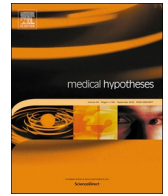




Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Letter to Editors

Comment on an article: “High dose folic acid is a potential treatment for pulmonary hypertension, including when associated with COVID-19 pneumonia”



Dear Editor-in-Chief Mehar S. Manku,

We have read with great attention the article, High dose folic acid is a potential treatment for pulmonary hypertension, including when associated with COVID-19 pneumonia “written by colleagues Wiltshire et al. (Authors), published online in the forthcoming October issue of Journal [1]. This very interesting article hypothesized role of folic acid for COVID-19 pneumonia with pulmonary hypertension. Due to our studies and experiences, but also of rare opinions of other distinguish colleagues, we strongly agree with the hypothesis of Authors. Importantly, we welcome the opportunity to make a short comment as well.

There is an evident connection between homocysteine and nitric oxide (NO) metabolism. Hyperhomocysteinemia leads to reduction in NO bioavailability [2]. Oxidative stress, impaired of NO synthase pathway and mitochondria dysfunction associated with impaired homocysteine metabolism leads to aging tissue degeneration [3]. Homocysteine increases activity of NO synthase and induces inhibition of nitric oxide production in platelets [4,5]. Homocysteine is an independent risk factor for coronary heart disease and cerebrovascular disease. Hyperhomocysteinemia could play a key role through free radicals production by homocysteine oxidation. The high toxicity of these free radicals to vascular endothelial cells, could promote and increase synthesis of oxidized low-density lipoprotein [6]. In addition, vascular changes, caused by increased levels of homocysteine, may provoke pulmonary hypertension [7]. Furthermore, the Authors also note that hyperhomocysteinemia may occur in patients with pulmonary hypertension [1].

Values of folic acid and B12 are in negative correlation with levels of homocysteine [8]. Fortunately, folates could protect blood vessels and prevent DNA damage caused by hyperhomocysteinemic oxidative stress [9]. A large prospective study reported a significant lowering effect on homocysteine levels of daily supplementation combining folic acid and vitamins B 12/B 6 [10]. Risk of side effects is minimal if the daily dose of folic acid is in between 1 and 5 mg [11]. In light of this facts, proper intake of vitamin and diet control should be established as early as possible, not only in COVID-19 population but also in other health individuals in the age of SARS-Cov-2. Importantly, for this purpose, it includes adequate dietary intake of folate and vitamins B6/B12, intake of proteins rich in methionine that help to regulate homocysteine biochemical pathways, and avoid unhealthy lifestyle choices such an alcohol abuse, high coffee intake, as well as smoking habits [12].

Nevertheless, hyperhomocysteinemia, if persistent, should be promptly decreased in acute phase of COVID-19 with folic acid, and in some cases with the addition of vitamin B12 or B6.

Funding

This report received no specific grant from any funding agency in the public, commercial, or not for profit sectors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mehy.2020.110338>.

References

- [1] Wiltshire E, Pena AS, MacKenzie K, Shaw G, Couper J. High dose folic acid is potential treatment for pulmonary hypertension, including when associated with COVID-19 pneumonia. *Med Hypotheses* 2020;143:110142 <https://doi.org/10.1116/j.mehy.2020.110142>.
- [2] Lai WK, Kan MY. Homocysteine-induced endothelial dysfunction. *Ann Nutr Metab* 2015;67(1):1–12. <https://doi.org/10.1159/000437098>.
- [3] Ostrakhovitch EA, Tabibzadeh S. Homocysteine and age-associated disorders. *Ageing Res Rev* 2019;49:144–64. <https://doi.org/10.1016/j.arr.2018.10.010>.
- [4] Djuric D, Jakovljevic V, Zivkovic V, Srejovic I. Homocysteine and homocysteine-related compounds: an overview of the roles in the pathology of the cardiovascular and nervous systems. *Can J Physiol Pharmacol* 2018;96(10):991–1003. <https://doi.org/10.1139/cjpp-2018-0112>.
- [5] Mutus B, Rabini RA, Staffolani R, Ricciotti R, Fumelli P, Moreti N, et al. Diabetologia 2001;44(8):978–82. <https://doi.org/10.1007/s0012501005801>.
- [6] Azzini E, Ruggeri S, Polito A. Homocysteine: its possible emerging role in at-risk population groups. *Int J Mol Sci* 2020;21(4):1421. <https://doi.org/10.3390/ijms21041421>.
- [7] Ozerol IH, Pac FA, Ozerol E, Ege E, Yologlu S, Temel I, et al. Plasmaendothelin-1, homocysteine and serum nitric oxide values in patients with left-to-right shunt. *Indian Heart J* 2004;56(6):653–7.
- [8] B-Vitamin Treatment Trialists' Collaboration. Homocysteine-lowering trials for prevention of cardiovascular events: A review of the design and power of the large randomized trials. *Am Heart J* 2006; 151(2): 282-7. doi.org/10.1016/j.ahj.2005.04.025.
- [9] Mattson MP, Shea TB. Folate and homocysteine metabolism in neural plasticity and neurodegenerative disorders. *Trends Neurosci* 2003;26(3):137–46. [https://doi.org/10.1016/S0166-2236\(03\)00032-8](https://doi.org/10.1016/S0166-2236(03)00032-8).
- [10] Lonn E, Held C, Arnold JM, Probstfield J, McQueen M, Micks M, et al. Heart outcomes prevention evaluation (HOPE) 2 investigators. homocysteine lowering with folic acid and b vitamins in vascular disease. *N Engl J Medicine* 2006;354(15):1567–77. <https://doi.org/10.1156/NEJMoa060900>.
- [11] Belcastro V, Pierguidi L, Castrioto A, Menichetti C, Gorgone G, Ientile R, et al. Hyperhomocysteinemia recurrence in levodopa-treated Parkinson's disease patients. *Eur J Neurol* 2010;17(5):661–5. <https://doi.org/10.1111/j.1468-1331.2009.02984.x>.
- [12] Refsum H, Smith AD, Ueland MP, Nexø E, Clarke R, McPartlin J, et al. Facts and recommendations about total homocysteine determinations: An expert opinion. *Clin Chem* 2004;50(1):3–32. <https://doi.org/10.1373/clinchem.2003.021634>.

<https://doi.org/10.1016/j.mehy.2020.110338>

Received 29 August 2020; Accepted 4 October 2020

Available online 07 October 2020

0306-9877/ © 2020 Elsevier Ltd. All rights reserved.

Omer Ć. Ibrahimagić^a, Suljo Kunić^{b,*}

^a Department of Neurology, University Clinical Centre Tuzla, 75000 Tuzla,
Bosnia and Herzegovina

^b Department of Neurology, Primary Health Care Centre Tuzla, 75000
Tuzla, Bosnia and Herzegovina

E-mail address: suljo.kunic@hotmail.com (S. Kunić).

* Corresponding author at: Veljka Lukića Kurjaka Street 66, 75000 Tuzla,
Bosnia and Herzegovina.