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Olfactory Disturbances as Presenting Manifestation Among Egyptian Patients with COVID-19: Possible Role of Zinc

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Abstract

COVID-19 is a severe acute respiratory syndrome caused by coronavirus 2 (SARS-CoV-2). Deficiency of zinc has been supposed to contribute to loss of smell and taste in COVID-19 patients. Our study aimed to assess the serum zinc levels among patients with COVID-19 of various severities, with and without olfaction dysfunction, and to evaluate the effect of zinc therapy in recovery of smell dysfunction among such patients. This study included 134 patients; real-time reverse transcription-polymerase chain reaction (rRT-PCR) proved SARS-CoV-2. Serum zinc levels were measured for all infected patients. One hundred and five patients were detected to have anosmia and/or hyposmia and were categorized randomly into 2 groups; the first group included 49 patients who received zinc therapy and the second group included 56 patients who did not received zinc. All patients were followed up for the recovery duration of olfactory and gustatory symptoms and duration of complete recovery of COVID-19. Olfactory dysfunction was reported in 105 patients (78.4%). Serum zinc levels were not significantly different between the patient subgroups regarding disease severity or the presence or absence of olfactory and/or gustatory dysfunction ($p > 0.05$). The median duration of recovery of gustatory and/or olfactory function was significantly shorter among patients who received zinc therapy than those who did not received zinc ($p < 0.001$), while the median duration of complete recovery from COVID-19 was not significantly different among the two groups ($p > 0.05$). Although the zinc status of COVID-19 patients did not exhibit a significant role in development of anosmia and/or hyposmia or disease severity, zinc therapy may have a significant role in shortening the duration of smell recovery in those patients without affecting the total recovery duration from COVID-19.

Keywords COVID-19 · Anosmia · Hyposmia · Zinc

Introduction

The 2019 novel coronavirus disease (COVID-19) is a viral infection, a severe acute respiratory syndrome caused by coronavirus 2 (SARS-CoV-2). The first case was diagnosed in Wuhan, China, in 2019 and caused multiorgan manifestation. Cases have been reported in more than 180 countries to the World Health Organization (WHO), including more than one million deaths [1]. The common symptoms of COVID-19 are fever, tiredness, dry cough, body pain, nasal congestion, rhinorrhea, pain in the throat or diarrhea, anosmia, and/or loss of taste [2].

Patients infected with SARS-CoV-2 presented with mild disease, and only 5% develop viral pneumonia and multiorgan failure [3].

Sinonasal conditions that impair the travel of odorants to the intact olfactory mucosa can result in anosmia [4]. Temporary anosmia can result from nasal congestion from various causes including respiratory viral infection [5]. In

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the pre-COVID-19 era, about 14 to 30% of all patients presented with olfactory impairment resulting from sinonasal diseases [6–8]. The incidence of olfactory dysfunction in COVID-19 is ranging from 68 to 85%, while taste dysfunction prevalence is ranging from 71 to 88.8% in SARS-CoV-2-infected patients [9].

Zinc is one of the most important trace metals in humans; it comes second to iron in concentration but with no special zinc store [10]. Plasma zinc concentration is about 1 μg/ml and represents about 0.1% of the whole body zinc [8, 11]. Internal homeostasis is regulated by 10 solute-linked carrier 30 (SLC30 or ZnT) exporters and 14 solute-linked carrier 39 (SLC39 or ZIP) importers [12, 13]. Zinc homeostasis is affected in overweight people; diabetic patients; ischemic heart diseases; drug intake as angiotensin-converting enzyme (ACE) inhibitors; angiotensin 2 receptor antagonists and thiazides; and intake of iron, calcium, and non-digestible plant ligands [14, 15]. Measuring of plasma zinc levels is a useful clinical test for zinc deficiency [16]. Zinc regulates the differentiation, proliferation, maturation, and function of lymphocytes and other leukocytes [13]. Also, zinc participates in viral recognition by the zinc finger protein ZCCHC3 which triggers the antiviral response [17, 18].

Zinc deficiency could be mild, moderate, or severe and present in about 17% of world population [19]. Mild and moderate zinc deficiencies are quit common globally [20]. Older people are more liable to zinc deficiency complications [19]. Skin diseases, growth retardation, high susceptibility to infections (including pneumonia), and others could be caused by severe zinc deficiency [21, 22]. In a clinical trial, daily intake of 20 mg zinc sulfate for 5 months reduced the morbidity of lower respiratory tract infection in comparison to placebo [23]. Interferon-alpha production is upregulated and its viral activity is increased with zinc intake. Also, SAR-CoV RNA polymerase activity was partially inhibited by zinc [24].

Chloroquine and hydroxychloroquine increase cellular uptake of zinc which may inhibit viral replication activity [25, 26]. Also, zinc is known to reduce angiotensin-converting enzyme 2 which is required for SARS-CoV-2 and SARS-CoV entry into target cells [27]. Deficiency of zinc has been supposed to contribute to loss of smell and taste in patients with COVID-19. Acute zinc deficiency occurs during acute infection which could lead to reduction in taste bud cell alkaline phosphatase activity, changing in salivary proteins containing zinc or leading to neurological dysfunction [28, 29]. The current research was designated to assess the relative frequency of olfactory disorders among patients with COVID-19 and to evaluate the serum levels of zinc and identify its possible relation with both the development of olfactory disorders and the disease severity, and to shed light on the possible role of zinc therapy regarding the improvement of impaired olfaction among patients with COVID-19.

Materials and Methods

Study Design and Setting

The current prospective clinical trial study included 134 patients with COVID-19, who were randomly selected from the Quarantine Department of Qena University Hospitals, Faculty of Medicine, South Valley University, Qena, Egypt, during the period from May 2020 to August 2020. Prior to start of the study, an institutional ethical committee approval was taken (ethical approval code: SVU-MED-MBC004-2020-04). A written informed consent was obtained from all participants in this study. Diagnosis of SARS-CoV-2 was based on history of epidemiologic exposure. Clinical manifestations include (1) respiratory symptoms and/or fever; (2) imaging features of SARS-CoV-2 infection; (3) total leucocytic counts showing normal or reduced lymphocyte count in early stage [30]; (4) imaging features of COVID-19, also diagnosed by real-time reverse transcription-polymerase chain reaction (rRT-PCR) in samples from respiratory tract swabs which were performed at Central Laboratories, Ministry of Health and Population, Cairo, Egypt.

Patients with history of nasal surgery, sinusitis, nasal polyposis allergic rhinitis, head injury, or chronic nasal disease were excluded. Also, patients with anosmia and/or hyposmia before the diagnosis of COVID-19 were excluded.

Data Collections

Demographic data were recorded for all patients including age, sex, BMI, comorbidities, and smoking. Full history was taken from all patients with special stress about the presence or absence of anosmia (loss of smell) or hyposmia (decrease sense of smell). The diagnosis of anosmia and hyposmia was according to the physician's decision. In addition, proper examination of nasal cavity and paranasal sinuses was performed.

COVID-19 was categorized into mild, common, severe, and extremely severe in accordance with the 6th edition for Diagnostic Standards for COVID-19 [31]. Consequently, mild COVID-19 was considered to be associated with mild clinical symptoms, with no pneumonia manifestations on imaging. Patients with common COVID-19 had fever, respiratory tract, or other symptoms, and imaging that showed pneumonia. Severe COVID-19 was considered to meet one of the following conditions: (1) shortness of breath, 30 beats/min; (2) in the resting state, pulse oxygen saturation < 93%, arterial blood oxygen pressure (PaO_2)/oxygen concentration (FiO_2) < 300 mmHg; or (3) pulmonary imaging showed lesion progression > 50% within 24–48 h. Extremely severe COVID-19 needed to meet one of the following conditions: (1) development of respiratory failure requiring mechanical ventilation; (2) shock; (3) combined organ failure requiring ICU monitoring [32].

Table 1 Demographic and clinical data of the included SARS-CoV-2-infected patients

Variables		COVID-19 severity (n = 134)								p value
		Mild (n = 45)		Common (n = 57)		Severe (n = 21)		Extremely severe (n = 11)		
Age (mean ± SD, years)		31.8 ± 13.1		47.8 ± 15.8		59.1 ± 9.5		69.5 ± 6.5		< 0.001*
Sex (no, %)	Male	24	53.3%	33	57.9%	15	71.4%	6	54.5%	0.570
	Female	21	46.7%	24	42.1%	6	28.6%	5	45.5%	
BMI (mean ± SD, kg/m^2)		26.4 ± 2.4		27.4 ± 2.2		26.6 ± 2.8		25.6 ± 3.3		0.084
Comorbidities	No	41	91.1%	44	77.2%	10	47.6%	6	54.5%	0.003*
	Diabetes mellitus	2	4.4%	5	8.8%	5	23.8%	3	27.3%	
	Hypertension	0	0%	8	14%	5	23.8%	1	9.1%	
	Ischemic heart disease	2	4.4%	0	0%	1	4.8%	1	9.1%	
Smoking	No	29	64.4%	38	66.7%	13	61.9%	9	81.8%	0.696
	Yes	16	35.6%	19	33.3%	8	38.1%	2	18.2%	
Death	No	45	100%	56	98.2%	20	95.2%	9	81.8%	0.013*
	Yes	0	0	1	1.7%	1	4.8%	2	18.2%	

*Significant p value < 0.05. Data were expressed as mean ± SD or numbers and percentages

The patients with anosmia and/or hyposmia were divided randomly into two groups; the first group included 49 patients with olfactory dysfunction, who received zinc therapy (220 mg zinc sulfate equivocal to 50 mg elemental zinc twice daily [33]) plus the Egyptian protocol of treatment of COVID-19 and the second group included 56 patients with olfactory dysfunction, who received the Egyptian protocol of COVID-19 treatment without zinc therapy. Follow-up of all included patients until complete recovery of COVID-19 (pharyngeal swap becomes negative) and complete recovery of olfactory symptoms and the recovery durations for the included patients were recorded in days.

Biochemical and Molecular Assays

1. Diagnostic kit (PCR-Fluorescence probing) of nucleic acid was used for the qualitative estimation of the ORF1ab and a specific conserved sequence of coding nucleocapsid protein N genes of novel coronavirus (2019-nCOV). This kit was supplied by Sansure Biotech Inc., Hunan Province, China, with catalog no. S3102E, using a 7500 real-time fluorescence quantitative RT-PCR system (Applied Biosystems, Foster City, CA, USA) to detect RNA through fluorescent signal changes [34].
2. Serum levels of zinc were measured once for all patients prior to zinc therapy; 3 ml of peripheral venous blood samples was collected in plain collection tubes for serum recovery. Samples were left to clot for 30 min at 37 °C before centrifugation, and sera obtained were aliquoted into 1-ml cryotubes and stored at − 20 °C until biochemical assays of zinc. Zinc level was measured colorimetrically (Spectrum Diagnostics, Cairo, Egypt, Catalog No. 330001) [35–39].

Statistical Analysis

Analysis of data was performed using Statistical Program for Social Science (SPSS) version 24. The Kolmogorov-Smirnov test was used to check for data normality. Qualitative data was expressed as frequency, numbers, and percentages. Parametric quantitative data was expressed as mean ± standard deviation, while median and inter-quartile range used for non-parametric data. For comparison between the two groups, the chi-square test (χ^2) was used for qualitative variables. Independent-samples t test was used to compare between two quantitative variables when normally distributed (parametric data), while for abnormally distributed variables (non-parametric data), the

Table 2 Frequency of olfactory dysfunction among the total included patients with COVID-19 in terms of disease severity

Variables		Mild and common COVID-19 (n = 102)		Severe and extremely severe COVID-19 (n = 32)		p value
Olfactory dysfunction (anosmia)	No	38	37.3%	16	50%	0.2
	Yes	64	62.7%	16	50%	
Olfactory dysfunction (hyposmia)	No	83	81.4%	26	81.3%	0.98
	Yes	19	18.6%	6	18.8%	

Table 3 The relation between serum zinc levels according to the disease severity among the total included patients with COVID-19 disease

Variables	COVID-19 severity (n = 134)				p value
	Mild (n = 45)	Common (n = 57)	Severe (n = 21)	Extremely severe (n = 11)	
Zinc (mean ± SD, μg/ml)	0.67 ± 0.18	0.62 ± 0.14	0.73 ± 0.18	0.72 ± 0.22	0.084

Mann-Whitney U test was used. One-way ANOVA test was used to compare more than two quantitative variables for parametric data. Probability (p value) > 0.05 was considered insignificant, p value < 0.05 was considered significant; and p value < 0.001 was considered as highly significant.

Results

Demographic Data of the Included COVID-19 Patients

The study included 134 patients diagnosed as COVID-19 who were categorized according to disease severity into mild (45 patients (24 males and 21 females)), common (57 patients (33 males and 24 females)), severe (21 patients (15 males and 7 females)), and extremely severe (11 patients with extremely severe symptoms (6 males and 5 females)). The mean ± SD of age (years) of patient groups were 31.8 ± 13.1, 47.8 ± 15.8, 59.1 ± 9.5, and 69.5 ± 6.5 respectively. The mean age was statistically significantly higher in patients with extremely severe disease than in others (p value < 0.001) (Table 1).

There were no significant differences regarding gender, BMI, and smoking status among COVID-19 patients of various diseases (p value > 0.05; Table 1). Both comorbidity frequency (diabetes mellitus, hypertension, and ischemic heart disease) and deaths were statistically significantly higher in severe and extremely severe COVID-19 patients as shown in Table 1 (p value < 0.05).

Smell Dysfunction Among Patients with COVID-19

In the current study, olfactory dysfunction (anosmia and hyposmia) was present in 105 out of the 134 patients (78.4%). Anosmia was reported in 80 patients (59.7%) and hyposmia in 25 patients (18.6%). There was no significant relation between olfactory dysfunction and severity of COVID-19 disease (Table 2).

Serum Zinc Levels Among the Included Patients with COVID-19

The mean serum zinc levels of all patients with different grades of severity are presented in Table 3. The serum zinc (mean ± SD, μg/ml) in patients with mild, common, severe, and extremely severe COVID-19 was 0.67 ± 0.18, 0.62 ± 0.14, 0.73 ± 0.18, and 0.72 ± 0.22. The difference between mean serum zinc levels among patients with COVID-19 of various severities was of marginal significance that may be explained by the small number of the included patients.

Zinc Levels and Olfactory Dysfunction Among Patients with COVID-19

Serum zinc levels in COVID-19 patients with anosmia and hyposmia are presented in Table 4. Despite lower serum zinc levels in patients with anosmia (0.59 ± 0.1 μg/dl) and in patients with hyposmia (0.57 ± 0.1 μg/dl) than patients without, this difference did not reach a significant level (p > 0.05; Table 4). There was no significant difference between serum zinc levels of COVID-19 patients with anosmia (0.58 ± 0.1) vs. those with hyposmia (0.65 ± 0.1) (p > 0.05).

Zinc Therapy and Recovery of COVID-19-Induced Olfactory Dysfunction

The median duration of recovery of olfactory function was 7 days (range 5–9 days) in COVID-19 patients who received zinc therapy which was significantly lower than in those who did not received (median 18 days with range 14–22 days) (p value < 0.05) (Table 5; Fig. 1). Additionally, zinc therapy did not influence the duration of complete recovery of COVID-19 disease among patients who received it (median 12 with range 8–17 days) vs. those who did not (median 12 with range 8–20 days) (p > 0.05).

Discussion

COVID-19 (coronavirus disease) was first discovered in Wuhan, China, in December 2019 [40] with obscure

Table 4 Serum zinc levels according to the type of olfactory dysfunction among the included COVID-19 patients

Olfactory dysfunction		Zinc (μg/dl) (mean ± SD)	p value
Anosmia	No (n = 54)	0.61 ± 0.1	0.754
	Yes (n = 80)	0.59 ± 0.1	
Hyposmia	No (n = 109)	0.63 ± 0.1	0.313
	Yes (n = 25)	0.57 ± 0.1	

Table 5 Duration of recovery of olfactory disturbances in relation to zinc therapy among COVID-19 patients

Variables		Zinc therapy		*p* value
		No (n = 56)	Yes (n = 49)	
Duration of smell recovery (days)	Median IQR	18 14–22	7 5–9	< 0.001*

*Significant p value < 0.05. Data were expressed as median and IQR (inter-quartile range)

characteristics of the disease. In Egypt, anosmia and hyposmia are common complaints in COVID-19 that interfere with quality of life. All age groups are at risk for infection and severe disease. However, the risk of fatal disease is highest in patients aged 65 years and older [41, 42]. The current study found that older age patients are more frequently affected by severe and extremely severe COVID-19, but young age patients are more frequently affected by mild to common disease. This comes in agreement with Liu et al. [43] who reported that elderly patients with COVID-19 are more likely to progress to severe COVID-19 disease in comparison with young- and middle-aged COVID-19 patients. Also, Yang et al. [44] and Mahase [45] reported similar findings, as in old aged, the cell-mediated immune function and humeral immune function reduced [46]. Other high-risk groups for COVID-19 are people with certain comorbidities as diabetes mellitus, hypertension, and ischemic heart diseases particularly when not controlled regardless of their age [47–50], which were in line with our findings which revealed that comorbidities (diabetes mellitus, hypertension, and ischemic heart disease) and deaths were significantly frequent in severe and extremely severe COVID-19 patients. Additionally, Marhl et al. [51] reported an increased risk of COVID-19 among diabetic patients because of the associated chronic inflammation, liver dysfunction, and dysregulation of angiotensin-converting enzyme 2 (ACE2). Also, Singh et al. [52] reported an increased severity and incidence of COVID-19 in diabetic patients. As regards smoking, there was no significant difference between different COVID-19 grades of severity which was in accordance with several researchers [53, 54].

In the current study, the frequency of anosmia and hyposmia among the included COVID-19 patients was 59.7% and 18.6% respectively. Online cross-sectional survey by Yan et al. noticed that 40 patients out of 59 patients tested positive for COVID-19 (68%) reported loss of smell, which was near to the results of the present study.

Zinc has been reported to inhibit coronavirus RNA polymerase activity in vitro [24], and is claimed to play a role in antiviral immune responses. SARS-CoV-2 infection depends on the metabolism of the host cell. Zinc is claimed to have antiviral effects demonstrated in various cases [54–56]. Examples include Coronaviridae, papilloma virus, picornavirus, metapneumovirus, herpes simplex virus, rhinovirus, varicella-zoster virus, human immunodeficiency virus (HIV), respiratory syncytial virus, and hepatitis C virus [57, 58]. Viral fusion with the host cell membrane could be prevented by zinc; also, it impairs the function of viral polymerase.

Although the current study revealed no significant difference in serum zinc levels between patients with different

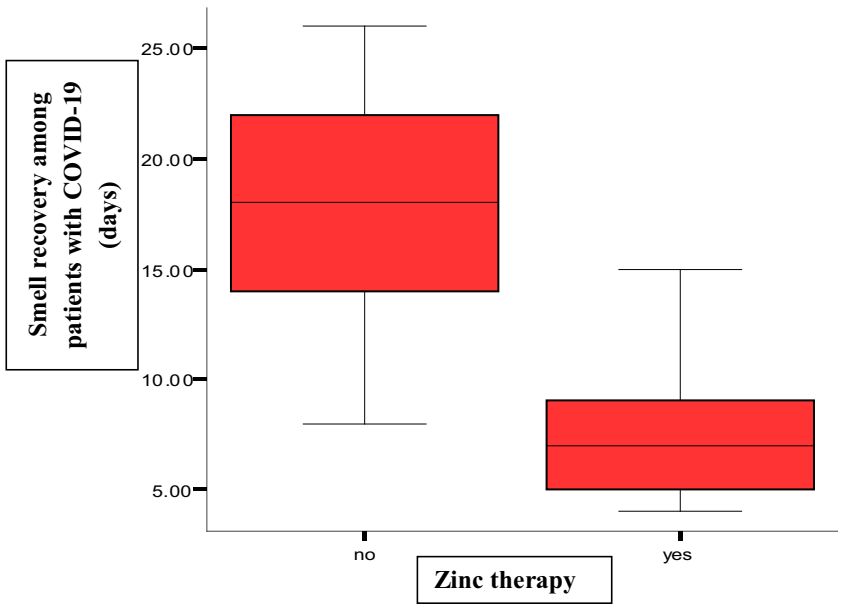

Fig. 1 Recovery days of olfactory dysfunction among patients with COVID-19 in relation to zinc therapy

COVID-19 grades of severity, p value was marginal (p = 0.084). To obtain conclusions, a larger study is necessary. It could be just by the inadequate statistical power due to the small sample size. A study reported the important role of zinc in reducing duration of symptoms of common cold, but not its severity [28].

Our results revealed significantly lower serum zinc levels in patients with olfactory impairment than those without, but did not reach a significant level. Pisano and Hilas reported that zinc deficiency is linked to taste and smell disorders in COVID-19 patients [59].

The findings of the current study showed that COVID-19 patients who received zinc therapy exhibited significantly lower duration of smell recovery than those who did not, without significant difference regarding the total recovery duration of COVID-19. This indicates that zinc therapy could improve the associated smell abnormality, but not affect the COVID-19 disease outcome. In a placebo-controlled randomized trial investigating the effect of zinc supplementation in treating smell dysfunction post-chemotherapy, Lyckholm and his colleges reported no significant value of zinc therapy in improving smell dysfunction [60]. In COVID-19 patients, deficient formation of type I and type II interferons was reported [59]. Zinc supplementation is claimed to reconstitute secretion of human interferon-alpha (IFN-a); it is suspected to have antiviral actions as in rhinovirus-infected cells [61, 62].

Conclusions

Zinc status could not have a role in development of anosmia and/or hyposmia among COVID-19 patients. Zinc therapy significantly reduced the recovery duration of anosmia/and or hyposmia in those patients without affecting the total recovery duration of COVID-19. Further larger scale studies should be performed to evaluate the possible role of zinc on the immune system in SARS-CoV-2 infection.

Authors' Contributions Study concept and design: AAA, MHH, AAG, ZFA, and SESB; patient selection and clinical evaluation and follow-up of patients: AAA, ZFA, AR, and MKE; blood sampling, molecular and biochemical assays: MHH and AK; statistical analysis: AAA, MHH, SESB, AR, MKE, and MAAS; literature research: AAA, SESB, MHH, MAAS, AR, and ZFA; first manuscript drafting: AAA, SESB, and MHH. The authors approved the final version of the manuscript.

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Compliance with Ethical Standards

Competing Interests The authors declare that they have no conflict of interest.

Ethics Approval and Consent to Participate The study was approved by the local Ethics Committee of Medical Research of the Faculty of Medicine, South Valley University, Qena, Egypt (ethical approval code: SVU-MED-MBC004-2020-04), and was conducted in accordance with the Declaration of Helsinki. Informed written consent was obtained from every participant who was anonymously enrolled.

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