Physiological predictors of long-term effects of COVID-19 in patients with SARS-CoV-2: Focus on lymphocyte proliferation-improving micronutrients

Sofia-Maria Karkhut[1], Iryna Muzyka[1,2], Khrystyna Dzhyoieva[1], Maryana Savytska[1], Yaryna Pohoretska[1], Nataliya Ivanchenko[3], Oksana Zayachkivska[1], John V. Schloss[4], Sandor Szabo[4*]

[1] Danylo Halytsky Lviv National Medical University, Lviv, Ukraine
[2] Yuriy Lypa Novoyavorivsk Distric Hospital, Novoyavorivsk, Lviv region, Ukraine
[3] State institution « Lviv oblast Center for Diseases Control and Prevention of Ministry of health of Ukraine, Lviv, Ukraine.
[4] American University of Health Sciences, Signal Hill, CA, USA

Patients with long-term effects of coronavirus disease, the so-called "long-term COVID-19 syndrome" (long-COVID-19) after SARS-CoV-2 infection, have a postponed recovery lasting from 4 weeks and up to six months, spread worldwide.

Physiological predictors based on human blood biomarkers and host-virus responses to SARS-CoV-2 are still unknown. There is growing evidence about the impact of micronutrients on improving lymphocyte proliferation and their essential roles for a functioning human immune system and regulating metabolic health. This paper aims to review information about micronutrients in patients with SARS-CoV-2 infection that determines long-COVID-19 outcomes and highlight the importance of diagnostics in predictors of long-COVID-19. We reviewed articles returned from searches on PubMed/SCOPUS/ Web of Science/ EMBASE databases using a combination of terms "long COVID-19", "long-term effects of COVID-19", "post-COVID-19 symptoms", "COVID-19 associated stress", "micronutrients". Evidence indicates the relationship between lymphocyte proliferation improving micronutrient level and long-COVID-19 induction. Zinc, selenium, iron, manganese have an immunomodulatory function in innate and adaptive immune responses to viral infection. Anti-inflammatory functions of Vits A and B groups include the regulation of lymphocyte proliferation and metabolic health. Further research using sampling and artificial intelligence-assisted algorithms could assist in the recognition of the correlation of micronutrients and long-COVID-19 clinical outcomes.

Keywords: long COVID-19; Zinc, Selenium, Iron, Manganese, Copper, lymphocytes proliferation, Metabolic health.

OPEN ACCESS

DOI 10.25040/ntsh2021.02.06

For correspondence: Danylo Halytsky Lviv National Medical University, 69 Pekarska str., Lviv, Ukraine, 79010

E-mail: sofiakarkhut@gmail.com

Received: Nov, 5, 2021

Accepted: Nov, 24, 2021

Published online: Dec, 29, 2021

ORCID IDs
Sofia-Maria Karkhut: https://orcid.org/0000- 0002-7714-3494
Iryna Musyka: https://orcid.org/0000-0001-7446-6063
Khrystyna Dzhyoieva https://orcid.org/0000-0002-9406-3090
Maryana Savytska: https://orcid.org/0000-0001-9404-4589
Yaryna Pohoretska: https://orcid.org/0000-0002-1252-0121
Nataliya Ivanchenko: https://orcid.org/ 0000-0002-0112-6962
Oksana Zayachkivska: https://orcid.org/0000-0002-4309-2473
John V. Schloss: https://orcid.org/0000-0002-6586-7508
Sandor Szabo: https://orcid.org/0000-0002-1185-797X

Disclosures: the authors declared no conflict of interest.

Author Contributions
Concept: Oksana Zayachkivska, Sandor Szabo;
Data Collection and/or Processing: Sofia-Maria Karkhut, Iryna Muzyka;
Writing Manuscript: Sofia-Maria Karkhut, Iryna Muzyka, Khrystyna Dzhyoieva, Maryana Savytska, Yaryna Pohoretska, Nataliya Ivanchenko;
Final review and editing: Oksana Zayachkivska, John V. Schloss, Sandor Szabo.

Ethical approval: not required for this review.

Funding: The study is a fragment of scientific research work of the Department of Normal Physiology, Danylo Halytsky Lviv National Medical University: "Study of the mechanisms of regulation of integrative systems of the organism in the conditions of the norm, functional disorders and finding out the ways of their correction".

* Presented during 5th International Symposium "SMART LION". Medical Imagining and Global Health, October 7–9, 2021.

DOI 10.25040/ntsh2021.02.06

Адреса для листування: Львівський національний медичний університет імені Данила Галицького, м. Львів, вул. Пекарська 69, Україна, 79010

E-пошта: sofiakarkhut@gmail.com

Надійшла до редакції: 05.11. 2021

Прийнята до друку: 24.11. 2021

Опублікована онлайн: 29.11. 2021

ORCID IDs
Sofia-Maria Karkhut: https://orcid.org/0000-0002-7714-3494
Iryna Musyka: https://orcid.org/0000-0001-7446-6063
Khrystyna Dzhyoiva https://orcid.org/0000-0002-9406-3090
Maryana Savytska: https://orcid.org/0000-0001-9404-4589
Yaryna Pohoretska: https://orcid.org/0000-0002-1252-0121
Nataliya Ivanchenko: https://orcid.org/0000-0002-0112-6962
Oksana Zayachkivska: https://orcid.org/0000-0002-4309-2473
John V. Schloss: https://orcid.org/0000-0002-6586-7508
Sandor Szabo: https://orcid.org/0000-0002-1185-797X

Конфлікт інтересів: автори декларують відсутність конфлікту інтересів.

Особистий внесок авторів
Концепція: Оксана Заячківська, Шандор Сабо;
Збір та обробка даних: Кархут Софія-Марія, Ірина Музика;
Написання тексту: Кархут Софія-Марія, Ірина Музика, Христина Джиоєва, Мар'яна Савицька, Ярина Погорецька, Наталія Іванченко;
Рецензування: ОксанаЗаячківська, Джон В. Шлосс, Шандор Сабо.

Дозвіл комісії з біоетики щодо проведення досліджень: для цього дослідження непотрібний.

Фінансування: Дослідження є фрагментом науково-дослідної роботи кафедри нормальної фізіології ЛНМУ імені Данила Галицького «Вивчення механізмів регуляції інтегративних систем організму в умовах норми, функціональних розладів та з'ясування шляхів їх корекції».

Фізіологічні предиктори довгострокових наслідків COVID-19 у пацієнтів з SARS-CoV-2: фокус на мікронутрієнти, що покращують проліферацію лімфоцитів

Софія-Марія Кархут[1], Ірина Музика[1, 2], Христина Джиоєва[1], Мар'яна Савицька[1], Ярина Погорецька[1], Наталія Іванченко, Оксана Заячківська[1], Джон В. Шлосс[4], Шандор Сабо[4**]

[1] Львівський національний медичний університет імені Данила Галицького, Львів, Україна
[2] КНП «Новояворівська лікарня імені Юрія Липи», м. Новояворівськ, Львівська обл., Україна
ДУ "Львівський обласний центр контролю та профілактики хвороб Міністерства охорони здоров'я України", Львів, Україна
[4]Американський університет медичних наук, Сігнал Хілл, Каліфорнія, США

Довгострокові наслідки коронавірусної хвороби, так званого «постковідного синдрому COVID-19» (long-COVID-19) після інфікування SARS-CoV-2, поширилися по всьому світу. Фізіологічні предиктори біомаркерів крові та реакції взаємодії «вірусу-господаря» на інфекцію SARS-CoV-2 досі невідомі. З'являється все більше доказів щодо позитивного впливу мікронутрієнтів на проліферацію лімфоцитів та їх важливу роль для функціонування імунної системи людини та регуляції метаболічного здоров'я. У цій статті розглянуто інформацію про те, як вміст мікронутрієнтів у пацієнтів із інфекцією SARS-CoV-2 визначає тривалі наслідки захворювання на COVID-19. Статті з пошукових запитів бібліографічних баз PubMed/SCOPUS/Web of Science/ EMBASE були переглянуті з використанням наступних термінів: "тривалий COVID-19", "довгострокові наслідки COVID-19", "постковідні симптоми", "стрес, пов'язаний з COVID-19", "мікронутрієнти". Дані джерела вказують на зв'язок між проліферацією лімфоцитів, вмістом мікронутрієнтів і тривалими наслідками COVID-19. Цинк, селен, залізо, магній беруть участь у реакціях природженого і набутого імунітету, а також мають імуномоделювальну дію проти вірусної інфекції. Вітаміни A і B володіють протизапальними функціями, регулюючи проліферацію лімфоцитів і метаболізм. Подальші дослідження з використанням біопроб і алгоритмів штучного інтелекту можуть допомогти у розпізнанні взаємозв'язку між мікронутрієнтами та довготривалими клінічними наслідками COVID-19.

Ключові слова: тривалий COVID-19, цинк, селен, залізо, марганець, мідь, проліферація лімфоцитів, метаболічне здоров'я.

** Оприлюднено під час 5-го міжнародного симпозіуму «SMART LION». Перспективи в медицині та глобальне здоров'я, 7-9 жовтня 2021 року.

Introduction

COVID-19 (coronavirus disease – 2019) is a highly contagious disease caused by SARS-CoV-2 (also known as 2019-nCoV). More than 80% of patients with COVID-19 have mild to moderate illness, and some patients are asymptomatic. However, between 10 and 20% of patients require hospitalization due to acute respiratory distress syndrome and multi-organ insufficiency. These complications are more common in older patients and immunosuppressed persons [1-3]. Overall, the mortality rate for COVID-19 is about 1-2%, and 4-6% for more virulent strains of the virus, especially in populations with high population density. One of the crucial features of COVID-19 is the development of long-term effects of coronavirus disease. This condition is called "long-term COVID-19 syndrome" (long-COVID-19), which often has no relation to the airway. Still, it can affect practically any organ and induce multiple systemic organ damage based on endothelial dysfunction [4,5].

Most of the symptoms of long-COVID-19 result from damage to the central and peripheral nervous systems, including the involvement of MRC1−microglial subpopulation as the result of an increasingly inflamed central nervous system (CNS) environment, specifically, the choroid plexus [6] and stress [7,8]. It is not surprising that the new disease created confusion, panic, and chaos that almost predictably led to stress [9,10]. Stress reactions are often the side products of economic problems or complicating factors, especially in long COVID-19. This global pandemic situation has harmful economic consequences. The World Bank report of June 8, 2020, states that COVID-19 produced "the fastest, steepest downgrades in consensus growth projections among all global recessions since 1990" [11]. Thus, preventive measures for long-COVID-19 are vital elements for mitigating the pandemics – individual lifestyle, which impacts their well-being – however, several questions about the physiological background of long COVID-19 causes are lacking. Based on the current evidence, this review will discuss physiological predictors and focus on the role of micronutrients that impact the improvement of lymphocyte proliferation and could determine long COVID-19. Their identification could help create appropriate personalized precisive, preventive, and diagnostic management strategies for patients with long-COVID-19.

Our study aimed to search the latest information by screening scientific literature in multiple databases including PubMed, Scopus, Web of Science, and EMBASE platforms, to identify relevant studies, using keywords like "long-COVID-19", "long-term effects of COVID-19", "post-COVID-19 symptoms", "COVID-19-associated stress", "micronutrients." Studies were included in research when they met the following conditions: conducted on adults (age > 18 years), published in English. The following studies were excluded: studies with children, nonhumans, cross-sectional and uncontrolled studies, vitamins C, D, and E effects on immune system improvement, which have been widely discussed in the literature recently. The publication dates of most of the selected articles are between 2007-2021 [fig.1].

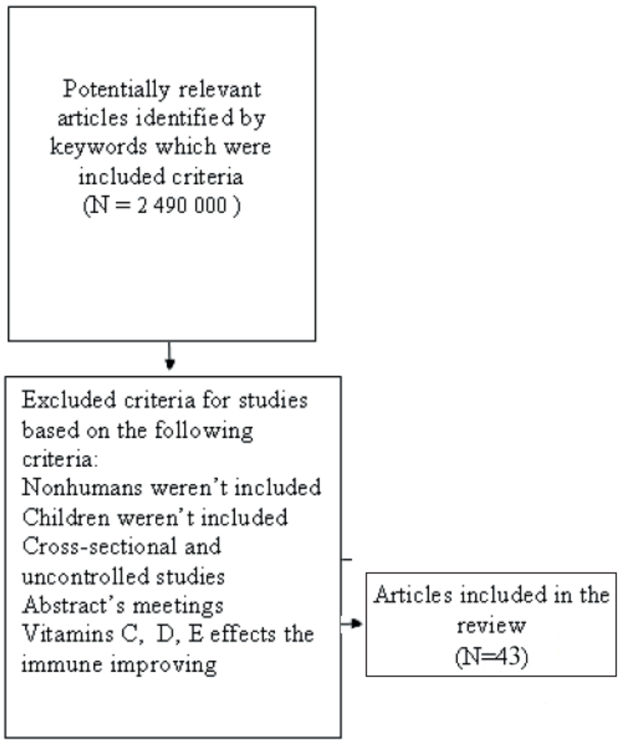


Figure1. Flowchart illustrating number of reviewed studies associated with lymphocyte proliferation improving in long COVID-19 screened with included and excluded criteria

Prevalent clinical manifestation of long COVID-19

The most common long-term consequences after SARS-CoV-2 infection are a wide range of signs, including muscle pain, fatigue, and various mental disorders, such as anxiety and depression, memory disorders, hair loss, anosmia, ageusia, and hearing loss and sleep disorders [12]. Some patients who needed hospitalization, even after six months of recovery, experienced one or more disease symptoms. Long COVID-19 has a significant effect on the brain, causes anxiety. Recent studies indicate that 30% of live-in survivors were diagnosed with psychiatric or neurological conditions within six months of infection [13]. Nerve signs and symptoms of long-COVID-19 may include fatigue, myalgia, headache, cognitive impairment ("brain mist"). At the same time, anxiety, depression, sleep disturbance, and post-traumatic stress disorder occur in 30-40% of patients who survive COVID-19 [14]. Pathophysiological mechanisms of long-term complications of COVID-19 include microvascular thrombosis, impaired immune regulation, and inflammation [2,7,12]

Other organ systems participating in long COVID-19 include respiratory, cardiovascular, hematological, gastroenterological, endocrine, and renal systems [15]. No studies show physiological changes that could play a crucial role in inducing the long COVID-19 syndrome.

Micronutrients as physiological predictors for the long COVID-19 syndrome

The speed and quality of the body's immune response depend on several factors. In particular, the lifestyle-related physical activity, which is important for releasing anti-inflammatory myokines [16], quality and quantity of sleep [17], and the necessary level of micronutrients, responsible for virus-host defensive responses [18]. For example, the rate of proliferation of lymphocytes depends on several micronutrients, including trace elements and metabolic compounds, and if they are not available in sufficient quantities, human immune defense declines [19]. Micronutrients are known to affect the lymphocyte proliferation rate. Table 1 contains those that affect the immune system the most: Zinc [20], selenium [21], iron [22,23], copper (Cu) [24], vitamin A [25], manganese (Mn) [26], biotin (B7) [27], thiamine (B1) [28].

Updates on the impact of micronutrients on immunity patients with SARS-CoV-2

COVID-19-associated stress could modulate cellular or organic integrity by declining natural redox-based functions, such as intercellular communication, vascular homeostasis, cell cycle, metabolic and bioenergetic signaling networks. They could induce a reciprocal relationship between the interaction of redox system agents and low-grade inflammation or metaflammation (inflammation with associated metabolic disorders) [38,39]. Since significant redox agents are involved in endothelial homeostasis during its injury in COVID-19, there are essential sulfur-containing metabolites for Hydrogen Sulfide production, L-arginine containing metabolites for Nitrogen Oxide (NO) production, tryptophan, lysine, arginine.

Some studies have shown a direct correlation between micronutrient deficiencies (e.g., zinc) responsible for the immune response and mortality from COVID-19 (fig. 1) [40-41]. Another essential micronutrient, selenium, has a similar clinical correlation with mortality and morbidity associated with COVID-19 [42]. However, 25% of Americans surveyed using a lymphocyte proliferation assay had a deficiency of five or more basic micronutrients. Most Americans (98%) have at least one deficiency, and about 33% have zinc deficiency [43]. It is well-known that micronutrient deficiency causes pro-inflammatory microbiota, which, in turn, affects the brain-gut axis and promotes stress-associated response, causing the body's defense resources to change. Thus, there is an urgent need to study predictors of changes in natural defensive reactions and functional reserve of the body, which form individual prerequisites for long-term COVID-19. There is a need to establish a quantitative correlation between nutritional deficiency and the severity of clinical signs of long COVID-19. Establishing a quantitative relationship between micro nutritional deficiencies and long COVID-19 recovery prognosis will determine their optimal correction and future use for the long COVID-19 prevention, clinical diagnosis, and treatment protocols.

The complexity and multifactorial origin of long COVID-19 syndrome require an interdisciplinary research approach, powerful enough to provide reliable shreds of evidence for detecting their predictors related to lymphocyte proliferation improving micronutrients. Appropriate use of micronutrients will create better health care policies for the long COVID-19 syndrome.

Table 1

Benefits of micronutrients for lymphocytes proliferation improvement using immunity and metabolic effects

Micronutrients	Effects on lymphocyte proliferation	Effects on others functions	Effects on metabolic health
Zinc (Zn)	↓Zinc reduces the number of lymphocytes, disrupts lymphocyte development, ↓proliferation, ↑apoptosis, and thymic atrophy; ↓IL-2 production by helper T cells, and defects in T cells subpopulations [20]	↓Zn correlates with glycated hemoglobin and is associated with inflammatory bowel disease [29] ↓Zn enhances liver damage, leading to ↑serum ALT, accumulation of lipids in the liver, oxidative injure, inflammation [30]	↑Zn improves glycemic control in T2DM [29] ↑Zn improves glucose tolerance, HOM-Abeta, ↓hyperglycemia, IR, glucose intolerance, obesity [31]; ↑ glucose uptake, GLUT4 translocation, ↓ both gluconeogenic enzyme activities, as well as insulin signaling inhibitors, ↓ cytokine production, activation of NFkB [29]
Selenium (Se)	↑Se associated with CD4+ T cell activation, distribution, and variation; inducing Th1 phenotype; ↑Se cytotoxicity of CD8+ T cells [21]; ↑the activity of NK cells; preserving T cell expansion → T cell-dependent antibody making → avoiding the vasoconstriction and changes in blood coagulation [21]	↓Se links to changes in cellular metabolism, oxidative stress and inflammation [29]	↓Se and ↑Se status linked to IR, T2DM; ↓Se associated with serum insulin ↑ insulin sensitivity, antioxidant activating [29]; ↓ Related to beta-cell oxidative damage [29]
Iron (Fe)	↓Fe leads to suppression of lymphocyte proliferation; Fe uptake via TfR1 is essential for B and T cell responses [22]; lymphocytes need Fe for the successful cellular and humoral response [22]	Plays an essential role in metabolism as a component of some proteins and enzymes; Involved in oxygen transport, DNA synthesis, energy production, electron and oxygen transport [22]	↓Fe → Anemia; ↓The cellular response to hypoxia is disturbed [22]
Copper (Cu)	↓ Cu leads to ↓T cells activation and ↓IL-2 production; breaks T and B cellular responses to mitogen stimulation [24]	↑Cu has antioxidant activity	↑Cu is associated with T2DM, IR, BMI, T2DM risk are associated with Cu/ceruloplasmin [32]; ↑Cu → ↑hepatic lipid/TAG content, lipogenic genes [29]
Vitamin A (Vit A)	Vit A induces T cell Migration and CD169+ macrophage development [25]; necessary for regulatory T cells and promotes IL-22 synthesis [25]	↓Vit A → inflammation and damage gut barrier integrality → impairs insulin sensitivity and blood glucose regulation [29]	↓Vit A → ↑beta cell apoptosis → glucose intolerance → ↓insulin reaction, [29]; ↓beta-cell mass; ↑Vit A is associated with insulin sensitivity [33]; ↓visceral adiposity ↑ RBP1 in T2DM and obesity [29]
Manganese (Mn)	Mn2+ ions antagonize the Ca2+ influx; [26] Mn supplementations maintain macrophages viability, decrease in intracellular Reactive Oxygen Species (ROS) and NO level [26]	↓Mn related with IBD [29]; ↑colon damage → intestinal leak → ↑inflammatory cytokines → ↑ oxidative stress → ↑DNA damage → ↓BMI [34]	↓Mn is associated with↑T2DM risk via IR → glucose intolerance [29]; ↑Mn → ↑insulin production, ↑antioxidant activity → ↓pancreatic oxidative injury → ↓ renal lipid peroxidation [29]
Biotin (Vit B7)	↓Vit B7 →↓ T regulatory cells, enhances differentiation of CD4+ T cells on the way to Th1 and Th17 cells; ↑levels of proinflammatory cytokines IFN-γ, IL-17 and TNF [27]	↓Vit B7 is associated with dysbiosis, Alopecia [29] ↑Biotin is associated with lower visceral fat mass [29]	↓Vit B7 →↓ blood glucose, ↓ glucose utilization and lipogenesis [35]
Thiamin (Vit B1)	↓Thiamine → upregulates microglial cell CD40 expression [28]	↓ Thiamine → hyperglycemia-induced GI injury→ neurological disorders [36]	Necessary for ideal insulin secretion [29]; ↓ Thiamine → diabetes [37]; ↑ Thiamine enhances glucose tolerance, ↓fasting blood glucose [29]

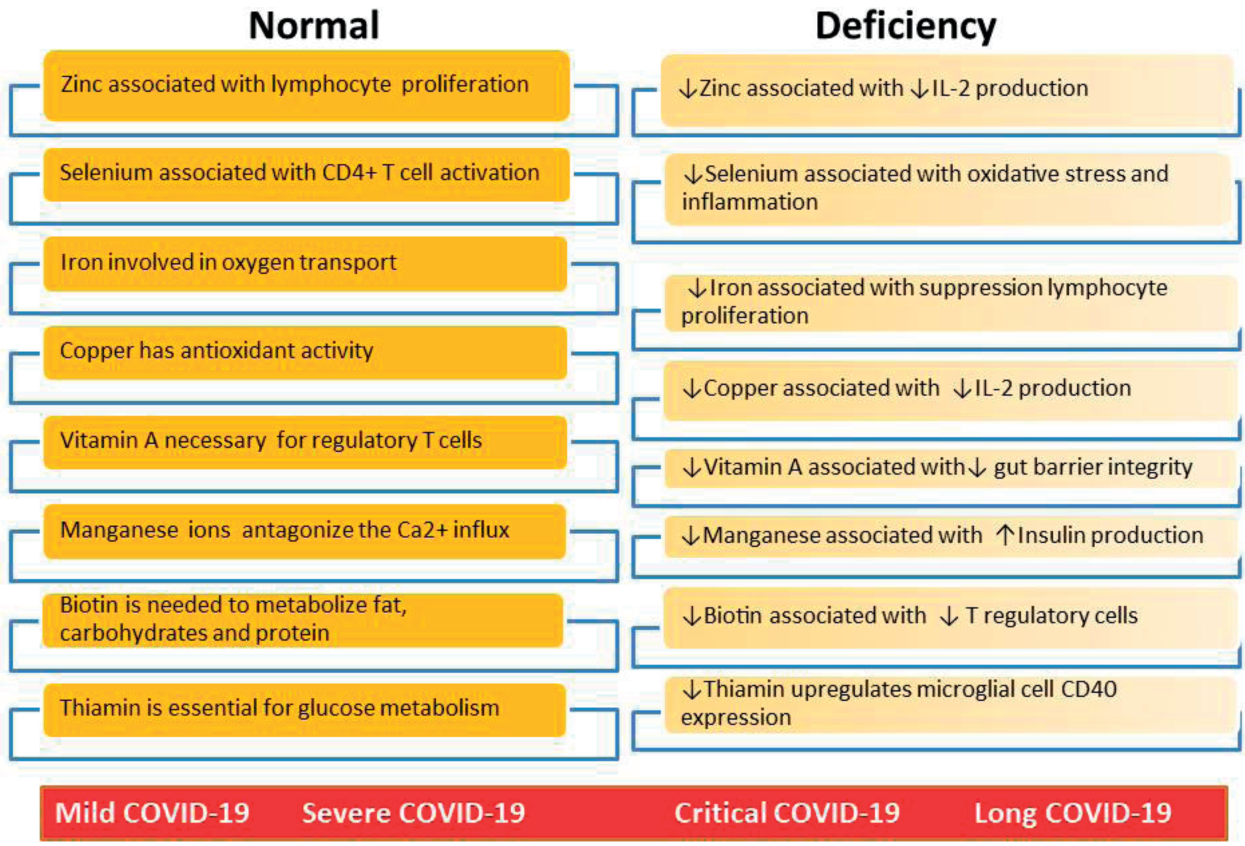


Figure 1. Micronutrient deficiencies correlate with critical COVID-19 and long COVID-19

Study limitation and future directions. According to the European Association of Clinical Microbiology, 45% of antibiotics prescribed since the start of the COVID-19 pandemic, have been unsubstantiated. The use of multiple antibiotics leads to the development of antimicrobial resistance and disruption of intestinal microbiota. Disruption of the gut microbiome can lead to irritable bowel syndrome and psychological disorders, such as depression, adjustment disorders, and anxiety. However, potentiating negative impact of irrational antibiotic therapy on the development of long COVID-19 syndrome is still unknown. Thus, complex micronutrient testing and gastrointestinal microbiota investigation will lead to better health care management of long COVID-19.

Abbreviations Used:

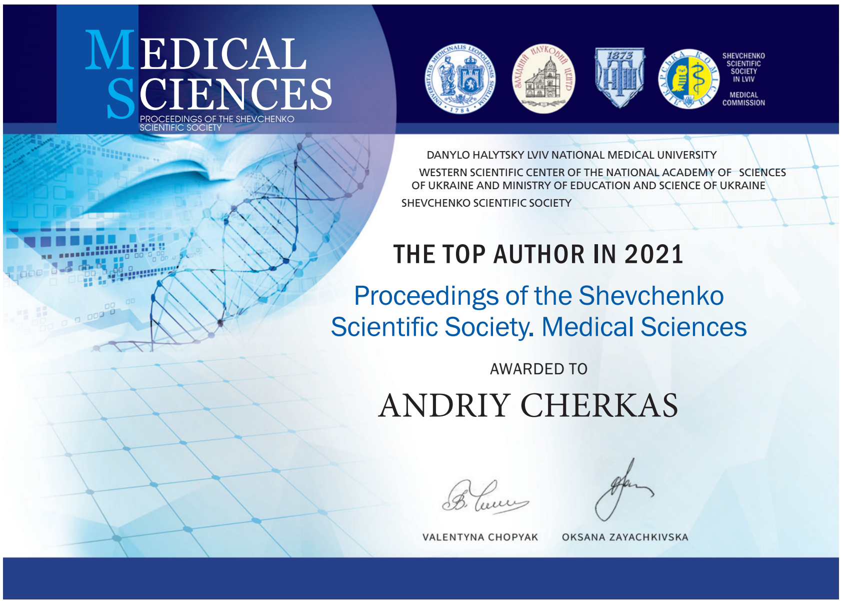
- GSH - glutathione
- GSSG - glutathione disulfide
- NAD/NADH - nicotinamide adenine dinucleotide
- NADP/NADPH – nicotinamide adenine dinucleotide phosphate
- ATP/ADP/AMP – adenosine triphosphate/ adenosine diphosphate/ adenosine monophosphate
- CD40 – cluster of differentiation 40
- T2DM – type 2 diabetes
- HTN – hypertension
- IBD – inflammatory bowel disease
- DNA – deoxyribonucleic acid
- TAG – triglycerides

References

1. Schultze JL, Aschenbrenner AC. COVID-19 and the human innate immune system. Cell. 2021 Apr 1.
2. Devaux CA, Rolain JM, Raoult D. ACE2 receptor polymorphism: Susceptibility to SARS-CoV-2, hypertension, multi-organ failure, and COVID-19 disease outcome. Journal of Microbiology, Immunology and Infection. 2020 Jun 1;53(3):425-35.

3. Chopyak Valentina; Lishchuk-Yakymovych Khrystyna; Pukalyak Roman. Immunological aspects of covid-2019: realities and prospects Immunology and Allergy: Science and Practice, 2020, 3-4: 34-41.
4. Fernández-de-Las-Peñas C, Palacios-Ceña D, Gómez-Mayordomo V, Rodríuez-Jiménez J, Palacios-Ceña M, Velasco-Arribas M, Guijarro C, de-la-Llave-Rincón AI, Fuensalida-Novo S, Elvira-Martínez CM, Cuadrado ML. Long-term post-COVID symptoms and associated risk factors in previously hospitalized patients: A multicenter study. Journal of Infection. 2021 Aug 1;83(2):237-79,
5. Carson G. Research priorities for Long COVID: refined through an international multi-stakeholder forum. BMC medicine. 2021 Dec;19(1):1-4.
6. Yang, A.C., Kern, F., Losada, P.M. et al. Dysregulation of brain and choroid plexus cell types in severe COVID-19. (2021) Nature 595, 565–571. https://doi.org/10.1038/s41586-021-03710-0
7. Szabo, S. (2020). COVID-19: New disease and chaos with panic, associated with stress. Proceeding of the Shevchenko Scientific Society. Medical Sciences, 59(1).
8. Kujawa A, Green H, Compas BE, Dickey L, Pegg S. Exposure to COVID‐19 pandemic stress: Associations with depression and anxiety in emerging adults in the United States. Depression and anxiety. 2020 Dec;37(12):1280-8.
9. Park CL, Russell BS, Fendrich M, Finkelstein-Fox L, Hutchison M, Becker J. Americans' COVID-19 stress, coping, and adherence to CDC guidelines. Journal of general internal medicine. 2020 Aug;35(8):2296-303.
10. Pearman A, Hughes ML, Smith EL, Neupert SD. Age differences in risk and resilience factors in COVID-19-related stress. The Journals of Gerontology: Series B. 2021 Feb;76(2):e38-44.
11. Aktar, M. A., Alam, M. M., & Al-Amin, A. Q. (2020). Global economic crisis, energy use, CO2 emissions, and policy roadmap amid COVID-19. Sustainable Production and Consumption.
12. Richter K, Kellner S, Hillemacher T, Golubnitschaja O. Sleep quality and COVID-19 outcomes: the evidence-based lessons in the framework of predictive, preventive and personalised (3P) medicine. EPMA Journal. 2021 Jun 8:1-210.
13. Taquet, Maxime, et al. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. The Lancet Psychiatry, 2021, 8.5: 416-427.
14. Nalbandian, Ani, et al. Post-acute COVID-19 syndrome. Nature medicine, 2021, 27.4: 601-615.
15. Yan Z, Yang M, Lai CL. Long COVID-19 syndrome: a comprehensive review of its effect on various organ systems and recommendation on rehabilitation plans. Biomedicines. 2021 Aug;9(8):966.
16. Severinsen MC, Pedersen BK. Muscle–organ crosstalk: the emerging roles of myokines. Endocrine reviews. 2020 Aug;41(4):594-609
17. Besedovsky, L., Lange, T., & Haack, M. (2019). The sleep-immune crosstalk in health and disease. Physiological reviews.
18. Gasmi A, Tippairote T, Mujawdiya PK, Peana M, Menzel A, Dadar M, Benahmed AG, Bjørklund G. Micronutrients as immunomodulatory tools for COVID-19 management. Clinical Immunology. 2020 Jul 22:108545.
19. Elmadfa I, Meyer AL. The role of the status of selected micronutrients in shaping the immune function. Endocrine, Metabolic & Immune Disorders-Drug Targets (Formerly Current Drug Targets-Immune, Endocrine & Metabolic Disorders). 2019 Dec 1;19(8):1100-15
20. Honscheid, Andrea; Rink, Lothar; Haase, Hajo. T-lymphocytes: a target for stimulatory and inhibitory effects of zinc ions. Endocrine, Metabolic & Immune Disorders-Drug Targets (Formerly Current Drug Targets-Immune, Endocrine & Metabolic Disorders), 2009, 9.2: 132-144.
21. Bae M, Kim H. The role of vitamin C, vitamin D, and selenium in immune system against COVID-19. Molecules. 2020 Jan;25(22):5346.
22. Girelli D, Marchi G, Busti F, Vianello A. Iron metabolism in infections: focus on COVID-19. In Seminars in Hematology 2021 Jul 24.
23. Biamonte, F., Botta, C., Mazzitelli, M., Rotundo, S., Trecarichi, E. M., Foti, D., ... & Costanzo, F. (2021). Combined lymphocyte/monocyte count, D-dimer and iron status predict COVID-19 course and outcome in a long-term care facility. Journal of translational medicine, 19(1), 1-10.
24. Raha S, Mallick R, Basak S, Duttaroy AK. Is copper beneficial for COVID-19 patients?. Medical hypotheses. 2020 Sep 1;142:109814.
25. Sarohan AR. COVID-19: endogenous retinoic acid theory and retinoic acid depletion syndrome. Medical hypotheses. 2020 Nov 1;144:110250.
26. Son, E. W., Lee, S. R., Choi, H. S., Koo, H. J., Huh, J. E., Kim, M. H., & Pyo, S. (2007). Effects of supplementation with higher levels of manganese and magnesium on immune function. Archives of pharmacal research, 30(6), 743-749.
27. Elahi A, Sabui S, Narasappa NN, Agrawal S, Lambrecht NW, Agrawal A, Said HM. Biotin deficiency induces Th1-and Th17-mediated proinflammatory responses in human CD4+ T lymphocytes via activation of the mTOR signaling pathway. The Journal of Immunology. 2018 Apr 15;200(8):2563-70.

28. Springer, Cham. Mikkelsen K, Apostolopoulos V. Vitamin B1, B2, B3, B5, and B6 and the immune system. InNutrition and immunity 2019 (pp. 115-125). Springer, Cham.
29. Barra, N. G., Anhê, F. F., Cavallari, J. F., Singh, A. M., Chan, D. Y., & Schertzer, J. D. (2021). Micronutrients impact the gut microbiota and blood glucose. Journal of Endocrinology, 250(2), R1-R21.
30. Himoto, T., Nomura, T., Tani, J., Miyoshi, H., Morishita, A., Yoneyama, H., ... & Masaki, T. (2015). Exacerbation of insulin resistance and hepatic steatosis deriving from zinc deficiency in patients with HCV-related chronic liver disease. Biological trace element research, 163(1), 81-88.
31. Jurowski, K., Szewczyk, B., Nowak, G., & Piekoszewski, W. (2014). Biological consequences of zinc deficiency in the pathomechanisms of selected diseases. JBIC Journal of Biological Inorganic Chemistry, 19(7), 1069-1079.
32. Yin, J., Wang, X., Li, S., Zhu, Y., Chen, S., Li, P., ... & Liu, L. (2019). Interactions between plasma copper concentrations and SOD1 gene polymorphism for impaired glucose regulation and type 2 diabetes. Redox biology, 24, 101172.
33. Bonet, M. L., Ribot, J., & Palou, A. (2012). Lipid metabolism in mammalian tissues and its control by retinoic acid. Biochimica et Biophysica Acta (BBA)-Molecular and cell biology of lipids, 1821(1), 177-189.
34. Pasternak, K., Kocot, J., & Horecka, A. (2010). Biochemistry of magnesium. Journal of Elementology, 15(3), 601-616.
35. Velazquez-Arellano A, Ortega-Cuellar D, Hernandez-Mendoza A, Moreno-Arriola E. A heuristic model for paradoxical effects of biotin starvation on carbon metabolism genes in the presence of abundant glucose. Molecular genetics and metabolism. 2011 Jan 1;102(1):69-77.
36. Thingholm LB, Rühlemann MC, Koch M, Fuqua B, Laucke G, Boehm R, Bang C, Franzosa EA, Hübenthal M, Rahnavard A, Frost F. Obese individuals with and without type 2 diabetes show different gut microbial functional capacity and composition. Cell host & microbe. 2019 Aug 14;26(2):252-64.
37. Moss, Carly J.; Mayhews, Suresh T. Thiamin status and supplementation in the management of diabetes mellitus and its vascular comorbidities. Vitam Miner, 2013, 2.111: 2.
38. Cumpstey AF, Clark AD, Santolini J, Jackson AA, Feelisch M. COVID-19–A Redox Disease What a Stress Pandemic Can Teach Us About Resilience and What We May Learn from the Reactive Species Interactome About its Treatment. Antioxidants and Redox Signaling. 2021 May 13(ja).
39. Cinti S, Graciotti L, Giordano A, Valerio A, Nisoli E. COVID-19 and fat embolism: a hypothesis to explain the severe clinical outcome in people with obesity. International Journal of Obesity. 2020 Aug;44(8):1800-2.
40. Wessels I, Rolles B, Slusarenko AJ, Rink L. Zinc deficiency as a possible risk factor for increased susceptibility and severe progression of COVID-19. British Journal of Nutrition. 2021 Jan 1:1-42. Salgo MP.
41. COVID-19: Zinc and Angiotensin-Converting Enzyme 2 (ACE2) Deficiencies as Determinants of Risk and Severity of Disease: A Narrative Review. Infectious diseases and therapy. 2021 Jul 11:1-1.
42. Moghaddam A, Heller RA, Sun Q, Seelig J, Cherkezov A, Seibert L, Hackler J, Seemann P, Diegmann J, Pilz M, Bachmann M. Selenium deficiency is associated with mortality risk from COVID-19. Nutrients. 2020 Jul;12(7):2098.
43. Joachimiak, M. P. (2021). Zinc against COVID-19? Symptom surveillance and deficiency risk groups. PLoS neglected tropical diseases, 15(1), e0008895.



MEDICAL SCIENCES

PROCEEDINGS OF THE SHEVCHENKO SCIENTIFIC SOCIETY

SHEVCHENKO SCIENTIFIC SOCIETY IN LVIV MEDICAL COMMISSION

DANYLO HALYTSKY LVIV NATIONAL MEDICAL UNIVERSITY
WESTERN SCIENTIFIC CENTER OF THE NATIONAL ACADEMY OF SCIENCES OF UKRAINE AND MINISTRY OF EDUCATION AND SCIENCE OF UKRAINE
SHEVCHENKO SCIENTIFIC SOCIETY

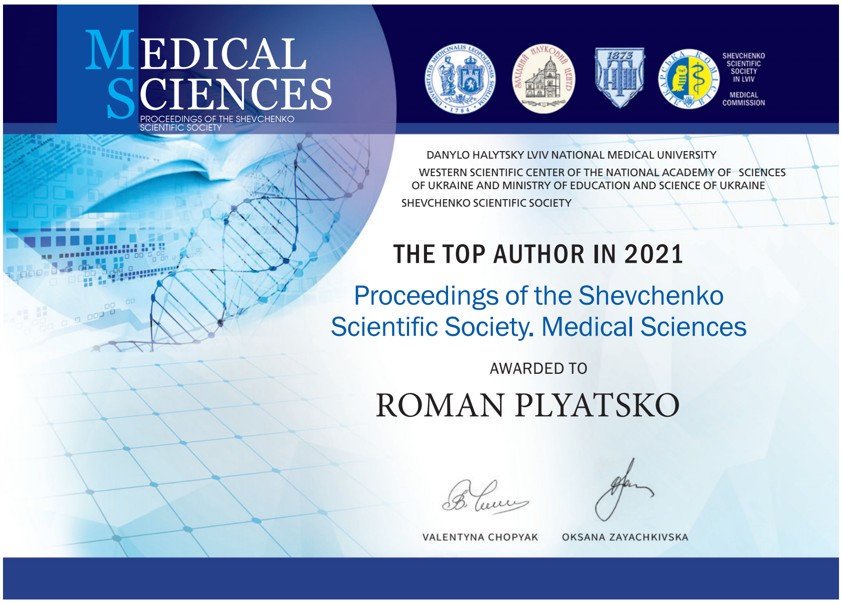
THE TOP AUTHOR IN 2021

Proceedings of the Shevchenko Scientific Society. Medical Sciences

AWARDED TO

ANDRIY CHERKAS

VALENTYNA CHOPYAK OKSANA ZAYACHKIVSKA



MEDICAL SCIENCES

PROCEEDINGS OF THE SHEVCHENKO SCIENTIFIC SOCIETY

SHEVCHENKO SCIENTIFIC SOCIETY IN LVIV MEDICAL COMMISSION

DANYLO HALYTSKY LVIV NATIONAL MEDICAL UNIVERSITY
WESTERN SCIENTIFIC CENTER OF THE NATIONAL ACADEMY OF SCIENCES OF UKRAINE AND MINISTRY OF EDUCATION AND SCIENCE OF UKRAINE
SHEVCHENKO SCIENTIFIC SOCIETY

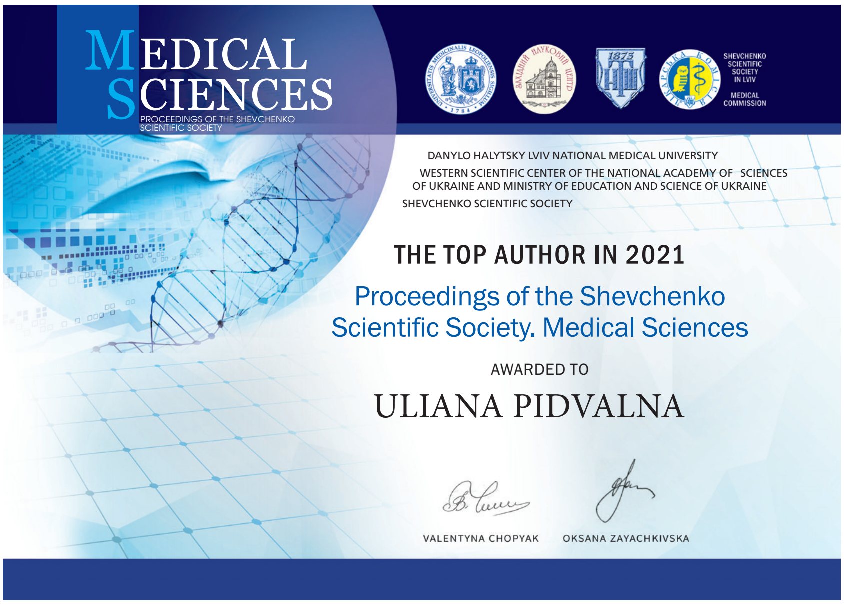
THE TOP AUTHOR IN 2021

Proceedings of the Shevchenko Scientific Society. Medical Sciences

AWARDED TO

ROMAN PLYATSKO

VALENTYNA CHOPYAK OKSANA ZAYACHKIVSKA



MEDICAL SCIENCES

PROCEEDINGS OF THE SHEVCHENKO SCIENTIFIC SOCIETY

SHEVCHENKO SCIENTIFIC SOCIETY IN LVIV MEDICAL COMMISSION

DANYLO HALYTSKY LVIV NATIONAL MEDICAL UNIVERSITY
WESTERN SCIENTIFIC CENTER OF THE NATIONAL ACADEMY OF SCIENCES OF UKRAINE AND MINISTRY OF EDUCATION AND SCIENCE OF UKRAINE
SHEVCHENKO SCIENTIFIC SOCIETY

THE TOP AUTHOR IN 2021

Proceedings of the Shevchenko Scientific Society. Medical Sciences

AWARDED TO

ULIANA PIDVALNA

VALENTYNA CHOPYAK OKSANA ZAYACHKIVSKA