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Editorial

Be well: A potential role for vitamin B in COVID-19

Coronavirus disease (COVID-19) is caused by the SARS-CoV-2 virus. In January 2020, the World Health Organization declared COVID-19 as a Public Health Emergency of International Concern and in March 2020, COVID-19 was characterized as a global pandemic that is responsible for infecting over 20 million and more than 700,000 deaths. COVID-19 symptoms are fever, cough, fatigue, headache, diarrhea, arthromyalgias, serious interstitial pneumonia that can lead to acute respiratory distress syndrome, sepsis-induced coagulopathy and multi-organ dysfunction [1]. In addition, the severe progression of COVID-19 results in cytokine storm with excessive production of pro-inflammatory cytokines [2]. Previously, outbreaks of similar viruses which belong to the β-coronavirus family occurred in 2002–2004 and 2012–2014, as severe acute respiratory syndrome (SARS) and as the Middle East respiratory syndrome (MERS), respectively [3,4].

Currently, there is no approved drug treatment or vaccine against the SARS-CoV-2 virus. Until these become available, one must include adequate and balanced nutrition for proper body functioning and boosting of the immune system. Micronutrients, vitamin C and vitamin D have gained much attention during the pandemic because of their anti-inflammatory and immune-supporting properties. Low levels of vitamins D and C result in coagulopathy and suppress the immune system, causing lymphocytopenia. Evidence has shown that the mortality rate is higher in COVID-19 patients with low vitamin D concentrations. Further, vitamin C supplementation increases the oxygenation index in COVID-19 infected patients [5]. Similarly, vitamin B deficiency can significantly impair cell and immune system function, and lead to inflammation due to hyperhomocysteinemia.

There is a need to highlight the importance of vitamin B because it plays a pivotal role in cell functioning, energy metabolism, and proper immune function [6]. Vitamin B assists in proper activation of both the innate and adaptive immune responses, reduces pro-inflammatory cytokine levels, improves respiratory function, maintains endothelial integrity, prevents hypercoagulability and can reduce the length of stay in hospital [7,8]. Therefore, vitamin B status should be assessed in COVID-19 patients and vitamin B could be used as a non-pharmaceutical adjunct to current treatments (Fig. 1).

1. Can vitamin B be used to manage COVID-19?

1.1. Vitamin B_1 (Thiamine)

Thiamine is able to improve immune system function and has been shown to reduce the risk of type-2 diabetes, cardiovascular disease, aging-related disorders, kidney disease, cancer, mental disorders and neurodegenerative disorders [6]. Thiamine deficiency affects the cardiovascular system, causes neuroinflammation, increases inflammation and leads to aberrant antibody responses [6]. As antibodies, and importantly T-cells, are required to eliminate the SARS-CoV-2 virus, thiamine deficiency can potentially result in inadequate antibody responses, and subsequently more severe symptoms. Hence, adequate thiamine levels are likely to aid in the proper immune responses during SARS-CoV-2 infection. In addition, the symptoms of COVID-19 are very similar to altitude sickness and high-altitude pulmonary edema. Acetazolamide is commonly prescribed to prevent high-altitude sickness and pulmonary edema through inhibition of the carbonic anhydrase isoenzymes and subsequently increases oxygen levels. Thiamine also functions as a carbonic anhydrase isoenzyme inhibitor [9]; hence, high-doses of thiamine given to people at early stages of COVID-19 could potentially limit hypoxia and decrease hospitalization. Further research is required to determine whether administration of high thiamine doses could contribute to the treatment of patients with COVID-19.

1.2. Vitamin B_2 (Riboflavin)

Riboflavin together with UV light cause irreversible damage to nucleic acids such as DNA and RNA, rendering microbial pathogens unable to replicate. Riboflavin and UV light has been shown to be effective against the MERS-CoV virus, suggesting that it could also be helpful against SARS-CoV-2 [10]. In fact, riboflavin-UV decreased the infectious titer of SARS-CoV-2 below the limit of detection in human blood [10] and in plasma and platelet products [11]. This could alleviate some of the risk of transfusion transmission of COVID-19 and as well as reducing other pathogens in blood products for critically ill COVID-19 patients.

1.3. Vitamin B_3 (Nicotinamide, Niacin)

Niacin acts as a building block of NAD and NADP, both vital during chronic systemic inflammation [12]. NAD^+ acts as a coenzyme in various metabolic pathways and its increased levels are essential to treat a wide range of pathophysiological conditions. NAD^+ is released during the early stages of inflammation and has immunomodulatory properties, known to decrease the pro-inflammatory cytokines, IL-1β, IL-6 and TNF-α. [13–15]. Recent evidence indicates that targeting IL-6 could help control the inflammatory storm in patients with COVID-19 [16]. Moreover, niacin reduces neutrophil infiltration and exhibits an anti-inflammatory effect in patients with ventilator-induced lung injury. In hamsters, niacin and nicotinamide prevents lung tissue damage [17]. In addition, nicotinamide reduces viral replication (vaccinia virus, human immunodeficiency virus, enteroviruses, hepatitis B virus) and

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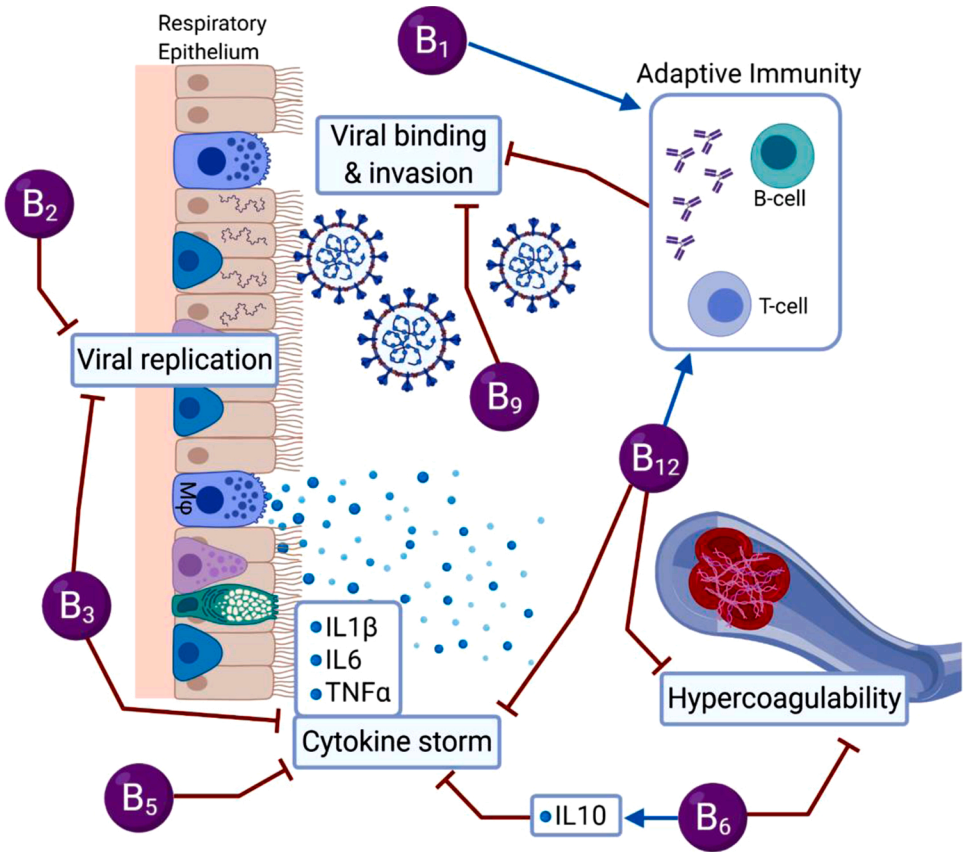

Fig. 1. Summary of the different roles vitamin B can play during COVID-19.

strengthens the body's defense mechanisms. Taking into account the lung protective and immune strengthening roles of niacin, it could be used as an adjunct treatment for COVID-19 patients [8,18].

1.4. Vitamin B_5 (Pantothenic acid)

Pantothenic acid has a number of functions, including cholesterol- and triglyceride-lowering properties, improves wound healing, decreases inflammation and improves mental health [6]. Even though there are limited studies demonstrating the effects of pantothenic acid on the immune system, it is a viable vitamin for future investigation.

1.5. Vitamin B_6 (Pyridoxal 5′-phosphate, Pyridoxine)

Pyridoxal 5′-phosphate (PLP) is an active form of pyridoxine, and is an essential cofactor in various inflammatory pathways with deficiency leading to immune dysregulation. PLP has an inverse relationship with plasma IL-6 and TNF-α in chronic inflammatory conditions. During inflammation, the utilization of PLP increases results in its depletion, suggesting that COVID-19 patients with high inflammation may have deficiency. Low PLP levels have been noted in patients with type-2 diabetes, cardiovascular disease and in the elderly [19–21], groups who are at higher risk of poorer COVID-19 outcomes. Dysregulation of immune responses and increased risk of coagulopathy have also been noted among COVID-19 patients. In a recent preprint it is suggested that PLP supplementation mitigates COVID-19 symptoms by regulating immune responses, decreasing pro-inflammatory cytokines, maintaining endothelial integrity and preventing hypercoagulability [22]. In fact, it was shown three decades ago that PLP levels reduce abnormalities in platelet aggregation and blood clot formation [23]. Recently researchers at Victoria University reported that vitamin B_6 (as well as B_2 and B_9) upregulated IL-10, a powerful anti-inflammatory and immunosuppressive cytokine which can deactivate macrophages and monocytes and inhibit antigen-presenting cells and T cells [24]. COVID-19 patients often respond to the virus by mounting an excessive T cell response and secretion of pro-inflammatory cytokines. It may be that PLP is able to contribute to dampening the cytokine storm and inflammation suffered by some COVID-19 patients.

1.6. Vitamin B_9 (folic acid, folate)

Folate is an essential vitamin for DNA and protein synthesis and in the adaptive immune response. Furin is an enzyme associated with bacterial and viral infections and is a promising target for treatment of infections. Recently, it was noted that folic acid was able to inhibit furin, preventing binding by the SARS-CoV-2 spike protein, preventing cell entry and virus turnover. Therefore it was suggested that folic acid could be beneficial for the management of COVID-19-associated respiratory disease in the early stages [25]. A recent preprint report that folic acid and its derivatives tetrahydrofolic acid and 5-methyl tetrahydrofolic acid have strong and stable binding affinities against the SARS-CoV-2, through structure-based molecular docking. Therefore, folic acid may be used as a therapeutic approach for the management of COVID-19 [26].

1.7. Vitamin B_{12} (cobalamin)

Vitamin B_{12} is essential for red blood cell synthesis, nervous system health, myelin synthesis, cellular growth and the rapid synthesis of DNA. The active forms of vitamin B_{12} are hydroxo-, adenosyl- and methylcobalamin. Vitamin B_{12} acts as a modulator of gut microbiota and low levels of B_{12} elevate methylmalonic acid and homocysteine, resulting in

increased inflammation, reactive oxygen species and oxidative stress [15]. Hyperhomocysteinemia causes endothelial dysfunction, activation of platelet and coagulation cascades, megaloblastic anemia, disruption of myelin sheath integrity and decreased immune responses [27–30]. However, SARS-CoV-2 could interfere with vitamin B_{12} metabolism, thus impairing intestinal microbial proliferation. Given that, it is plausible that symptoms of vitamin B_{12} deficiency are close to COVID-19 infection such as elevated oxidative stress and lactate dehydrogenase, hyperhomocysteinemia, coagulation cascade activation, vasoconstriction and renal and pulmonary vasculopathy [28,31]. In addition, B_{12} deficiency can result in disorders of the respiratory, gastrointestinal and central nervous systems [30]. Surprisingly, a recent study showed that methylcobalamin supplements have the potential to reduce COVID-19-related organ damage and symptoms [32]. A clinical study conducted in Singapore showed that COVID-19 patients who were given vitamin B_{12} supplements (500 μg), vitamin D (1000 IU) and magnesium had reduced COVID-19 symptom severity and supplements significantly reduced the need for oxygen and intensive care support [33].

2. What is the outcome?

Vitamin B not only helps to build and maintain a healthy immune system but it could potentially prevent or reduce COVID-19 symptoms or treat SARS-CoV-2 infection. Poor nutritional status predisposes people to infections more easily; therefore, a balanced diet is necessary for immuno-competence. There is a need for safe and cost-effective adjunct or therapeutic approaches, to suppress aberrant immune activation, which can lead to a cytokine storm, and to act as anti-thrombotic agents. Adequate vitamin intake is necessary for proper body function and strengthening of the immune system. In particular, vitamin B modulates immune response by downregulating pro-inflammatory cytokines and inflammation, reducing breathing difficulty and gastrointestinal problems, preventing hypercoagulability, potentially improving outcomes and reducing the length of stay in the hospital for COVID-19 patients.

Contributors

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References

[1] Z.Y. Zu, M.D. Jiang, P.P. Xu, W. Chen, Q.Q. Ni, G.M. Lu, L.J. Zhang, Coronavirus disease 2019 (COVID-19): a perspective from China, Radiology (2020), 200490.
[2] C. Zhang, Z. Wu, J.-W. Li, H. Zhao, G.-Q. Wang, The cytokine release syndrome (CRS) of severe COVID-19 and interleukin-6 receptor (IL-6R) antagonist tocilizumab may be the key to reduce the mortality, Int. J. Antimicrob. Agents (2020), 105954.
[3] A. Zumla, D.S. Hui, S. Perlman, Middle East respiratory syndrome, The Lancet 386 (9997) (2015) 995–1007.
[4] D. Schoeman, B.C. Fielding, Coronavirus envelope protein: current knowledge, Virol. J. 16 (1) (2019) 1–22.
[5] H. Shakoor, J. Feehan, S.A. Al Dhaheri, I.H. Ali, C. Platat, C.L. Ismail, V. Apostolopoulos, L. Stojanovska, Immune boosting role of vitamins D, C, E, zinc, selenium and omega-3 fatty acids: could they help against COVID-19? Maturitas (2020).
[6] K. Mikkelsen, V. Apostolopoulos, Vitamin B.1, B2, B3, B5, and B6 and the immune system, Nutr. Immunity (2019) 115–125.
[7] C.A. Michele, B. Angel, L. Valeria, M. Teresa, C. Giuseppe, M. Giovanni, P. Ernestina, B. Mario, Vitamin supplements in the era of SARS-Cov2 pandemic, GSC Biol. Pharm. Sci. 11 (2) (2020) 007–019.
[8] L. Zhang, Y. Liu, Potential interventions for novel coronavirus in China: a systematic review, J. Med. Virol. 92 (5) (2020) 479–490.
[9] Z.O. Ozdemir, M. Senturk, D. Ekinci, Inhibition of mammalian carbonic anhydrase isoforms I, II and VI with thiamine and thiamine-like molecules, J. Enzyme Inhib. Med. Chem. 28 (2) (2013) 316–319.
[10] I. Ragan, L. Hartson, H. Pidcoke, R. Bowen, R. Goodrich, Pathogen reduction of SARS-CoV-2 virus in plasma and whole blood using riboflavin and UV light, Plos One 15 (5) (2020), e0233947.
[11] S.D. Keil, I. Ragan, S. Yonemura, L. Hartson, N.K. Dart, R. Bowen, Inactivation of severe acute respiratory syndrome coronavirus 2 in plasma and platelet products using a riboflavin and ultraviolet light-based photochemical treatment, Vox Sang. (2020).
[12] Y. Boergeling, S. Ludwig, Targeting a metabolic pathway to fight the flu - boergeling - 2017, FEBS J. - Wiley Online Library (2020).
[13] K. Mikkelsen, V. Apostolopoulos, B vitamins and ageing, biochemistry and cell biology of ageing: part I biomedical science, Springer (2018) 451–470.
[14] K. Mikkelsen, L. Stojanovska, V. Apostolopoulos, The effects of vitamin B in depression, Curr. Med. Chem. 23 (38) (2016) 4317–4337.
[15] K. Mikkelsen, L. Stojanovska, M. Prakash, V. Apostolopoulos, The effects of vitamin B on the immune/cytokine network and their involvement in depression, Maturitas 96 (2017) 58–71.
[16] B. Liu, M. Li, Z. Zhou, X. Guan, Y. Xiang, Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)? J. Autoimmun. (2020), 102452.
[17] A. Nagai, H. Matsumiya, M. Hayashi, S. Yasui, H. Okamoto, K. Konno, Effects of nicotinamide and niacin on bleomycin-induced acute injury and subsequent fibrosis in hamster lungs, Exp. Lung Res. 20 (4) (1994) 263–281.
[18] M. Mario, J. Nina, S. Urs, Nicotinamide riboside—the current State of research and therapeutic uses, Nutrients 12 (6) (2020) 1616.
[19] C. Merigliano, E. Mascolo, R. Burla, I. Saggio, F. Vernì, The relationship between vitamin B6, diabetes and cancer, Front. Genet. 9 (2018) 388.
[20] C.O. Lengyel, S.J. Whiting, G.A. Zello, Nutrient inadequacies among elderly residents of long-term care facilities, Can. J. Diet. Pract. Res. 69 (2) (2008) 82–88.
[21] W.A. Nix, R. Zirwes, V. Bangert, R.P. Kaiser, M. Schilling, U. Hostalek, R. Obeid, Vitamin B status in patients with type 2 diabetes mellitus with and without incipient nephropathy, Diabetes Res. Clin. Pract. 107 (1) (2015) 157–165.
[22] J. Desbarats, Pyridoxal 5'-Phosphate to Mitigate Immune Dysregulation and Coagulopathy in COVID-19, 2020.
[23] V. Van Wyk, H.G. Luus, Ad.P. Heyns, The in vivo effect in humans of pyridoxal-5′-phosphate on platelet function and blood coagulation, Thrombosis Res. 66 (6) (1992) 657–668.
[24] K. Mikkelsen, M.D. Prakash, N. Kuol, K. Nurgali, L. Stojanovska, V. Apostolopoulos, Anti-tumor effects of vitamin B2, B6 and B9 in promonocytic lymphoma cells, Int. J. Mol. Sci. 20 (15) (2019).
[25] Z. Sheybani, M.H. Dokoohaki, M. Negahdaripour, M. Dehdashti, H. Zolghadr, M. Moghadami, S.M. Masoompour, A.R. Zolghadr, The Role of Folic Acid in the Management of Respiratory Disease Caused by COVID-19, 2020.
[26] V. Kumar, M. Jena, In Silico Virtual Screening-Based Study of Nutraceuticals Predicts the Therapeutic Potentials of Folic Acid and Its Derivatives Against COVID-19, 2020.
[27] N. Nemazannikova, K. Mikkelsen, L. Stojanovska, G.L. Blatch, V. Apostolopoulos, Is there a link between vitamin B and multiple sclerosis? Med. Chem. 14 (2) (2018) 170–180.

[28] W. Sabry, M. Elemary, T. Burnouf, J. Seghatchian, H. Goubran, Vitamin B12 deficiency and metabolism-mediated thrombotic microangiopathy (MM-TMA), Transfusion Apheresis Sci. 59 (1) (2020), 102717.
[29] M.M. Stipp, SARS-CoV-2: micronutrient optimization in supporting host immuno-competence, Int. J. Clin.Case Rep. Rev. 2 (2) (2020).
[30] B.H.R. Wolffenbuttel, H.J.C.M. Wouters, M.R. Heiner-Fokkema, M.M. Van der klauw, The many faces of cobalamin (vitamin B12) deficiency, Mayo Clin. Proc.: Innov. Quality Outcomes 3 (2) (2019) 200–214.
[31] S. Grangé, S. Bekri, E. Artaud-Macari, A. Francois, C. Girault, A.-L. Poitou, Y. Benhamou, C. Vianey-Saban, J.-F. Benoist, V. Châtelet, Adult-onset renal thrombotic microangiopathy and pulmonary arterial hypertension in cobalamin C deficiency, Lancet (London, England) 386 (9997) (2015) 1011.
[32] L.M.J. dos Santos, Can vitamin B12 be an adjuvant to COVID-19 treatment? GSC Biol. Pharm. Sci. 11 (3) (2020) 1–5.
[33] C.W. Tan, L.P. Ho, S. Kalimuddin, B.P.Z. Cherng, Y.E. Teh, S.Y. Thien, H.M. Wong, P.J.W. Tern, J.W.M. Chay, C. Nagarajan, A cohort study to evaluate the effect of combination vitamin D, magnesium and vitamin B12 (DMB) on progression to severe outcome in older COVID-19 patients, medRxiv (2020).

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