International Journal of Nutritional Sciences

Open Access

Austin Publishing Group

Short Communication

Deficiencies in Rare Trace Elements and Severity of COVID-19: A Prospective Cohort Study

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Received: July 17, 2024
Accepted: August 02, 2024
Published: August 09, 2024

Abstract

Background & Aims: Recent data show that not only micronutrients but also rare trace elements play an important role in the immune system. We therefore compared admission levels of rare trace elements in patients with a mild and severe course of coronavirus disease 2019 (COVID-19) and described its association with adverse outcomes.

Methods: We performed an analysis of the rare trace elements including arsenic, chromium, manganese, molybdenum, nickel and vanadium at admission in consecutively hospitalized patients with COVID-19 from March until April 2020 at the Cantonal Hospital Aarau (Switzerland). We studied associations of the above-mentioned trace elements with severe disease progression, a composite endpoint consisting of in-hospital mortality and/or need for intensive care unit treatment with logistic regression.

Results: In total, 67 patients were analyzed with a median age of 67 years of which 63% (n=42) were male. Patients with a severe course of COVID-19 were more males (83% versus 52%, p=0.01) and had more often a chronic obstructive pulmonary disease (13% versus 0%, p=0.01). Median values of analyzed trace elements were similar in both groups with no significant differences. Logistic regression analysis, adjusted for age and gender showed a significant association between manganese levels and the composite endpoint (adjusted OR 0.94, 95% CI 0.89 – 0.99, p=0.03).

Conclusions: Little difference in levels of rare trace elements was found in COVID-19 patients with severe disease compared to patients with mild disease. However, lower manganese where associated with higher risk for severe course of COVID-19.

Keywords: Trace elements; COVID-19; SARS-CoV-2; Hospital outcomes

Introduction

Early during the coronavirus disease 19 (COVID-19) pandemic the influence of vitamins and minerals on the susceptibility and severity of the disease was hypothesized for several reasons [1,2]. First, advanced age and malnutrition – conditions often associated with micronutrients deficiencies – were found to be a major risk factor [3]. Second, for some micronutrients, such as vitamin C or zinc, the importance for the immune system and infection susceptibility is well described [4], while for other trace elements, such as chromium or manganese, the role in immunity remains unclear. Recent data suggest that trace elements may directly influence inflammatory processes in various situations. For example in mice models, a diet low in molybdenum led to thymic atrophy and an imbalance of the immune system [5], while exposure to arsenic led to a changed ratio of Th1/Th2/Th17/Treg cells in liver and kidney [6]. A meta-analysis reported that chromium supplementation decreased C-reactive protein levels in patients with chronic inflammation [7]. Consequently, deficiencies in some trace elements may increase the risk of an infection or reaction to an infection. In a previous analysis [8] we described levels of micronutrients for which the influence on the immune system is well established in patients hospitalized with COVID-19. Within the same cohort, we also measured levels of rare trace elements including arsenic, chromium, manganese, molybdenum, nickel and vanadium, for which little information is currently available in patients with COVID-19. Herein, we describe the association of levels of these trace elements with a severe course of COVID-19, a composite endpoint consisting of in-hospital mortality and/or need for Intensive Care Unit (ICU) in hospitalized patients with COVID-19.

Citation: Gregoriano C, Voelkle M, Jacquemai M, Neyer P, Bernasconi L, et al. Deficiencies in Rare Trace Elements and Severity Of COVID-19: A Prospective Cohort Study. Int J Nutr Sci. 2024; 9(2): 1089.

Table 1: Baseline characteristics stratified to disease severity.

	All	Mild disease	Severe disease	p-value
	n=67	n=44	n=23	
Socio-demographics				
Age (years), median (IQR)	67.0 (58.6, 74.2)	69.1 (60.0, 75.8)	65.3 (56.0, 72.6)	0.21
Gender (male), n (%)	42 (63)	23 (52)	19 (83)	0.01
Nationality				
Swiss, n (%)	42 (63)	29 (66)	13 (57)	0.11
Others, n (%)	15 (22)	9 (20)	6 (26)	
Unknown, n (%)	10 (15)	6 (14)	4 (17)	
Pre-existing risk-factors				
Active smoker, n (%)	5 (10)	4 (12)	1 (6)	0.54
Immunosuppressant, n (%)	1 (1)	0 (0)	1 (4)	0.16
Pre-admission history				
Transfer from another hospital, n (%)	19 (28)	7 (16)	12 (52)	<0.01
Symptom onset before admission (days), median (IQR)	7.0 (5.0, 11.0)	7.0 (5.0, 11.0)	8.0 (5.0, 12.0)	0.86
Comorbidities				
Cancer, n (%)	5 (7)	4 (9)	1 (4)	0.48
Hypertension, n (%)	40 (60)	29 (66)	11 (48)	0.15
Coronary artery disease, n (%)	17 (25)	13 (30)	4 (17)	0.28
Chronic heart failure, n (%)	3 (4)	3 (7)	0 (0)	0.2
Asthma, n (%)	13 (19)	8 (18)	5 (22)	0.73
Chronic obstructive pulmonary disease, n (%)	3 (4)	0 (0)	3 (13)	0.01
Obstructive sleep apnea syndrome, n (%)	10 (15)	6 (14)	4 (17)	0.68
Active rheumatic disease, n (%)	1 (1)	0 (0)	1 (4)	0.16
Chronic kidney disease, n (%)	18 (27)	15 (34)	3 (13)	0.06
Diabetes, n (%)	20 (30)	13 (30)	7 (30)	0.94
Age-adjusted Charlson comorbidity index , median (IQR)	3.0 (2.0, 6.0)	3.0 (2.0, 7.0)	3.0 (2.0, 4.0)	0.32
Clinical frailty score, median (IQR)	3.0 (2.0, 4.0)	3.0 (2.0, 5.0)	3.0 (2.0, 3.0)	0.22
Outcomes				
Overall length of hospital stays (days), median (IQR)	9.0 (5.0, 19.0)	7.0 (4.0, 10.5)	19.0 (9.0, 24.0)	<0.01
ICU care, n (%)	20 (30)	0 (0)	20 (87)	<0.01
Need for mechanical ventilation, n (%)	16 (24)	0 (0)	16 (70)	<0.01
In-hospital mortality, n (%)	9 (13)	0 (0)	9 (39)	<0.01
Trace element				
Arsenic, median (nmol/l), (IQR)	4.4 (2.1, 7.1)	4.9 (2.9, 7.4)	3.8 (1.8, 6.3)	0.44
Chromium, median (nmol/l), (IQR)	11.8 (8.8, 15.0)	11.4 (8.7, 15.0)	12.5 (8.9, 15.6)	0.77
Manganese, median (nmol/l), (IQR)	26.7 (19.5, 33.5)	28.4 (19.5, 38.6)	26.0 (20.6, 31.5)	0.22
Molybdenum, median (nmol/l), (IQR)	8.0 (5.2, 10.8)	7.9 (5.0, 10.6)	8.4 (5.8, 10.8)	0.62
Nickel, median (nmol/l), (IQR)	17.6 (14.6, 21.0)	18.2 (15.1, 21.1)	16.3 (13.7, 19.2)	0.17
Vanadium, median (nmol/l), (IQR)	5.1 (4.3, 5.6)	5.1 (4.4, 5.6)	4.9 (4.1, 6.0)	0.97
Nutritional assessment				
NRS ≥ 3, n (%)	9 (19)	7 (21)	2 (14)	0.58
BMI				
18.5 - 24.9 kg/m^2, n (%)	16 (32)	13 (36)	3 (21)	0.49
25 - 29.9 kg/m^2, n (%)	19 (38)	12 (33)	7 (50)	
>30 kg/m^2, n (%)	15 (30)	11 (31)	4 (29)	

Abbreviations: BMI: Body Mass Index; ICU: Intensive Care Unit; IQR: Interquartile Range; NRS: Nutritional Risk Screening

Table 2: Association of trace element levels and composite endpoint.

	Univariable OR (95% CI), p-value	Adjusted OR* (95% CI), p-value
Arsenic	0.99 (0.97-1.02), p=0.61	0.99 (0.97-1.02), p=0.60
Chromium	1.01 (0.94-1.09), p=0.77	1.03 (0.95-1.12), p=0.51
Manganese	0.97 (0.93-1.01), p=0.15	0.94 (0.89-0.99), p=0.03
Molybdenum	1.03 (0.97-1.09), p=0.37	1.05 (0.98-1.12), p=0.16
Nickel	0.97 (0.90-1.05), p=0.51	0.99 (0.91-1.06), p=0.70
Vanadium	0.91 (0.64-1.30), p=0.61	0.90 (0.61-1.33), p=0.61

*Adjusted for age and gender; Abbreviations: CI: Confidence Interval; OR: Odds Ratio

Methods

We performed an analysis of the rare trace elements arsenic, chromium, manganese, molybdenum, nickel and vanadium at admission in consecutively hospitalized patients with COVID-19 from March 17 until April 30 2020 at the Cantonal Hospital Aarau, a tertiary care hospital in Switzerland. The study was approved by the local ethics committee (EKZN 2020-01306). Details regarding the methodology and patient characteristics have been published elsewhere [3]. In short, COVID-19 diagnosis was established through a positive real-time Reverse Transcription Polymerase Chain Reaction test (RT-PCR) taken from nasopharyngeal swabs or lower respiratory tract specimens. Sociodemographic and medical data were extracted from chart abstraction and electronic medical records. All included patients gave written general informed consent.

Blood samples were obtained within the first four days of hospitalization. Patients who received multivitamin supplements containing analysed trace elements before the blood draw were excluded from our study. Trace elements were measured by inductively coupled plasma mass spectrometry in collision mode (helium). The method was set up without digestion

and simple dilution with an alkaline solution containing an internal standard element (rhodium).

Results

In total we included 67 patients with a median age of 67 years of which 63% (n=42) were male. Detailed information regarding the cohort stratified by disease severity are presented in Table 1 including median levels of trace elements.

The group with a severe course of COVID-19 had more males (83% versus 52%, p=0.01) and more often a chronic obstructive pulmonary disease (13% versus 0%, p=0.01). Median values of analysed trace elements were similar in both groups with no significant differences. Further, we performed a logistic regression analysis, which was adjusted for age and gender. We found a significant association between manganese levels and the composite endpoint (adjusted OR 0.94, 95% CI 0.89 – 0.99, p=0.03) (Table 2).

Discussion

Zeng et al. published a study on whole blood levels of various trace elements in patients with COVID-19 [9]. In contrast to this study, where levels of chromium, manganese and arsenic were significantly different in severe and mild courses, we found no differences in micronutrient levels when comparing patients with a mild and severe course of COVID-19. We found an association of lower manganese levels with higher risk for the composite of ICU admission and/or in-hospital mortality, in contrast to the above-mentioned study, where arsenic was associated with disease severity and chromium with mortality.

Metals are structural parts or cofactors in over half of known proteins. Manganese is a cofactor in various enzymes, e.g. manganese superoxide dismutase, and plays a role in protection from reactive oxygen species [10]. It has been shown that higher cytosolic manganese levels inhibited viral infections in vitro and that in cases of viral infections manganese is released into the cytosol [10]. Furthermore, treatment with manganese activated the innate immune system by inducing the production of type I-interferons. Recent data reported that lower local type I-interferon response was found in critically ill patients with COVID-19 [12]. Thus, higher manganese levels in patients may have an influence on this inflammatory pathway, which also plays a role in COVID-19.

Conclusion

In conclusion, this small observational study found little difference in levels of rare trace elements including arsenic, chromium, manganese, molybdenum, nickel, and vanadium in COVID-19 patients with severe disease compared to patients with mild disease. However, lower manganese where associated with higher risk for a severe course of COVID-19. Further research is needed to better understand the role of trace elements in COVID-19 and other infections.

Author Statements

Acknowledgement

We thank all participating patients and their families, and all healthcare workers at the Cantonal Hospital Aarau for their great dedication to reduce the burden of this severe disease.

Statement of Authorship

Conceptualization, M.V., C.G. and P.S.; data curation, C.G., P.N. and L.B.; statistical analysis, M.V., J.M, C.G. and P.S.; writing—original draft preparation: M.V., J.M, C.G. and P.S.; writing—review and editing, P.N., L.B., and B.M. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest Statement

P.S. and B.M. received research support paid to the Institution from Thermofisher, bioMerieux, Roche Diagnostics, Nestle Health Science, and Abbott Nutrition. All other authors reported no conflict of interest.

Funding Sources

This research was funded by Research Council KSA (Cantonal Hospital Aarau), (1410.000.131).

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