Olfactory disturbances as presenting manifestation among Egyptian patients with COVID-19: Possible role of zinc

Mohammed H. Hassan (mohammedhosnyhassaan@yahoo.com)
Faculty of Medicine, South Valley University, Qena, Egypt https://orcid.org/0000-0003-2698-9438
Aida A. Abdelmaksoud
South Valley University, Faculty of Medicine, Qena, Egypt
Ali A. Ghweil
South Valley University, Faculty of Medicine, Qena, Egypt
Alaa Rashad
South Valley University, Faculty of Medicine, Qena, Egypt
Zaki F. Aref
South Valley University, Faculty of Medicine, Qena, Egypt
Ashraf Khodeary
Faculty of Medicine, Sohag University, Sohag, Egypt
Mahmoud Kammal Elsamman
Faculty of Medicine, Sohag University, Sohag, Egypt
Mennatallah Ali Abdelrhman Sayed
King Salman International University, Egypt
Shamardan ES Bazeed
Faculty of Medicine, South Valley University, Qena, Egypt

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Abstract

Background: 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. Also, to evaluate the effect of zinc therapy in recovery of smell dysfunction among such patients.

Methods: 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 who were categorized randomly into 2 groups, the first group included 49 patients received zinc therapy and a second group included 56 patients who did not receive zinc. Follow up of all patients for recovery duration of olfactory and gustatory symptoms and duration of complete recovery of COVID-19.

Results: Olfactory dysfunction was reported in 105 patients (78.4%). Serum zinc levels weren't significantly differs between the patients' 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 received zinc therapy than those who did not received zinc (p< 0.001), while the median duration of complete recovery from COVID-19 wasn't significantly differ among the two groups (p□0.05).

Conclusion: Although zinc status of COVID19 patients didn't exhibited a significant role in development of anosmia and/or hyposmia or disease severity, but 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.

Introduction

The 2019 novel coronavirus disease (COVID-19) is a viral infection; severe acute respiratory syndrome caused by coronavirus 2 (SARS-CoV-2). The first case was diagnosed in Wuhan, China, in 2019 and cause multiorgan manifestation. Cases have been reported in more than 180 countries to World Health Organization (WHO), including more than one million deaths. [1]. The common symptoms of COVID-19 are: fever, tiredness, and 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 by mild disease, only 5% develops 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 the pre-COVID-19 era, about 14% to 30% of all patients were 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 the humans; it comes second to iron in concentration but with no special zinc store [10]. Plasma zinc concentration is about 1µg/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 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 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 five 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 could lead to reduction in taste bud cells 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. Also, 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 in 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-2infection; (3) total leucocytic counts showing normal, or reduced lymphocyte count in early stage [30], 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, history of 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, co morbidities and smoking. Full history was taken from all patients with special stress about presence or absence of anosmia (loss of smell) or hyposmia (decrease sense of smell). In addition to subjective smell tests (using coffee or chocolate), formal smell tests may be required which give more accurate level of loss of smell, in that a minimum concentration of a chemical at which the patient can detect, can be given and compared to the average threshold for that patient's age group e.g. chemosensory test and butanol threshold test [31]. 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 [32]. 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 (PaO2)/oxygen concentration (FiO2) < 300mmHg; or (3) pulmonary imaging showed lesion progression > 50% within 24-48 hours. Extremely severe COVID-19 needed meet one of the following conditions: (1) development of respiratory failure requiring mechanical ventilation; (2) shock; (3) combined organ failure requiring ICU monitoring [33].

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 (220mg zinc sulfate equivocal to 50 mg elemental zinc twice daily [34]) 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 till 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 corona virus (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 [35].

2. Serum levels of zinc were measured for all patients, 3 ml of peripheral venous blood samples was collected in plain collection tubes for serum recovery. Samples were left to clot for 30 minutes 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) [36-40].

Statistical analysis

Analysis of data was performed using Statistical Program for Social Science (SPSS) version 24. 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 two groups, the Chi-square test ($\chi 2$) was used for qualitative variables, while independent-samples t-test of significance: was used for normally distributed parametric data. For abnormally distributed quantitative variables (non-parametric data), the Mann-Whitney U test was used. Probability (P-value) P-value > 0.05 was considered insignificant, P-value < 0.05 was considered significant; 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 patient 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 others (p-value < 0.001) (Table 1).

There were no significant differences regarding to gender, BMI and smoking status among COVID-19 patients of various disease, p-value > 0.05 (Table 1). Both co-morbidities 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 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 were presented in (Table 3). The serum zinc (mean±SD, µg/ml) in patients with mild, common, severe and extremely severe COVID-19 were (0.67 ± 0.18, 0.62 ± 0.14, 0.73 ± 0.18, and 0.72±0.22). There was no significant difference between mean serum zinc levels among patients with COVID-19 of various severities.

Zinc levels and olfactory dysfunction among patients with COVID-19

Serum zinc level in COVID 19 patients with anosmia and hyposmia were 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 didn't reach a significant level (p□0.05), (Table 4). There was no significant difference between serum zinc levels 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 didn't received (median 18 days with range 14-22 days), p value< 0.05 (Table 5 and Figure 1). Additionally, zinc therapy did not influence the duration of complete recovery of COVID-19 disease among patients who received zinc therapy (median 12 with range 8-17 days) vs. those who didn't received (median 12 with range 8-20 days), p□0.05.

Discussion

COVID-19 (Coronavirus disease) first discovered in Wuhan, china December 2019 [41] with obscure characteristics of the disease. In Egypt, anosmia and hyposmia are common complaints in COVID19 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 [42,43]. 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 [44] 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 [45] and Mahase [46] reported similar findings, as in old age-the cell-mediated immune function and humeral immune function reduced [47]. Other high risk groups for COVID-19 are people with certain co-morbidities as diabetes mellitus, hypertension, and ischemic heart diseases particularly when not controlled regardless their age [48,49,50,51], which were in line with our findings which revealed that co-morbidities frequency (diabetes mellitus, hypertension, and ischemic heart disease) and deaths were significantly frequent in severe and extremely severe COVID 19 patients. Additionally, Marhl et al [52] who reported increase 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 [53] reported an increased severity and incidence of COVID-19 in diabetic patients. As regard smoking, no significant difference between different COVID-19 grades of severity which was in accordance with several researchers [54, 55].

In the current study, the frequency of anosmia and hyposmia among the included COVID-19 patients were 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 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-CoV2 infection depends on the metabolism of the host cell. Zinc claimed to have antiviral effects demonstrated in various cases [55, 56, 57]. Examples include coronaviridae, papilloma virus, picornavirus, metapneumovirus, herpes simplex virus, rhinovirus, varicella-zoster virus, human immunodeficiency virus (HIV), respiratory syncytial virus and the hepatitis C virus [58, 59]. Viral fusion with the host cell membrane could be prevented by zinc also it impairs the function of viral polymerase.

The current study revealed that no significant difference in serum zinc levels between patients with different COVID-19 grades of severity which was in agreement with a study reported the important role of zinc in reducing duration of symptoms of common cold, but not its severity [60].

Our results revealed significantly lower serum zinc levels in patients with olfactory impairment than those without, but didn't reach a significant level. Pisano and Hilas reported that zinc deficiency is linked to taste and smell disorders in COVID-19 patients [61].

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 didn't without significant difference regarding the total recovery duration of COVID-19 which indicates that zinc therapy could improves the associated smell abnormality, but not affects 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 [62]. In COVID-19 patients it was reported deficient formation of type I and type II interferons [60]. Zinc supplementation claimed to reconstitute secretion of human interferon alpha (IFN-a), it is suspected to have antiviral action as in rhinovirus-infected cells [63,64].

Conclusions

Zinc status couldn't have a role in development of anosmia and/or hyposmia among COVID19 Patients. Zinc therapy significantly reduce the recovery duration of anosmia/and or hyposmia in those patients without affecting the total recovery duration of COVID19. Further larger scale studies should be performed to evaluate the possible role of zinc on the immune system in SARS-CoV-2 infection.

Declarations

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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.

Authors' contributions

Study concept and design: AAA, MHH, AAG, ZFA and SESB; patients' 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.

Competing interests

The authors declare no competing interests.

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Tables

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

Variables		COVID 19 severity								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
Co-morbidities	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	44	97.8%	57	100%	20	95.2%	9	81.8%	0.013*
	Yes	0		1	2.2%	1	4.8%	2	18.2%	

*Significant P-value□0.05. Data were expressed as mean± SD or numbers and percentages

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 severity of COVID-19 disease

Variables	COVID 19 severity				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

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	18	7	< 0.001*
	IQR	14 – 22	5 - 9	

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

Figures

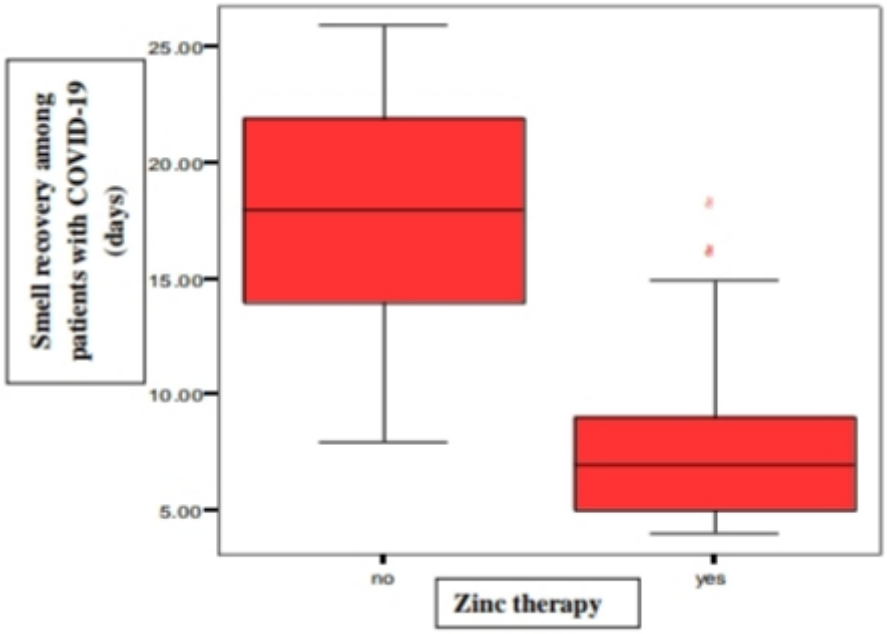

Figure 1

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