The role of vitamin D deficiency with COVID-19, a review

Zinah Abbass Ali; Hiba Resheed Behayaa; Samar Hasan Shammar and Thana Mohammed Juda

Department of Clinical Biochemistry, College of Medicine, University of Babylon, Iraq

Email: hibbarashed@gmail.com

Abstract: In several population Coronavirus disease 2019 (COVID-19) appeared without symptoms or with slight symptoms, the complication of COVID-19 like, SARS-CoV-2 virus may lead to death by injuries the cell of pulmonary, initiating acute respiratory distress syndrome (ARDS) and hypoxia. In addition it destroy endothelial cells, triggering intravascular hemolysis by changing clotting mechanisms, micro-embolization and microvascular thrombosis. A weaker immune system appeared in patients with complications from COVID-19, mainly caused by hypovitaminosis D.

The role of vitamin D increases defenses from respiratory viruses, like rhinovirus and influenza A virus. Vitamin D deficiency might be the main causes for covid-19 complications. Still, this suggestion might be payable to inverse connection.

The conservation of serum vitamin D concentrations is important for keeping immune system well, improving general health, reducing the severity of disease and deaths, and reducing the costs of healthcare.

Keywords: Coronavirus disease 2019 (COVID-19), renin-angiotensin converting enzyme (ACE), vitamin D.

Introduction

In several population Coronavirus disease 2019 (COVID-19) appeared without symptoms or with slight symptoms, COVID-19 complication (in some patients) like pneumonia, microvascular thrombosis, acute respiratory distress

syndrome (ARDS), myocardial disease and cytokine storm [1]. Thus, there is a necessity to protect people from COVID-19, if it has mutated it become more infectious, and to diminish the danger of disease severity and the rate of mortality. Worldwide vaccination against COVID-19 have been agreed for emergency cases and considered as a shine in the fight against COVID-19. But, in the immune system the role of vaccines have not been proven, while, roughly cases of complicated COVID-19, and mortality, in patients with completely vaccination were appeared [2].

Most patients with weaker immune system develop complications, mainly cause by hypovitaminosis D. Usually, subjects who are susceptible have low level of angiotensin-receptor converting enzyme-2 (ACE-2) and vitamin D. Adequacy of vitamin D corrects the level of ACE-2 [3].

Previous revision about parallel viral infections, found that supplementation with vitamin D to maintenance the immune system have an chief effect beside the vaccination [4].

Coronaviruses

Coronaviruses (CoV) are viruses with big family that causes diseases fluctuating from the communal cold to complicated diseases. in China (Wuhan) in late 2019, the epidemic of an emergent (COVID-19) rapidly spread worldwide and caused by new coronavirus [5].

A positive-sense RNA viruses are coronaviruses that have a specific gene. In humans, the gene Beta-coronavirus responsible from respiratory infection. The relationship among SARS-CoV-2 and SARS-CoV about 79% [6].

As the disease spread rapidly and reached several countries, COVID-19 stated as pandemic non epidemic on 12 March 2020 by World Health Organization (WHO) [7]

Medical Features of COVID-19

The period of incubation for infection by SARS-CoV-2 is 14 days following contact and around four to five days with most patients[8]. People with all ages can obtain infection by SARS-CoV-2, though young and adult people are the common. In hospitalized patients with established COVID-19, from 49 to 56 years was the rang range of age [9].

The natural symptom include cough, temperature, lethargy, painful throat, headache, myalgia, vomiting, sickness, dyspnea and diarrhea. Thus, there are no distinctive symptom that recognize COVID-19 from upper lower respiratory infections. After seven days from infection, COVID-19 patients have another complication like pneumonia, pulmonary failure and death [10].

Pneumonia notable mostly by temperature, dyspnea, cough and bilateral infiltration appeared by chest imaging. The period between the start of disease to dyspnea about five days, in hospitalize patients nearly one week and in acute respiratory distress syndrome (ARDS) patients reached to more than seven days. At the two or three weeks the recovery was beginning. Rendering to the WHO, the time for recovery from fourteen days (for mild symptom) and twenty one to forty five days (for severe COVID-19)[11]. Ten days required for recover the cases with median period of hospitalization. Elderly patients have poor outcomes and death when compared with co-morbidities patients (50–75% of a fatality). Also cases with no symptom may have a neutral laboratory rather than clinical abnormalities [12].

Pathogenesis of corona virus

Numerous clinical investigation of infection by COVID-19 are associated to virus causes distresses in immune system and causes tissue damage. These alterations divided into three categories depend on unusual responses to interferon,

cytokine alterations, alterations of cells in the immune system, and complication with neutrophil extracellular traps (NETS) and thrombosis **[13]**.

These categories comprise (1) decrease the effect of the immune system with defects by B-cell, (2) a hyper-inflammation by T-cell damage and higher levels of cytokines by Interleukin 6 *(*IL-6*)*, nterleukin-1β *(*IL-1β*)*, Tumor necrosis factor alpha (TNF-α*)*, and (3) cell damage **[14]**.

Epidemiology of COVID-19

COVID-19 had infected about 141,594,845 people (until 20 April 2021), greater than 302,139,776 were died in 223 countries and producing community and commercial disturbance around the world **[15]**.

People with all ages have a risk for infection by COVID-19 and severe disease. Still, the severity COVID-19 elevated in people with age ≥65 years (with home treatment), or people not intake vaccine against COVID-19 or people with poor replies to COVID-19 vaccines, and people with chronic disease **[16]**.

Statistics about health situations in COVID-19 show that the severity of COVID-19 elevated in patients with chronic disease like: heart disease, respiratory disease, kidney disease, diabetes, neuro disorders and weight gain **[17]**.

The risk seems to be greater in patients with complications. Further situations causes elevated the severity of COVID-19 include: cancer, cystic fibrosis, immunodeficiency, liver disease and pregnancy. Also people with transplantation receivers and taking medications for immunosuppressive might have elevated the severity of COVID-19 **[18]**.

Vitamin D

An essential controller of calcium level is vitamin D, it is a fat-soluble steroid. In addition, vitamin D affected the immune system, it promotes antimicrobial effect at mucosal surfaces and controlling T cells [19].

Vitamin D (25 (OH)2 D) act as hormone which maintenance calcium, magnesium, and phosphate absorption and homeostasis, regulating many characteristics of health in human, like immune and inflammatory responses to infections [20].

The vitamin D have systemic regulatory effect. Vitamin deficiencies are linked with higher threat of numerous diseases (like, respiratory infections, diabetes, neuro disorders and cancer) [21].

The deficiency of vitamin D

In most populations hypovitaminosis D is common. Hypovitaminosis D occur in poor ethnic, particularly in subjects with darker skin, in homes treatment, health centers, and prisons [22].

Vitamin D affect all body systems by multiple mechanisms, mainly the immune system. So, vitamin D deficiency must define as a complex clinical syndrome causing by "inability of circulatory D3 and 25(OH)D to enter target cells due to insufficient concentrations in circulation", avoiding living functions [23].

Elevated fat quantity, lead to additional restoration of vitamin D and 25(OH)D and elevated the catabolism of inactive form of vitamin D and active form 25(OH)D,25 causing low availability of active form [24]. Chronic hypovitaminosis D caused by several disorders. Examples obesity, metabolic disorder syndrome, immune disease and infections, may be COVID-19, but there is no indication to support that [25].

Antiviral resistances against respiratory viruses increases by Vitamin D, like influenza A virus. Hypovitaminosis D might be a risk factor for elevated severity of covid-19 **[26]**.

The role of vitamin D levels in corona virus.

Vitamin D decreasing the severity and occurrence of respiratory infections, this fact is well documented. There was a relationship between concentration of vitamin D and the rate of infection. Infection rate rises significantly with vitamin D values less than 30 ng/ml **[27]**.

The protecting outcome of vitamin D is employed by several mechanisms like activity of angiotensin converting enzyme (ACE-2) receptor, activating of innate and adaptive immune reactions and decreasing the level of cytokines **[28]**.

Several investigation has discovered vitamin D effects on the treatment and COVID-19 complications and its possible role in reduce COVID-19 frequency. Vitamin D has antiviral effect and inhibition of replication of viral in monocytes and macrophages **[29]**.

Vitamin D prevented respiratory infections by its effects like stimulating the chemotaxis of T-lymphocytes, induce apoptosis and autophagy in the infected epithelium by clearing respiratory pathogens **[30]**.

Severe symptoms in COVID-19 patients have low T-lymphocyte levels. Meanwhile supplementation of vitamin D rises T-lymphocytes level, this outcome sustenance the theory that vitamin D might be suitable in COVID-19 management **[31]**.

COVID-19 progression in some patients is the greatest vital difficulties of the epidemic. Educations demonstrated an elevated rate of thrombosis and cytokine in cases with severe COVID-19. These actions are accountable for fatal effects **[32]**.

Reduces the risk of cytokine storm and thrombosis by the intake of sufficient amount of vitamin D **[33]**.

It has been stated that vitamin D deficiency might trigger inflammation and cytokine storm in COVID-19 and vitamin D deficiency (VDD) might be linked to severity and mortality of COVID-19. Thus, the effect of vitamin D deficiency on COVID-19 infection required extensive attention **[34]**.

Diagnosis

In agreement with China National Health Commission, the disease of COVID-19 is known based on the history of family and symptom, beside SARS-CoV-2 proved by several techniques: real-time reverse transcriptase-polymerase chain reaction (RT-PCR) measurment, higher gene sequencing, and assessment of immunoglobulin M (IgM) and G (IgG) antibodies **[35]**.

Other laboratory tests, containing CBC and biochemical markers, are generally nonspecific. Commonly normal or low count of leukocyte. lymphopenia; a lymphocyte count may be**.**

The lung X-ray (CXR) usually displays bilateral infiltrations but might be typical (in the early stage of disease). The lung CT is more useful for diagnosis. Pleural effusion/thickening, and lymphadenopathy are Less common abnormalities **[36]**.

Thorax CT in early period of COVID-19, displays several small plaques, marked in the lung periphery. In severe cases, pulmonary consolidation may be occur. Rarely detected of Pleural effusion. Lung CT scan used to recognize COVID-19 in supposed and non-symptom cases with negative result of RT-PCR; numerous of them with positive result of PCR after repetitive **[37]**.

Treatment

The most active way to defend society from covid-19 is Vaccination, while healthy people with normal vitamin D levels should not be presented with vitamin D and cod liver oil supplementation. Notably, several reviews proposing that

supplementation with vitamin D may was useful for hypovitaminosis D persons **[38]**.

A practical method for the clinical investigation must be focusing on risk groups; subjects might be verified before intake of vitamin D dosage, comprising dark skin people, pregnant women; and patients with chronic diseases. For subjects with insufficient vitamin D levels less than 50 nmol/L, supplementation daily with 1000-2000 IU could be a harmless, the best way to maintain the level of vitamin D, recover health of bone, and help to protective against respiratory tract infections **[39]**.

In spite of vitamin D effect, but the role of vitamin D in protective or handling of COVID-19 not suggested by any government or by WHO. This might be due to (i) absence of larger sample size, (ii) Design heterogeneity, dosage of drug and population characteristics, (iii) effectiveness of clinicians and (iv) the influence of society, race, gender, age on vitamin D effect. This opinions to the information is essential to extent a final decision on vitamin D utilization **[40]**.

Conclusion

Generally, vitamin D has an influence on the immune system. Yet, the influence of vitamin D on the danger of developing the disease and the way of COVID-19 is still not completely understood. Now, there is no recommendations concerning the role of vitamin D in the treatment of COVID-19, though, certainly, its exact rate in the blood lead to a fewer complication of disease.

References

[1] Chen G, Wu D, Guo W, Cao Y, Huang D & Wang H.[2020]: Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest.130, pp. 2620-2629.

[2] Shatrughan P & Hardeep Kaur.[2022]: Impact of COVID-19 on maternal and child health services. medical journal of Babylon. 19(4), pp.61-83.

[3] Sunil J Wimalawansa.[2022]: Overcoming Infections Including COVID-19, by Maintaining Circulating 25(OH)D Concentrations Above 50 ng/mL. Pathology and Laboratory Medicine International. 14, pp. 37–60.

[4] Cantorna MT, Snyder L, Lin YD & Yang L.[2015]: Vitamin D and 1,25(OH)2D regulation of T cells. Nutrients. 7, pp. 3011-3021.

[5] Lai C-C, Shih T-P, Ko W-C, Tang H-J & Hsueh P-R.[2020]: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges. Int J Antimicrob Agents. 55, pp 1-10.

[6] Lu R, Zhao X, Li J, Niu P, Yang B & Wu H.[2020]: Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 395, pp. 565–74.

[7] Weisberg SP, Connors TJ, Zhu Y, Baldwin MR, Lin W-H & Wontakal S. [2021]: Distinct antibody responses to SARS-CoV-2 in children and adults across the COVID-19 clinical spectrum. Nat Immunol. 22, pp. 25–31.

[8] Burke RM, Midgley CM, Dratch A, Fenstersheib M, Haupt T & Holshue M. [2020]: Active Monitoring of Persons Exposed to Patients with Confirmed COVID-19 - United States. MMWR Morb Mortal Wkly Rep. 69(9), pp. 245–6.

[9] Chen N, Zhou M, Dong X, Qu J, Gong F& Han Y. [2020]: Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 395, pp. 507–13.

[10] Wang D, Hu B, Hu C, Zhu F, Liu X & Zhang J. [2020]: Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 323(11), pp. 1061–9.

[11] Wu Z & McGoogan JM. [2020]: Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 323(13), pp. 1239–42.

[12]   Zu F, Yu T, Du R, Fan G, Liu Y& Liu Z. [2020]: Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 395 (10229), pp. 1054–62.

[13]   Abdul Waheed Y A H & Al-Shireefy H M M.[2022]: Incidence of acute kidney injury in hospitalized COVID-19 patients Incidence of acute kidney injury in hospitalized COVID-19 patients. medical journal of Babylon. 19(4), pp. 143-165.

[14]   Dupont T, Caillat-Zucman S, Fremeaux-Bacchi V, Morin F, Lengline E & Darmon M.[2021]: Identification of distinct immunophenotypes in critically ill coronavirus disease 2019 patients. Chest. 159(5), pp. 1884–93.

[15]   Valdester C Pinto J, Luiz F W G M & Rodrigo C C. [2021]: Prevalence of COVID-19 in children, adolescents and adults in remote education situations in the city of Fortaleza, Brazil. International Journal of Infectious Diseases. pp. 20–26.

[16]   Panovska-Griffiths J, Kerr CC, Stuart RM, Mistry D, Klein DJ& Viner RM.[2020]: Determining the optimal strategy for reopening schools, the impact of test and trace interventions, and the risk of occurrence of a second COVID-19 epidemic wave in the UK: a modelling study. Lancet Child Adolesc Health. 4, pp. 817–27.

[17]   Shah AUM, Safri SNA, Thevadas R, Noordin NK, Rahman AA & Sekawi Z.[2020]: COVID- 19 outbreak in Malaysia: actions taken by the Malaysian government. Int J Infect Dis. 97, pp. 108–16.

[18]   Macartney K, Quinn HE, Pillsbury AJ, Koirala A, Deng L & Winkler N. [2020]:Transmission of SARS-CoV-2 in Australian educational settings: a prospective cohort study. Lancet Child Adolesc Health. 4, pp. 807–16.

[19]   Chauss D, Freiwald T & McGregor R.[2022]: Autocrine vitamin D signaling switches off pro-inflammatory programs of TH1 cells. Nat Immunol. Pp. 23-74.

[20]   Holick, M. F.[2006]: High Prevalence of Vitamin D Inadequacy and Implications for Health. Mayo Clin. Proc. 81 (3), pp. 353–373.

[21]   Christakos S, Dhawan P, Verstuyf A, Verlinden L & Carmeliet G.[2016]: Vitamin D: Metabolism, Molecular Mechanism of Action, and Pleiotropic Effects. Physiol. Rev. 96 (1), pp. 365–408.

[22]   Islamoska S, Petersen JH & Benfield T. [2022]: Socioeconomic and demographic risk factors in COVID-19 hospitalization among immigrants and ethnic minorities. Eur J Public Health. 32(2), pp. 302–310.

[23]   Aldridge RW, Lewer D & Katikireddi SV. [2020]: Black, Asian and Minority Ethnic groups in England are at increased risk of death from COVID-19: indirect standardisation of NHS mortality data. Wellcome Open Res. 5, pp.88.

[24]   Wortsman J, Matsuoka LY & Chen TC. [2000]: Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr. 72(3), pp. 690–693.

[25]   Phommasone K, Xaiyaphet X & Garcia-Rivera JA. [2022]:A case-control study of the causes of acute respiratory infection among hospitalized patients in Northeastern Laos. Sci Rep. 12(1), pp.939.

[26]   Bergman P.[2021]: The link between vitamin D and COVID-19: distinguishing facts from fiction. J Intern Med. 289, pp.1-3.

[27]   Bergman P, Norlin A C, Hansen S & Björkhem-Bergman L. [2015]: Vitamin D Supplementation to Patients with Frequent Respiratory Tract Infections: a Post Hoc Analysis of a Randomized and Placebo-Controlled Trial. BMC Res. Notes. 8, pp. 380- 391.

[28]   K. Shah, V.P. Varna, U. Sharma & D. Mavalankar. [2022] Does vitamin D supplementation reduce COVID-19 severity?: a systematic review. QJM: An International Journal of Medicine. pp.1–8.

[29]   White JH. [2012]: Vitamin D metabolism and signaling in the immune system. Rev Endocr Metab Disord. 13, pp. 21-29.

[30]   Adams JS, Ren S, Liu PT, Chun RF, Lagishetty V& Gombart AF.[2009]: Vitamin D-directed rheostatic regulation of monocyte antibacterial responses. J Immunol. 182, pp. 4289-4295.

[31]   Chen G, Wu D, Guo W, Cao Y, Huang D & Wang H.[2020]: Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest. 130, pp. 2620-2629.

[32]   Hu B, Huang S & Yin L. [2021]: The cytokine storm and COVID-19. J Med Virol. 93, pp. 250-256.

[33]   Daneshkhah A, Agrawal V, Eshein A, Subramanian H, Roy HK & Backman V. [2020]: Evidence for possible association of vitamin D status with cytokine storm and unregulated inflammation in COVID-19 patients. Aging Clin Exp Res. 32, pp. 2141-2158.

[34]   Mohammad S, Mishra A & Ashraf MZ. [2019]: Emerging role of vitamin D and its associated molecules in pathways related to pathogenesis of thrombosis. Biomolecules. 9, pp. 640- 649.

[35]   Shen K, Yang Y, Wang T, Zhao D, Jiang Y & Jin R. [2020]: Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: experts' consensus statement. World J Pediatr.

[36]   Singhal T. [2020]: A Review of Coronavirus Disease-2019 (COVID-19). Indian J Pediatr. 87(4), pp. 281–6.

[37]   Huang P, Liu T, Huang L, Liu H, Lei M & Xu W. [2020]: Use of chest CT in combination with negative RT-PCR assay for the 2019 novel coronavirus but high clinical suspicion. Radiology. 295(1), pp. 22–3.

[38]   Jolliffe DA, Camargo CA & JrSluyter JD. [2021]: Vitamin D supplementation to prevent acute respiratory infections: a systematic review and meta-analysis of aggregate data from randomised controlled trials. Lancet Diabetes Endocrinol. pp.9-92.

[39] Zhang Y, Lu Y, Wang S, Yang L, Xia H & Sun G. [2021]:Excessive Vitamin A Supplementation Increased the Incidence of Acute Respiratory Tract Infections: A Systematic Review and Meta-Analysis.Nutrients. pp.1-13.

[40] Murai IH, Fernandes AL, Sales LP, Pinto AJ, Goessler KF & Duran CSC. [2021]: Effect of a single high dose of vitamin D3 on hospital length of stay in patients with moderate to severe COVID-19: a randomized clinical trial. J Am Med Assoc. 325, pp. 1053–60.