



Can Vitamins, as Epigenetic Modifiers, Enhance Immunity in COVID-19 Patients with Non-communicable Disease?

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Abstract

Purpose of Review The highly infectious transmissible disease, the novel SARS-CoV-2, causing the coronavirus disease (COVID-19), has a median incubation time of 5 to 15 days. The symptoms vary from person to person and many are “hidden carriers.” Few people experience immediate reaction and even death within 48 h of infection. However, many show mild to chronic symptoms and recover. Nevertheless, the death rate due to COVID-19 transmission is high especially among patients with non-communicable diseases. The purpose of this review is to provide evidence to consider vitamins as epigenetic modifiers to enhance immunity and reduce inflammatory response in COVID-19 patients with non-communicable diseases.

Recent Findings Clinical evidence has suggested the risk of getting infected is high among individuals with non-communicable diseases such as cardiovascular disease, type-2 diabetes, cancer, acute respiratory distress syndrome, and renal disease, as well as the elderly with high mortality rate among the cohort. The impact is due to an already compromised immune system of patients. Every patient has a different response to COVID-19, which shows that the ability to combat the deadly virus varies individually. Thus, treatment can be personalized and adjusted to help protect and combat COVID-19 infections, especially in individuals with non-communicable diseases.

Summary Based on current published scientific and medical evidence, the suggestions made in this article for combination of vitamin therapy as epigenetic modifiers to control the unregulated inflammatory and cytokine marker expressions, further needs to be clinically proven. Future research and clinical trials can apply the suggestions given in this article to support metabolic activities in patients and enhance the immune response.

Keywords COVID-19 · Vitamin · Pandemic · Non-communicable disease · Immunotherapy

Introduction

After December 2019, the ongoing death rate due to a novel flu-like coronavirus disease (COVID-19) pandemic has suddenly spread aggressively and continues to increase exponentially. The human to human COVID-19 (SARS-CoV2) is transmitted through the species barrier due to close contact, causing symptoms including extreme fever, cough, pneumonia, acute respiratory disorders, multi-organ failure, and eventually, high mortality among infected patients [1]. The

symptoms appear between 5 and 15 days. The “hidden” human carriers also risk the transmission of the virus between close contacts [2]. Nonetheless, the exact mechanism of transmission still needs to be checked clinically. COVID-19, a highly contagious transmissible disease, has proven to be resistant to the body’s own defense mechanism. With corona cases increasing globally, important biological and clinical trends among patients with special conditions are being reported.

The high mortality rate of COVID-19 is being largely observed in patients with non-communicable diseases (NCDs) including cardiovascular disease (CVD), long-term type-2 diabetes (T2D), and renal disease, together along with the elderly population with/without history of NCDs [3, 4]. More findings are needed; however, to analyze why vulnerable populations are affected and to define clearly the connection between COVID-19 and patients with NCDs. The COVID-19 virus invades the respiratory tract cells and causes thick mucus

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formation leading to lung damage and the septic shock which was also observed in patients with vulnerability with acute respiratory distress symptoms (ARDS) [5]. Previous studies clinically consider a compromised immune system for NCD patients (including smokers and non-smokers) [6, 7]. The affected immune system has a significant effect on the cell's metabolic activity and gene expression [8]. Just as NCDs strike people with reduced resistance or impaired health condition, the “opportunistic” COVID-19 has mainly impacted patients with NCDs with a compromised immune system [9].

Because NCDs are the world's leading cause of death, patients receive micronutrient therapy strategies to treat undernutrition, improve immunity, and prevent infection [10, 11]. At the UN High-Level Meeting on the Prevention and Control of Non-Communicable Diseases, held in New York, USA in September 2011, prevention strategies for NCDs have already been addressed with a view to prenatal nourishment, improving diet and nutrients, and preventing undernutrition and infections. Since NCDs are highly dependent on the individual lifestyle [12], dietary intake and environmental conditions and exposure often play a role in each person's personal response to a specific disease [13]. The European Non-communicable Disease Prevention and Control Office (NCD Office) of the World Health Organization (WHO), in cooperation with the Russian Federation Ministry of Health, has developed a plan to tackle the “customized” approach to prevention and control of NCDs. Treatment of patients can be personalized to help develop a model that characterizes the phenotype and genotype of patients for a more targeted, life-saving treatment due to specific medications and treatment. It is noteworthy that this individualized approach has a potential of obtaining positive results for COVID-19 patients, if individuals are thoroughly tested and treated according to their unique metabolic function.

For COVID-19, which largely is controlling the molecular/genetic immune system of the host, its complete causal relationship has not been identified with the immune system. However, changes in COVID-19 patients along with the physiological factors can be seen in affected body tissue, particularly in the lungs that contribute towards lung injury and ultimately cardiac arrest [14, 15]. Circulative factors such as interleukin factors (IL-4, IL-6, IL-10, and IL-13) and interferons (IFN- γ), tumor necrosis factor (TNF- α) nuclear factor- κ B (NF- κ B), cytotoxic T lymphocyte-associated antigen-4 (CTLA4), and Toll-like receptors-4 (TLR-4) are typically seen in patients with the majority of major NCDs [16–18]. The infection may be targeting gene transcription and regulation of inflammatory markers and chromatin structure machinery of NCD patients [19].

In addition to the body's vital functions, vitamins have an important role to play in immunopathological and physiological response of the body. Studies have shown effective treatment for patients with the addition of vitamins and the

reduction of inflammatory circulatory markers [20]. The highly regulated machinery depends on these epigenetic modifiers obtained mainly from the diet [21]. As gene regulation and suppression is evident in various vitamin-regulated mechanisms that control epigenetic changes such as DNA methylation, histone modification, and post-translation modifications [22, 23], inflammatory markers are widely known to be controlled by such micronutrients as well [24–27]. Both fat- and water-soluble vitamins have proven to be crucial to epigenetic modification to strengthen the immune system and cell growth of an organism as important micronutrients for patients with NCDs [28].

Because there is currently no clinically approved COVID-19 medication or vaccine available, attempts to improve the immunity of NCD patients with COVID-19, vitamin deficiencies should also be tested. The tests would fulfill the requirement to track and regulate proper metabolic activity and immune reactions towards enhanced inflammatory markers. Clinical evidence also suggests that vitamin C is beneficial against SARS coronavirus [29] and COVID-19 is 82% comparable with SARS-CoV [30, 31]. There is also an urgent need to reduce high mortality rates due to COVID-19 and concentrate on an innovative and individual patient strategy to boost therapy effectiveness. The general associations and conclusions identified and reviewed suggest the value of micronutrients to public health experts, and so it is strongly recommended that clinical professionals investigate the alternative treatment further.

Immune Response, Vitamin Deficiency in NCDs, and Relation to COVID-19

Multiple pathways are activated in NCDs. Patients with NCDs are more prone to infections which can be related with high mortality rates [32] as also observed in COVID-19 patients. Mechanisms may be linked to vitamin deficiency and its effects that lead to impaired immune response. Therefore, early intervention of both clinical and individual preventive and control strategies to help prevent the spread of the infection is important, particularly in people with compromised immunity. The widespread distribution of COVID-19 has shown a high mortality rate in NCDs and in people with low immunity. A new, holistic approach to providing people with the right vitamin doses can lead to more effective and individual centric therapy. Scientific and clinical data show that immune responses in CVD, T2D, ARDS, cancer, renal diseases, and autoimmune disorders are strongly compromised. Genetic control of inflammatory markers should be considered as clinically relevant circulatory markers for COVID-19 in individuals with the abovementioned NCDs. The fact that vitamins have been recognized as epigenetic modifications in gene expression in methylation, citrullination, acetylation, and

Table 1 Type of NCDs with respective inflammatory response markers and vitamin deficiencies

Type of NCD	Enhanced inflammatory markers	Vitamin deficiency generally observed	Ref.
CVD	CRP IL-6 TLR4	Vitamin D	[20, 34–42]
T2D	IL-4 IL-10 IL-13 IFN- γ	Vitamin B ₉ Vitamin B ₁₂ Vitamin A Vitamin C	[43]
ARDS	TNF- α NF- κ B	Vitamin E Vitamin D/E	[44–47]
Cancer	GR α CTLA4 PD1	Vitamin E Vitamin B ₁₂ Vitamin D	[48–50]
Renal diseases	T lymphocytes B lymphocytes Th1/Th2 ratio	Vitamin E Vitamin D Vitamin A	[51]

NCD, non-communicable disease; *CVD*, cardiovascular disease; *T2D*, type-2-diabetes; *ARDS*, acute respiratory distress syndrome

phosphorylation [33] can be clinically associated. As can be seen in Table 1, clinical evidence suggests that NCD patients are highly specific with immune sensitive molecules and are deficient in certain types of vitamins [52].

Fatal outcomes have been found in COVID-19 patients causing acute myocardial injury (MI) and chronic damage. Epidemiological data consistently show an increased risk of CRP, TLR4, and IL-6 with subsequent cardiovascular events [34–36]. The CVD incidence history shows an altered polymorphism of the $-174/\text{GC}$ that suggests a possibility for CV event in patients along with the SNP variant of the CRP gene with higher plasma levels [37]. On the other hand, the circulating TLR-4 signal also promotes myocardial infarction. Active vitamin D metabolite signaling pathways control various interleukin factor including IL-6, CRP, and TLR [53]. The epigenetics of this clearly illustrates that vitamin D deficiency is observed in CVD patients [38] with other promoter elements also regulated by vitamins A, E, and B_{9/12}. It is worth noting that COVID-19 increases the risk of CVD among patients and may be causing over-expression of immune response factors that influence the risk of CV events for COVID-19 patients due to vitamin deficiencies. T2D individuals have significant levels of IL-4, IL-10, IL-13, and IFN- γ and TNF- α [54]. Individuals having a highly compromised immune system can be explained due to impaired insulin secretion, over-stressed cell organelles such as endoplasmic reticulum and oxidative stress, and glucotoxicity [55]. The cellular stress in T2D induces inflammatory response due to specific cytokines and chemokines [56]. In addition to T2D patients being prone to infections, the patients suffer from vitamins B₉ (folic acid), B₁₂, A, C, and E deficiencies [43], hence

absence in maintenance of chromatin structure of cell genome, increased apoptosis, and absence of protein integrity. Overall, there is complete absence of epigenetic control of cellular processes in T2D individuals making them susceptible to infectious diseases.

Scientific evidence shows ARDS patients to express NF- κ B and GR α leading to dysregulated mechanisms which leads to up- or down-regulation of various pro-inflammatory mediators and increased oxidative stress [57]. Transcriptional mediators such as NF- κ B expressed in ARDS are attenuated by vitamin C; however, vitamin D and E deficiency in ARDS patients also indicate absence of epigenetic control on gene transcription due to possible absence of proper DNA methylation and histone modification status in the cells [44] which may contribute towards dysregulated transcriptional mechanism. Patients with COVID-19 tend to develop severe immune activation in lungs [14] and hence pneumonia. The clinical link between active inflammatory pathways in ARDS and the vitamin deficiency clearly indicates why COVID-19 causes high mortality in patients with chronic lung diseases.

Epidemiological data confirm higher prevalence of cancer patients with COVID-19. Cancer patients with history of immunosuppressants who are COVID-19 positive are also facing worse outcomes [58]. CTL4A and PD1 are two of the main immune adaptive response regulators that inhibit the normal T-regulatory cell in cancer-stricken patients. Inhibition of both tumor markers resulted in clinical trials to provide anti-CTL4A and anti-PD1 antibodies for cancer therapy, which may be useful for regulating a T cell proliferation signaling pathway [59, 60]. The possible balance between controlling CTL4A and PD1 expression [48], as well as providing vitamin

Table 2 Immune-responsive inflammatory markers and their epigenetic mechanism of gene regulation by different vitamins

Type of inflammatory marker	Type of vitamin controlling epigenetic mechanism	Vitamin-regulated epigenetic mechanism	Ref
CRP	Vitamin D	DNA methyl transferase/histone deacetylase of gene	[66–68]
TLR4	Vitamin E	Inhibition of MAPK activation	
IL-6	Vitamin B ₉	Promoter methylation	
	Vitamin B ₁₂	Decrease in epidermal growth factor (EGF) synthesis	
	Vitamin A	Regulating cell-mediated and humoral components/ lack of B cell switching and proliferation factors	
	Vitamin D	DNA methyl transferase/histone deacetylase of gene	[69–73]
IL-4	Vitamin D ₃	Inhibit the functional differentiation of Th1 cells	
IL-10	Vitamin D	DNA methyl transferase/histone deacetylase of gene	
IL-13	Vitamin D	Alteration of Th1/Th2 expression/production of IgE	
IFN- γ	Vitamin D	Hydroxylase activity	
TNF- α	Vitamin C	Methylation/demethylation cycle/histone modification	
NF- κ B	Vitamin A	Retinoid X receptor binds RA response elements (RAREs) and regulates gene promoter	[74–77]
	Vitamin E	Enhances binding of NF- κ B to the corresponding gene promoters	
GR α	Vitamin D	DNA methyl transferase/histone deacetylase of gene	
CTLA4	Vitamin D	Development of regulatory T cells by antagonizing inflammatory outcomes and promotes regulation	[78–80]
PD1	Vitamin D	DNA methyl transferase/histone deacetylase of gene	
T lymphocytes	Vitamin D ₃	DNA methyl transferase/histone deacetylase of gene	[73,
	Vitamin E	Regulating gene expression in response to T cell stimulation	81–86]
Vitamin B ₁₂	Relating to CD8 ⁺ cells		

Table 2 (continued)

Type of inflammatory marker	Type of vitamin controlling epigenetic mechanism	Vitamin-regulated epigenetic mechanism	Ref
		and the NK cell system	
B lymphocytes	Vitamin A	Retinoid X receptor binds RA response elements (RAREs) and regulates gene promoter	
	Vitamin D	DNA methyl transferase/histone deacetylase of gene	
Th1/Th2 ratio	Vitamin A	Binding of retinol to nucleosome complex on RA-target genes	
	Vitamin D	DNA methyl transferase/histone deacetylase of gene	

D supplements [61], has shown increased T-lymphocytic proliferation, expressing high VDR in cancer patients triggering the T cell differentiation immune response. The evidence clearly shows the degree of clinical infection manifestations in cancer patients with positive COVID-19 test.

Fatalities in kidney patients are also investigated, provided that COVID-19 patients with ongoing kidney and renal disease are controlled with a high degree of caution [62, 63]. Signs of kidney dysfunction include elevated proteinuria, urea and serum potassium, hematuria, and other clinical comorbidity [64]. Patients with a history of failure of kidney disease develop inflammation which contributes to the activation of the adaptive immunity of increased Th1/Th2 ratios and to T and B lymphocyte autoantibodies [51]. Infectious pathogens may easily enter the kidney patients. This possibility should also be timely addressed in COVID-19 patients to prevent end-stage renal diseases (ESRD). In kidney patients, vitamin D is discovered to be deficient, putting them at risk of CKD and hyperparathyroidism. The vitamin suppresses most of the adaptive immune system which can play an important role in protecting the host against first-line defense invasion of COVID-19. In the COVID-19 patients with kidney transplant [65], vitamin D may prove effective and this may also prevent graft rejection and regulate Th1/Th2 ratios.

Micronutrient therapy to be considered and given should be individual centric and based upon time and dose-response manner. Vitamin therapy seems feasible at this time due to absence of the vaccine or medication available for care to prevent multiple organ failure and immunologic deaths among COVID-19-positive patients with NCD. Table 2 summarizes the vitamins that control the immunomodulatory elements and the mechanism of action. If the population receives the right dose of vitamins specific to NCD and inflammatory

Table 3 Vitamin supplements recommended as alternate personalized therapy for NCD patients with COVID-19 to enhance the immune response of patients infected with SARS-CoV2

Type of NCD	Vitamin supplement to be given to COVID-19-positive patients with NCD	If elderly, additional vitamin to be provided [87]
CVD	Vitamin A	Cobalamin (vitamin B ₁₂)
	Vitamin D	
	Vitamin E	
	Vitamin B ₁₂	
T2D	Vitamin A	Cobalamin (vitamin B ₁₂)
	Vitamin C	
	Vitamin D	
	Vitamin E	
	Vitamin B ₉	
	Vitamin B ₁₂	
ARDS	Vitamin A	Cobalamin (vitamin B ₁₂)
	Vitamin D	
	Vitamin E	
Cancer	Vitamin A	Cobalamin (vitamin B ₁₂)
	Vitamin C	
	Vitamin D	
	Vitamin E	
	Vitamin B ₁₂	
Renal diseases	Vitamin A	Cobalamin (vitamin B ₁₂)
	Vitamin D (D ₃)	
	Vitamin E	
	Vitamin B ₁₂	

NCD, non-communicable disease; *CVD*, cardiovascular disease; *T2D*, type-2-diabetes; *ARDS*, acute respiratory distress syndrome

factors expressed, effects on respiratory health can be observed as DNA methylation, histone modification, and enzyme control, and the proper cell division of healthy cells can be regulated. This personalized therapy recommends a medical model that should characterize the COVID-19-positive individuals for diagnosis based on the type of NCDs.

Vitamin Therapy as a Personalized Approach

Based on primary observation on previous evidences, the types of vitamin combinations which can be given to patients are shown in Table 3. Based on clinical evidence, the table combines the types of vitamins which can be selected to enhance the immunity of patients to reduce the inflammatory response in NCD patients. There is strong need for personalized treatment for COVID-19 patients suffering from NCD as an alternative therapy [88]. The compilation of literature, shown in Table 3, citing clinical evidence for a potential vitamin link in the control of immune expression of inflammatory markers to treat an infectious pandemic [89], needs to be clinically validated. As vitamins regulate the epigenetic machinery, age, sex, smoking, ethnicity, and other environmental/lifestyle factors are also affected by changes to immune response. Several NCDs are driven by

genomic instability, hypermethylation, and hypomethylation of promoter gene regions involved in immunological marker and element regulation. Treating vitamins as major epigenetic modifiers will prove to be an effective approach to customized treatment, particularly for COVID-19 patients with different background factors that could have contributed in the past to develop the specific NCD. Vitamin therapy can be an effective and safe treatment as a custom drug. In COVID-19 patients, the storm of inflammatory or cytokine factors should be tested by assessing patients for different inflammatory markers and vitamin deficiency. In order to provide a metabolism for an individual against vitamin deficiency, all individuals should be screened for specific immune cell reactions and the factors represented by the specific NCD. The combination will improve care and lead to a more personalized approach. An exhaustive review is also needed for other factors such as pregnancy and other medical conditions. This can be used as time progresses and new clinical data for COVID-19 patients are available.

Conclusion

This study can serve as a primary link to open ways to look at important facts to cure people, otherwise having compromised

immune systems due to NCDs. This may include more studies and recommendation of personalized approach for patients to be treated. The benefit is that vitamin therapy has no side effect and has proven to be effective. The micronutrient combination is also recommended for the target population without NCD or help early in its prevention of infectious diseases for patients at risk for COVID-19. Other factors, such as smoking and drinking, should not be overlooked. This will also extend guidelines and policy changes to undernutrition and infections in low- and middle-income countries. Therefore, opportunistic infections can be better controlled in the future with low mortality rate, and vitamins can serve as useful epigenetic modifiers to genetically target and modify transcriptional and translational control of various inflammatory markers.

Compliance with Ethical Standards

Conflict of Interest The authors declare they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of major importance

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