseline and three months after baseline within each group. Mann-Whitney U test was used to compare zinc levels between groups with different degrees of taste loss.

RESULTS: Salivary zinc levels were significantly lower in the COVID-19 positive group with taste loss compared to levels in the group without taste loss or the negative controls ($p<0.005$). Three months after baseline, salivary zinc levels were significantly elevated in both COVID-19 positive groups ($p<0.001$).

CONCLUSIONS: COVID-19 patients with dysgeusia had significantly lower levels of salivary zinc than positive and negative controls. Zinc levels were elevated after recovery, which may indicate that salivary zinc is directly associated with taste abnormalities and COVID-19 outcomes. This study showed that taste impairment is associated with lower salivary zinc levels in COVID-19 patients.

Key Words:
Taste disturbance, Ageusia, Hypogeusia, Gustatory function, Salivary diagnostics, COVID-19.

Introduction

Fever, dry cough, shortness of breath, muscle pain, headache, sore throat, chest discomfort, diarrhea, nausea/vomiting, and malaise are the common symptoms of Coronavirus disease 2019 (COVID-19). Evidence suggests that loss of smell (anosmia) and taste (ageusia) are important symptoms of COVID-19[1-4]. For example, a study by Lee et al[5] showed that approximately 15.3% of COVID-19 patients (488/3,191) developed anosmia or ageusia in the early stages. The study also reported that a total of 367 (15.7%) patients with asymptomatic or mild infections (2,342 individuals) had anosmia or ageusia, with younger people being more affected. Taste dysfunction occurred in 10.2-22.5% of patients in the early published case series, which was more common than olfactory alterations[6,7].

Investigations on the pathogenesis of taste loss in COVID-19 patients are ongoing, but several mechanisms have been proposed. One of these pathways may be connected to zinc metabolism, which is thought to be involved in taste perception[8]. The potential function of zinc in antiviral responses suggests that the chelation of zinc by molecules related to the inflammatory process might result in hypozincemia or altered cellular zinc homeostasis in gustatory cells, leading to taste impairment[9]. Therefore, zinc supplements have gained attention as a potential prevention strategy for COVID-19 infections.

Saliva, the most abundant biofluid in the head and neck, has been discovered to be a medium for non-invasive detection of COVID-19[10]. The relationship between zinc and taste disturbance in COVID-19 infection is under investigated. This study aimed at exploring the potential relationship between zinc levels in saliva and the development of COVID-19-induced dysgeusia. Our specific research question was whether salivary zinc levels differed in COVID-19 infected patients with and without dysgeusia. To accomplish this goal, we measured and compared the zinc concentrations in the saliva of COVID-19 positive patients with and without ageusia or hypogeusia, as well as negative controls.

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Patients and Methods

Patient Characteristics and Saliva Samples Collections

The Institutional Review Board at King Abdulaziz University Faculty of Dentistry approved this cross-sectional study (#282-09-21, October 11th, 2021), which was conducted in compliance with the 2013 version of the 1975 Helsinki Declaration. Participants were selected from patients who underwent nasopharyngeal swabs for COVID-19. Patients who tested positive for COVID-19 were eligible to participate in this study if they agreed to the study protocol after being informed of the procedure and the study objectives. Written consent forms were signed by all the patients who agreed to participate.

Sample size calculation was performed using G*Power software (version 3.1, Kiel University, Germany). To detect at least 0.30 µg/dL difference of mean salivary zinc level, a total sample size of 111 participants was needed to obtain a type I error rate of 5% and a power greater than 80%. A total of 127 participants (74 males and 53 females) were included in this study. None of the participants was taking supplements, medications, or was on a diet that could affect taste. None of them had a medical condition, except for the symptoms of COVID-19. A questionnaire was used to assess their medical history and symptoms of COVID-19, including loss of taste and/or smell. The severity of taste loss and whether it was a general taste loss or specific to one of the four types of taste sensations (sweet, sour, salt, and bitter) was also recorded.

The patients were divided into three groups. Group I (TL) included 37 patients who were positive for COVID-19 with symptoms of taste loss. Group II (C+ve) included 46 patients who were positive for COVID-19 but did not experience taste loss. Group III (C-ve) included 44 volunteers who tested negative for COVID-19. Diagnosis of COVID-19 was confirmed by real-time reverse transcription-polymerase chain reaction (rRT-PCR) of nasopharyngeal swabs.

Groups I and II received the standard treatment protocol for COVID-19 without any supplements that may have affected the study results, such as vitamin C, vitamin D, or zinc. Three months after baseline, the patients were asked to report their compliance with the prescribed medication and recovery from COVID-19.

Saliva samples were collected from all participants at the incidence of infection (baseline) and from the COVID-19 positive groups three months later. The participants were instructed not to swallow the saliva produced in their mouths for 5 min and thereafter 5 mL of whole unstimulated mixed saliva was collected from each participant. Samples were stored in sterile single-use polypropylene test tubes at -80°C until all samples were collected, and the research period was completed.

Spectrophotometric Analyses

To eliminate cellular debris, each saliva sample was centrifuged at 14,000 rpm for 10 min. Subsequently, the supernatant was transferred to a test tube and diluted 1:5 with zinc-free deionized water.

Zinc concentrations in saliva samples were determined by a zinc assay kit (Abnova, Taipei, Taiwan) as per manufacturer's instructions. This kit measures zinc levels in various biological samples, including saliva. Fifty µL of the Zn^{2+} standard, study samples, and blank samples were added to a flat bottom 96-well plate in duplicate. Next, 2 µL of EDTA and 200 µL of the working reagent were added in each well. The plates were gently mixed and then incubated at room temperature (20-22°C) for 30 min. The optical density was measured at 425 nm.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) software package (version 20.0, IBM Corp., Armonk, NY, USA) was used to analyze the data. The median and interquartile range (IQR), mean and standard deviation, and range were reported for continuous variables. Categorical variables were reported as frequencies and percentages. Normality of distribution was tested using a Kolmogorov-Smirnov test. Wilcoxon signed-rank test was used to compare the zinc levels between baseline and three months after baseline within each group. Mann-Whitney U test was used to compare zinc levels between groups with different degrees of taste loss. Additionally, it was used to compare zinc levels between males and females in the TL, C+ve, and C-ve groups. Kruskal-Wallis' test was performed to evaluate the differences in zinc levels between different age groups in the TL, C+ve, and C-ve groups. The significance level was set at $p < 0.05$.

Table I. Comparisons of zinc levels between the TL, C+ve, and C-ve groups at baseline (incidence of infection) and at three months after baseline.

Zinc level (µg/ml)	TL group (n = 37)	C+ve group (n = 46)	C-ve group (n = 44)	Test of significance	*p*-value
Baseline					
Min.-Max.	0.08-0.78	0.17-1.50	0.25-1.53	H = 61.110	< 0.001*
Mean ± SD.	0.29 ± 0.14	0.69 ± 0.26	0.80 ± 0.26		
Median (IQR)	0.27 (0.20-0.34)	0.66 (0.50-0.88)	0.78 (0.65-0.99)		
Post hoc test		$p_1 < 0.001$*, $p_2 < 0.001$*, $p_3 = 0.1$			
Three months					
Min.-Max.	0.17-1.0	0.45-1.90	-	U = 190.50	< 0.001*
Mean ± SD.	0.56 ± 0.21	1.01 ± 0.33	-		
Median (IQR)	0.54 (0.43-0.68)	0.96 (0.78-1.20)	-		

H: Kruskal-Wallis' test, U: Mann-Whitney test, p_1: between TL and C+ve, p^2: between TL and C-ve, p_3: between C+ve and C-ve. *Statistically significant at $p < 0.05$.

Results

Subject Demographics

A total of 127 subjects participated in the study, of which 83 were COVID-19 positive, and 44 were negative. Of the positive participants, 37 (44.6%) had symptoms of dysgeusia or ageusia. Participants were assigned to three groups: 1) TL group: COVID-19 positive subjects with taste loss (n= 37, 21 males and 16 females); 2) C+ve group: COVID-19 positive subjects without taste loss (n=46, 32 males and 14 females); and 3) C-ve group: COVID-19 negative subjects (n= 44; 21 males and 23 females). No significant differences were found in sex among the three groups (p=0.1). Moreover, no significant difference (p=0.2) was found in the mean age among the TL, C+ve, and C-ve groups (35.35 ± 12.98, 40.11 ± 12.22, and 38.77 ± 8.81, respectively).

Zinc Levels and Taste Dysfunction among Study Groups

A comparison of the three groups revealed that baseline salivary zinc levels were significantly different (p<0.001) among the TL (0.29 ± 0.14), C+ve (0.69 ± 0.26), and C-ve (0.80 ± 0.26) groups. However, the difference was not statistically significant between C+ve and C-ve groups (p=0.1) when a pairwise comparison was performed using the post-hoc test (Table I). Three months after baseline, salivary zinc levels significantly increased (p<0.001) in both COVID-19 positive (TL and C+ve) groups (Table II). We also found that four patients in the TL group had a complete loss of taste and smell, whereas 32 patients reported a partial taste loss (Table III). The two groups showed no significant difference in zinc levels at the beginning of infection (p=0.9) or three months after baseline (p=0.9).

Zinc Levels Were Not Associated with Age or Sex in All Groups

Zinc levels were not significantly different between males and females in all three groups at baseline and after three months of baseline (Table IV). In addition, although the older age group (>50 years) showed a trend of lower zinc levels compared to the younger groups, it did not reach statistical significance (Table V). The TL group showed lower zinc levels at baseline and three months after baseline among all age groups.

Table II. Zinc level differences between baseline and three months after baseline within each group.

Group	Zinc level (µg/ml)	Baseline	Three months	Z statistic	*p*-value
TL group (n = 37)	Min.-Max.	0.08-0.78	0.17-1.0	5.040*	< 0.001*
	Mean ± SD.	0.29 ± 0.14	0.56 ± 0.21		
C+ve group (n = 46)	Min.-Max.	0.17-1.50	0.45-1.90	5.884*	< 0.001*
	Mean ± SD.	0.69 ± 0.26	1.01 ± 0.33		

Z: Wilcoxon signed-rank test. *Statistically significant at $p < 0.05$.

Table III. The relation between zinc levels and the degree of taste loss in the TL group.

Zinc level (µg/ml)	Symptom		U	*p*-value
	Partial loss of taste (n = 32)†	Complete loss of taste (n = 4)†		
Baseline				
Min.-Max.	0.08-0.78	0.18-0.34	62.0	0.9
Mean ± SD.	0.29 ± 0.14	0.28 ± 0.08		
Three months				
Min.-Max.	0.17-1.0	0.30 ± 0.90	60.50	0.9
Mean ± SD.	0.57 ± 0.21	0.56 ± 0.26		

U: Mann-Whitney U test, †Does not add up to the total of the TL group because of missing data.

Table IV. Zinc level differences between males and females in the TL, C+ve, and C-ve groups.

Group	TL		C+ve		C-ve	
Sex	Male (n = 21)	Female (n = 16)	Male (n = 32)	Female (n = 14)	Male (n = 21)	Female (n = 23)
Baseline zinc level (µg/ml)						
Min.-Max.	0.08-0.78	0.12-0.41	0.17-1.50	0.22-0.98	0.25-1.32	0.45-1.53
Mean ± SD.	0.31 ± 0.17	0.27 ± 0.08	0.72 ± 0.29	0.62 ± 0.19	0.78 ± 0.28	0.81 ± 0.25
Median	0.26	0.27	0.75	0.62	0.81	0.77
U (*p*-value)	161.50 (0.8)		169.50 (0.2)		241.50 (1.0)	
Three months zinc level (µg/ml)						
Min.-Max.	0.21-1.0	0.17-0.89	0.45-1.90	0.63-1.50	-	-
Mean ± SD.	0.56 ± 0.23	0.57 ± 0.19	1.04 ± 0.37	0.95 ± 0.21	-	-
Median	0.53	0.56	0.96	0.93	-	-
U (*p*-value)	159.0 (0.8)		206.0 (0.7)			

U: Mann-Whitney U test.

Table V. Zinc level differences between different age groups in the TL, C+ve, and C-ve groups.

Group	TL			C+ve			C-ve		
Age	20-35 (n = 20)	36-50 (n = 12)	> 50 (n = 5)	20-35 (n= 16)	36-50 (n= 21)	> 50 (n = 9)	20-35 (n= 15)	36-50 (n= 24)	> 50 (n = 5)
Baseline zinc level (µg/ml)									
Min.-Max.	0.12-0.78	0.17-0.50	0.08-0.34	0.21-0.99	0.17-1.50	0.44-0.99	0.25-1.10	0.34-1.53	0.39-0.84
Mean ± SD.	0.30 ± 0.15	0.32 ± 0.11	0.20 ± 0.11	0.61 ± 0.24	0.79 ± 0.28	0.61 ± 0.19	0.80 ± 0.24	0.82 ± 0.29	0.65 ± 0.18
Median	0.27	0.34	0.23	0.63	0.82	0.51	0.87	0.79	0.67
H (*p*-value)	2.992 (0.2)			5.783 (0.06)			2.014 (0.4)		
Three months zinc level (µg/ml)									
Min.-Max.	0.17-1.0	0.29-0.98	0.27-0.54	0.59-1.60	0.45-1.90	0.65-1.0			
Mean ± SD.	0.58 ± 0.22	0.60 ± 0.22	0.39 ± 0.11	0.95 ± 0.28	1.13 ± 0.39	0.85 ± 0.12			
Median	0.58	0.59	0.42	0.95	1.0	0.83			
H (*p*-value)	4.649 (0.1)			4.747 (0.09)			-		

H: H for Kruskal-Wallis' test.

Discussion

Loss of taste and smell was noted as a common complaint that interfered with quality of life during the COVID-19 outbreak. In addition, zinc deficiency was thought to contribute to the loss of smell and taste. Moreover, since the 1980s[11], zinc supplements have been utilized to recover taste as zinc enhances the conduction from taste buds to gustatory nerve fibers. Therefore, this study was designed to determine the zinc levels in saliva samples of COVID-19 patients with different degrees of taste loss and the role of zinc in the recovery of taste dysfunction in these individuals. We found that salivary zinc level was significantly lower in COVID-19 patients with dysgeusia compared to patients with no dysgeusia or non-infected participants.

In vitro cell culture models of SARS-CoV-1 have shown that zinc deficiency increases pro-inflammatory cytokines and reduces antibody formation. In contrast, increasing intracellular zinc concentrations inhibit viral RNA polymerase activity and viral multiplication[12-14]. In the current study, we found a significant difference in zinc levels between COVID-19-positive and-negative patients at the initial diagnosis. This could be explained by the fact that zinc has been shown to have antiviral effects against infections such as coronaviridae, papillomavirus, metapneumovirus, herpes simplex, rhinovirus, varicella-zoster, HIV, and hepatitis C virus[15,16]. Zinc inhibits viral polymerase function and prevents viral fusion with the host cell membrane[17,18].

Our results showed that 37 out of 83 (44.6%) COVID-19 patients had ageusia or hypogeusia. Different studies showed variable percentages of incidences of taste disturbance in COVID-19 patients. Yang et al[19] found that 68% of patients who tested positive for COVID-19 experienced smell and taste loss[19]. In addition, a systematic review found that 20% of COVID-19 patients had ageusia and 33% of patients had dysgeusia[20]. Furthermore, a recent meta-analysis on 817 patients found that nearly half of the COVID-19 patients (49.8%) had ageusia or dysgeusia[21].

Our findings revealed significantly lower saliva zinc levels in patients with taste impairment than in those without ($p<0.001$). In addition, patients with a complete loss of taste (ageusia) had lower zinc levels than patients with a partial loss of taste (hypogeusia); however, this did not reach the significance level. After three months of baseline, both groups of COVID-19 patients showed a considerable increase in zinc levels. Pisano and Hilas[22] found that zinc deficiency was correlated with taste and smell disorders. Similarly, gustatory function was improved in patients with idiopathic dysgeusia after zinc supplementation in a randomized clinical trial compared with a placebo[23]. SARS-CoV-2 infections might affect the homeostasis of cellular zinc levels in injured oral gustatory cells, which could be one of the reasons for COVID-19-related ageusia/dysgeusia[24]. Another suggested mechanism of taste loss is related to the angiotensin-converting enzyme 2 (ACE2) receptors, which are abundantly expressed on the surface of the tongue and oral mucosa. It has been shown that SARS-CoV-2 can bind to ACE2 receptors and infect the cells[20]. Therefore, damage to these cells may explain the ageusia in the early stages of COVID-19 infections.

Larger scale studies might be conducted to investigate the relationship between different severities of taste impairment and salivary zinc levels. Furthermore, the influence of zinc on the immune system in SARS-CoV-2 infections could be investigated by testing the relation between zinc levels and different inflammatory cytokines in saliva and blood.

Conclusions

The present study showed that COVID-19 patients with ageusia or hypogeusia had significantly lower levels of salivary zinc than patients without taste loss and negative controls. An elevated zinc level was commensurate with recovery and improved taste sensation within three months. This indicates that zinc could be directly associated with taste abnormalities and COVID-19 outcomes.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

Study conception and design: A.A. Badahdah, S. Alghamdi, and E. Elfirt. Data collection and experiments: A. Banjar, E. Elfirt, A. Elfirt, and A. Almarghlani. Analysis and

interpretation of the results: L. Bahanan, A. Banjar, S. Alghamdi, A.A. Badahdah. Draft manuscript and preparation: E. Elfirt, and A. Elfirt. All authors gave their final approval and agreed to be accountable for all aspects of the work.

Informed Consent

Written consent forms were signed by all the patients who agreed to participate.

Ethics Approval

The Institutional Review Board at King Abdulaziz University Faculty of Dentistry approved this cross-sectional study (#282-09-21, October 11th, 2021), which was conducted in compliance with the 2013 version of the 1975 Helsinki Declaration.

References

1) Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395: 507-513.
2) Kim ES, Chin BS, Kang CK, Kim NJ, Kang YM, Choi J-P, Oh DH, Kim J-H, Koh B, Kim SE. Clinical course and outcomes of patients with severe acute respiratory syndrome coronavirus 2 infection: a preliminary report of the first 28 patients from the Korean cohort study on COVID-19. J Korean Med Sci 2020; 35: e142.
3) Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, Dequanter D, Blecic S, El Afia F, Distinguin L. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Otorhinolaryngol 2020; 277: 2251-2561.
4) Jang Y, Son H-J, Lee S, Lee EJ, Kim TH, Park SY. Olfactory and taste disorder: The first and only sign in a patient with SARS-CoV-2 pneumonia. Infect Control Hosp Epidemiol 2020; 41: 1103-1125.
5) Lee Y, Min P, Lee S, Kim S-W. Prevalence and duration of acute loss of smell or taste in COVID-19 patients. J Korean Med Sci 2020; 35: e174.
6) Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, Dequanter D, Blecic S, El Afia F, Distinguin L, Chekkoury-Idrissi Y, Hans S, Delgado IL, Calvo-Henriquez C, Lavigne P, Falanga C, Barillari MR, Cammaroto G, Khalife M, Leich P, Souchay C, Rossi C, Journe F, Hsieh J, Edjlali M, Carlier R, Ris L, Lovato A, De Filippis C, Coppee F, Fakhry N, Ayad T, Saussez S. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Otorhinolaryngol 2020; 277: 2251-2261.
7) Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M, Oreni L, Rusconi S, Gervasoni C, Ridolfo AL, Rizzardini G, Antinori S, Galli M. Self-reported Olfactory and Taste Disorders in Patients With Severe Acute Respiratory Coronavirus 2 Infection: A Cross-sectional Study. Clin Infect Dis 2020; 71: 889-890.
8) Risso D, Drayna D, Morini G. Alteration, Reduction and Taste Loss: Main Causes and Potential Implications on Dietary Habits. Nutrients 2020; 12: 3284.
9) Lozada-Nur F, Chainani-Wu N, Fortuna G, Sroussi H. Dysgeusia in COVID-19: Possible Mechanisms and Implications. Oral Surg Oral Med Oral Pathol Oral Radiol 2020; 130: 344-346.
10) Adeoye J, Thomson P. 'The Double-Edged Sword' - An hypothesis for Covid-19-induced salivary biomarkers. Med Hypotheses 2020; 143: 110124.
11) Henkin RI. Zinc in taste function. Biol Trace Elem Res 1984; 6: 263-280.
12) Kermali M, Khalsa RK, Pillai K, Ismail Z, Harky A. The role of biomarkers in diagnosis of COVID-19 - A systematic review. Life Sci 2020; 254: 117788.
13) Zhang L, Liu Y. Potential interventions for novel coronavirus in China: A systematic review. J Med Virol 2020; 92: 479-490.
14) te Velthuis AJ, van den Worm SH, Sims AC, Baric RS, Snijder EJ, van Hemert MJ. Zn(2+) inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. PLoS Pathog 2010; 6: e1001176.
15) Cai H, Zhang Y, Ma Y, Sun J, Liang X, Li J. Zinc binding activity of human metapneumovirus M2-1 protein is indispensable for viral replication and pathogenesis in vivo. J Virol 2015; 89: 6391-6405.
16) Kumar A, Kubota Y, Chernov M, Kasuya H. Potential role of zinc supplementation in prophylaxis and treatment of COVID-19. Med Hypotheses 2020; 144: 109848.
17) Ishida T. Review on the role of Zn2+ ions in viral pathogenesis and the effect of Zn2+ ions for host cell-virus growth inhibition. Am J Biomed Sci Res 2019; 2: 28-37.
18) Skalny AV, Rink L, Ajsuvakova OP, Aschner M, Gritsenko VA, Alekseenko SI, Svistunov AA, Petrakis D, Spandidos DA, Aaseth J, Tsatsakis A, Tinkov AA. Zinc and respiratory tract infections: Perspectives for COVID-19 (Review). Int J Mol Med 2020; 46: 17-26.
19) Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, Ji R, Wang H, Wang Y, Zhou Y. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis 2020; 94: 91-95.
20) Carrillo-Larco RM, Altez-Fernandez C. Anosmia and dysgeusia in COVID-19: A systematic review. Wellcome Open Res 2020; 5: 94.

21) Aziz M, Perisetti A, Lee-Smith WM, Gajendran M, Bansal P, Goyal H. Taste changes (Dysgeusia) in COVID-19: a systematic review and meta-analysis. Gastroenterology 2020; 159: 1132-1133.

22. Pisano M, Hilas O. Zinc and taste disturbances in older adults: a review of the literature. Consult Pharm 2016; 31: 267-270.

23) Heckmann SM, Hujoel P, Habiger S, Friess W, Wichmann M, Heckmann JG, Hummel T. Zinc gluconate in the treatment of dysgeusia—a randomized clinical trial. J Dent Res 2005; 84: 35-38.

24) Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, Li T, Chen Q. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci 2020; 12: 1-5.