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The Role of Fat-Soluble Vitamins A and D in the Pathogenesis of Coronavirus: With a Focus on Pregnant Mothers

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ABSTRACT
Coronavirus is known to be the leading cause of lung infection and mortality in 2020. In the meantime, recognizing the factors influencing the increase in the immune system and better therapeutic performance is highly debated. Decreased exposure to sunlight leads to vitamin D deficiency and thus to an inherent immune deficiency that subsequently acts as a trigger for the virus replication. Numerous observations indicate the role of various vitamin compounds in corona disease. This paper examines the role of fat-soluble vitamins in the immune system and its effect on the patients with corona among the pregnant women. Studies show that low concentrations of vitamins D and A increase the risk of the disease incidence. Vitamins also amplify the risk of corona in the people with high-risk factors such as obesity, diabetes, kidney and liver problems, by affecting liver function and changes in retinoid metabolism. Adequate levels of vitamins can be presented as a potential strategy for the prevention and treatment of corona.

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INTRODUCTION

Coronavirus (CoVs) is considered as a member of Orthocoronavirinae sub family, the coronavirus family, and the Nidovirals order. The subfamily of Orthocoronavirinaes includes α-coronavirus, β-coronavirus, γ-coronavirus, and delta-coronavirus. Coronaviruses imposed a remarkable amount of enzymatic infection in species such as birds and mammals. In addition, it is the main reason of human infection in recent years. There is some famous and fatal β-CoV including SARS-CoV and MERS-CoV caused severe and deadly respiratory infections in human. These viruses were the first reason of people death in 2002 and 2012, respectively (1, 2). Recently, many cases of patients with pneumonia as the result of a new β-coronavirus were recognized in December 2019 in Wuhan, China. The World Health Organization (WHO) identified Coronavirus as the new coronavirus 2019 (2019-nCoV) occurred on January 12, 2020. The Chinese eliminated quickly SARS-CoV-2 from the apatite and reached to the sequence of the SARS-CoV-2 genome on January 7, 2020, (3). The COVID-19 genome is considered as a positive sense single-stranded RNA. Findings of the sequential analysis revealed that COVID-19 possesses a common and similar genomic structure of coronavirus and is a member of the β-coronavirus cluster consisted of SARS-CoV and MERS-CoV. There is 82 % similarity between COVID-19 and SARS-CoV. COVID-19, as a global pandemic, is prevalent in all over the world. Recently, no cure or vaccine has been still identified for this fatal virus. Since there is not

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any treatment for this virus, all people should try to control its spreading and it is necessitate to do a lot of examinations to find the best solution for this complicated problem (4).

Vitamin D and mechanisms reducing microbial infections

Vitamin D metabolism and its benefits are well-known(5). By irradiating UVB with 7-dehydrocholesterol, vitamin D3 is produced as a result of a thermal reaction in the skin. Vitamin D3 or its oral type is changed into 25(OH) D in the body organs such as liver and it is converted to the metabolic metabolite, 1, 25(OH) 2D (calcitriol) in our kidney or some other organs. A remarkable amount of vitamin D results from the calcitriol attached to the vitamin D receptor nucleus, which applies active chromatin complexes that are genetically or epigenetically involved in converting the transcription product (6). The significant performance of calcitriol is assisting regulate serum calcium concentrations acting as a feedback loop with parathyroid hormone (PTH) playing an important role in the body (5).

There are many mechanisms attributed to Vitamin D that can help in reducing the risk of microbial infection and mortality. Studies by Rondanelli and colleagues in 2018 found that using vitamin D in some different ways decreased the risk of common colds, including physical barriers, natural cellular immunity, and acquired immunity (7). Vitamin D helps Cell junction (such as E-cadherin) (8) . Some articles discuss how the virus disrupts the integrity of the connections and increases the infection by viruses and other microorganisms (9).

The effect of vitamin D on tissues and coronavirus

Vitamin D makes strong intrinsic cellular immunity by the inducement of antimicrobial peptides. Antimicrobial peptides including human cathelicidin LL-37 (antimicrobial peptides stored in lysosomes of macrophages and polymorphonuclear leukocytes (10) and defensins (cysteine-rich small cationic proteins) (11) . Cathelicidins shows direct antimicrobial activities opposed to a series of microbes such as gram-positive and gram-negative bacteria, enveloped or non-enveloped viruses and fungi (12). These host-derived peptides eliminates invasive pathogens by perforating their cell membranes and have the ability in neutralizing the biological activities of endotoxins (13). Various acts attributed to them have been clarified. In 2011, Barlow and colleagues employed a mouse model to represent that LL-37 can decrease the replication of the influenza A virus (14). Martinez et al., stated that 1, 25(OH) 2D could reduce rotavirus replication in glass and in living organisms in 2020. According to a clinical study 4000IU/d vitamin D cause a reduction in dengue virus infection (15). In addition, Vitamin D plays a significant role in strengthening cellular immunity by a reduction in the flow of cytokines induced by the innate immune system. Primary and anti-inflammatory cytokines were induced by innate immune system in response to viral and bacterial infections in patients with COVID-19 (16). Vitamin D has a remarkable power in reducing and confining Th1 cytokines production including tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ)(17). Vitamin D can decrease of primary inflammatory cytokines expressions and increase anti-inflammatory cytokines expressions by macrophages (18).

Vitamin D is identified as an immune system modulator (7). 1, 25(OH) 2D3 retrains the mediated responses by Th1 helper cells by impeding the production of IL-2 and IFN-γ inflammatory cytokines. In addition, 1,25(OH)2D3 improve cytokines' production by Th2 helper cells assisting the increase in indirect suppression of Th1 cells by several kinds of cells (19). Moreover, 1,25(OH)2D3 induces T regulatory cells and improve the development of inflammatory processes (20). Serum 25(OH)D concentration, reduced with age (21), is considered as a major factor for COVID-19 due to the increase in the case fatality rates (CFRs) with age (22). This situation is the result of the reduced time passed in the sun and a significant reduction in producing vitamin D due to lower levels of 7-dehydrocholesterol in the skin (23). In addition, several mediations decrease serum concentrations of 25(OH)D by activating the pregame-X receptor (24). These drugs consisted of antiepileptic, anti-neoplastic, anti-inflammatory, anti-hypertensive, anti-viral, endocrine drugs, and some herbal or natural remedies. The use of drugs is depended on age and to the extent you will be older, your medication usage will be more. Distribution of Vitamin D increases the expression of antioxidant-related genes (glutathione reductase and glutamate-cysteine ligase modifying subunits) (25). Increased glutathione production stores ascorbic acid (vitamin C) possessing antimicrobial activity (26) has been proposed for the prevention and treatment of COVID-19 (27). Some researchers suggested taking vitamin D at the peak of COVID-19 epidemics on March 23, 2020 (28).

The remarkable role of vitamin A

Researchers recognize Vitamin A as the first and main fat-soluble vitamin in the body structure of plants in the form of β-carotene. There is an inverse association

among consumption of animal dietary fat and beta-carotene and the CHM incidence(29). In general, Retinol, retinal, and retinoic acid are three main active vitamin A in the structure of body. vitamin A levels impose a remarkable effect on the human immune system and is identified as an antiseptic (30, 31). Researchers stated that impairment observed in immune response is the result of insufficient specific nutrient. Insufficient Vitamin A can lead to severe measles and diarrhea in children may be the result of vitamin A deficiency (31).

The first biological performance of vitamin A consisted of maintaining visual acuity, integrity and development epithelial tissue and mucus. Green and Mellanby in 1928 found that this vitamin could strengthen anti-inflammatory responses in the body structure. Therefore, its name as "anti-inflammatory vitamin" was the result of its function in the body (32, 33).

Vitamin A supplement has been indicated to reduce the complications and death in different infectious diseases including measles, diarrhea, pneumonia, human immune system infection (HIV) and malaria, according to a study conducted by Semba and the colleagues (28).

Jee et al., pointed that following diets containing insufficient vitamin A deactivates coronavirus vaccines and led to the susceptible clave sensitive to infectious disease(34) . Moreover, a study by West et al., indicated that the infection resulted from infectious bronchitis virus (IBV) as a kind of coronavirus in chickens with a low-vitamin A diet were more than those chicken with a sufficient vitamin A diet (35).

Immune system organs include organs or tissues in which immune system cells are multiplied, differentiated, and matured, eventually leading to immune system function. Research has shown that these organs need to maintain adequate levels of vitamin A in order to function properly, as thymocytes need vitamin A to multiply and regulate apoptosis (36-38). In thymus, endogenous retinoid synthesis and glucocorticoid-like retinoids may regulate proliferation and selection of thymus (37).

Vitamin A regulates bone mineral density by binding to the retinoic acid receptor (RAR) in the bone marrow cell nucleus. This binding leads to a significant increase in expressing the levels of apoptotic genes including Bcl-2, Fas, and others. However, particular mechanisms that apoptotic genes use to cause the regulation of bone marrow homeostasis called for an urgent and further investigation(36).

Vitamin A has a significant role in innate and adaptive immune systems. Therefore, it can strengthen the immune system performance and create an advanced defense in confronting with different infectious diseases. Nowadays, a bulk of research studies examined the probable effect of vitamin A on the performance of immune system at the molecular level and more examinations are conducting on the therapeutic effects of vitamin A in preventing and curing different infectious diseases. Therefore, vitamin A is identified as a probable option for curing new coronavirus and preventing lung infection (39).

Epidemiological and clinical findings on COVID-19

The first stage in proposing this premise is reviewing the epidemiological and clinical findings attributed this disease and its relationship to the concentration of vitamin D. regarding present and available literature on this virus, COVID-19 infection has a strong association with producing pre-inflammatory cytokines increasingly (40) , reactive protein C (16), high risk of pneumonia (40), sepsis (4), and acute respiratory syndrome (4), and heart failure (4). the CFR was 10% -6% for people with cardiovascular disease, chronic airways, diabetes, and high blood pressure in China (22). COVID-19 imposed an evident effect on two areas including China with air pollution in a high amount (41) and the north of Italy (42).

Vitamin D has probable benefits regarding clinical and epidemiological features of diseases with respect to the high risk of COVID-19 CFR. These productive roles are mentioned in Table 1 and they were obtained from observational examinations on the incidence or the spread of disease because of serum vitamin D concentrations. With comparison of the randomized controlled trials (RCTs) results for the participants who have been or are being treated with placebo, it is preferred to attribute the cause to health consequences. However, many vitamin D RCTs did not find any decrease in the disease risk attributed to vitamin D supplement (43).

The disagreement upon the observational examinations and RCTs is due to some reasons consisted of examining patients with relatively high concentrations of vitamin D, taking low doses of vitamin D, and the non-measurement of baseline concentrations of 25(OH)D.

A bulk of research studies revealed that using this vitamin depends on nutritional status; for example, the samples with low values of 25(OH) D were accepted, which indicated better resilience against coronavirus by giving them adequate supplement and increasing the appropriate concentration. However, two completed RCTs illustrated that the incidence of cancer (44) and diabetes mellitus (45) were significantly reduced in their secondary analyzes.

Reduction in 1, 25- dihydroxyvitamin D or vitamin D active metabolism is a factor dependent on age imposing effect on the immune response. In addition, age influences the increase of parathyroid hormone concentration (PTH).

A study in the United States based on 312962 paired measurements of PTH and 25(OH) D was conducted from July 2010 to June 2011. For the participants with a concentration of 20 ng/ml, PTH from 27pg/ml for less than 20 years to 54 pg/ml for more than 60 years increased (46). Serum calcitriol concentrations are reversibly dependent on PTH concentrations.

Table 1: How vitamin D is associated with clinical and epidemiological findings for incidence and CFR (45).

(clinical) Features	Association with 25(OH)D
Severe cases related to pneumonia	Reverse association with Community-acquired pneumonia (CAP)
Increased production of primary cytokines of inflammation such as IL-6	Reverse association
Increased CFR	Reverse association
Increased risk of sepsis	Reverse association
Risk of Acute Respiratory Stress Syndrome (ARDS)	Reverse association
Risk of heart attack	Reverse association
The risk of diabetes	Reverse association
(epidemiological) Features	**Association with 25(OH)D**
It began in China and had spread more to the Midwest in December	Low values of 25(OH)D in winter
Men are more likely to have CFR than women	Smoking reduces 25(OH)D .
CFR increases with age	Chronic disease rates increase with age; Vitamin D reduces the risk of chronic diseases.
Higher CFR for diabetics	Diabetics have a lower 25(OH)D.
Higher CFR for diabetics	Lower 25(OH)D is associated with an increased risk of recurrence.
Higher CFR for people with pressure	Lower 25(OH)D may be associated with an increased risk of recurrence.
Higher CFR for cardiovascular diseases	Lower 25(OH)D is associated with an increased risk of recurrence.
Higher CFR for chronic respiratory diseases	For chronic obstructive pulmonary disease (COPD) patients, 25(OH) D is inversely related to risk, severity, and exacerbation.
Higher rates in areas with high air pollution	Air pollution is associated with lower concentrations of 25(OH)D

Another examination in Norway investigated calcitriol from 140pmol/L for 39-20 years to 98 pmol/L for over 80 years, while an increase in 25(OH)D serum from 24ng/mL for 39-20 years to 27ng/mL for over 80 years on patients with a mean age of 50 years (47).

Seasonal requirements for many viral infections are related to low concentrations of 25(OH)D due to low

UVB doses temperate climates in winter and rainy seasons in tropical climates such as RSV virus (48). This is perfectly suited for influenza and SARS-CoV (49, 50).

The infection risk of COVID-19 is more and more when you are working in a hospital attending patients infected by this virus. For example, forty of the 138 patients admitted to Zhongnon Hospital from January 1 to 28, were medical staff, and more than 17 people became infected while working at the hospital (40). Almost 1700 staffs in Chinese health care setting were infected with this virus and six of these workers passed away on February 14, 2020.

Supplying Vitamin D for increasing the concentrations of 25(OH)D decreases nosocomial infections (51). Concentrations of at least 40-50 ng/mL (100-125 nmol/L) were the basis of observational examinations (52). As COVID-19 spread as an epidemic in the world, all patients and staffs should take vitamin D supplements to increase their 25(OH) D concentrations as an assistant medication in inhibiting and spreading the infection. Investigations into this hypothesis are worthwhile.

It is recommended to take Magnesium supplement along with using vitamin D. Magnesium activates vitamin D and modulates calcium and phosphate homeostasis and influences development of bone and its' maintenance. It observed that all the enzymes metabolizing vitamin D are necessary as a co-factor in enzymatic reactions of the liver and kidneys (53). Magnesium doses should be in the range of 250-500 mg/d and calcium doses twice more.

The premise of reduction the risk of influenza and COVID-19 death by with the assistance of Vitamin D should be investigated by researches on specifying appropriate doses, concentrations of 25(OH)D, and safety issues. Vitamin D RCT is a proper model for ICU ventilated patients in Atlantia and Georgia (54).

In his book on coronavirus in 2020, Fairchild wrote, "evidence suggests that multiple micronutrient supplements with immune supportive roles may mediate the performance of immune system and decrease the risk of infection. Vitamins C, D, and zinc are well recommended. This virus necessitates an appropriate design for conducting clinical studies on dosage and nutrient composition in different samples to confirm the advantages of nutritional supplements opposed to infection." In addition, Vitamin C helps the activity of natural killer cells, thus strengthening the immune system. Neutrophil phagocytosis increased by 20% in people who took vitamin C. Vitamin C inhibits NLRP3 and reduces IL-1B secretion. Vitamin C protects mitochondria from oxidative damage as a result of N-protein binding to COVID-19 (55).

Reverse association of vitamin D with vitamin A

Vitamins A, D, E, and K are among the fast soluble vitamins interacting regularly with each other. For example, it was indicated that the performance of vitamin D necessitates vitamin A (56). Examinations found that ligand RXR with 9-cis-retinoic acid (9-cis-RA), the active hormonal form of vitamin A, strengthen the expression of the gene dependent on vitamin D and have a remarkable role in the previous and well known signal of Vitamin D. in the absence of 9-cis-RA, vitamin D has a weak attachment to DNA and imposes an insufficient effect on expressing the gene. On the contrary, the existence of 9-cis-RA provides remarkable agonistic activity to the vitamin D receptor ligand with very low agonist activity. The documents indicate that main and probable disorders in vitamin A or D due to diets or other factors create inverse and forbidding corresponding relationship between them. This relationship lies in the fact that vitamins A and D balance their potentially toxic individual effects (57); for example vitamin A can reduce and modulate the toxicity of vitamin D (58).

There is a revers reaction between both vitamins in this manner that Vitamin D has a revers reaction with vitamin A and provides a reduction in the toxicity of vitamin A.

Although there is little examination on the effect of reduced sunlight and/or vitamin D deficiency on vitamin A metabolism, medium doses of vitamin D leads to the reduction in vitamin A stores body organ such as the liver and less levels of vitamin A in the blood (59). Findings revealed that chickens exposed to UV light (which produces vitamin D) decreases liver reserves and retinol blood levels (60).

Using vitamin D supplements at the same time remarkably leads to the high amount of vitamin A necessary for toxicity. For instance, a 2003 study by Myhere et al., indicated that the average dose of toxicity in Vitamin A when added to the diet was 23,000 IU more per kilogram of body weight in a day (61).

The probable toxicity of taking high vitamin A may be based on the amount of vitamin D that was taken. In addition, insufficient vitamin D increases the probable toxicity of vitamin A. Indeed, taking prefabricated retinol with normal doses in the United States in the form of multivitamins may cause osteoporosis in adults with low vitamin D concentrations (62).

Regarding the effect of vitamin A on vitamin D in humans, the amount of vitamin A in a meal inhibits the increase in serum calcium due to vitamin D (63). Retinoic acid can act as an anti-vitamin D in mice (64). High doses of vitamin A are harmful to liver. High levels of retinoid inhibit nitric oxide (NO) production.

NO is a vasodilator and has antiviral activity. NO inhibition depends on more severe symptoms and is slowly removed from the bloodstream in rhinovirus infections (55).

The sun's UV-B spectrum changes 7 dehydrocholesterol to the active form of vitamin D (calcitriol). Reflecting sunlight for 30 minutes on body skin with while clothing or putting sunscreen can lead to the synthesis of 10,000 to 20,000 IU of vitamin D. In addition, more radiation alters excess vitamin D into the skin into inactive metabolites and accumulation of melanin pigment in the skin reduces vitamin D production (65).

Vitamin A is also affected by temperature changes; light and heat both catabolize vitamin A. In another study, twin calves were given 6 mg of carotene daily for 100lb of body weight. Then, they were placed at high and low temperatures. High temperatures lead to usage of liver vitamin A increasingly. Moreover, during 38 days, that calf exposed to sunlight lost more liver vitamin A than its' counterpart in the shade (66). According to the role of retinoic acid in cell development and distinguish, some parts of the virus growth is modulated by vitamin A. A number of viral infections are influenced by retinoids (67). In the case of cytomegalovirus, for example, exposing to retinoic acid cells increases viral gene expression and susceptibility to the infection.

Vitamins A and D, liver, and corona

Liver damage in the patients infected by coronavirus may be the result of infection in liver cell. Approximately 10-2% of COVID-19 patients having diarrhea and SARS-CoV-2 RNA has been identified in stool and blood samples (68). This situation indicates a viral contact in the liver. To enter the target cell, SARS-CoV-2 and SARS-CoV connects to the angiotensin-converting enzyme 2 (ACE2) receptor, replicated virus and subsequently infected other cells of the upper respiratory tract and lungs. Then, The patients show clinical signs (40).

Pathological examination on patients infected by SARS revealed that the virus in patients' liver tissue, however the virus titer was to some extent low because of the lack of viral accumulation (69). On the other hand, this situation for patients with MERS was different. It was observed that patients with MERS were infected with viral particles invisible in liver tissue.

In addition, Alsaad et al., in a 2018 study reported that although gamma-glutamyl transferase (GGT) as a diagnostic biomarker for the damage of cholangiocyte was not pointed in COVID-19 examinations. Moreover, the level of this marker in 30 (54%) patients of sample of 56 participants with COVID-19 was increased. An increase in levels of alkaline phosphate has been seen in one (8.1%) patient of the total patients (70).

In another study, Chai et al., in 2019 pointed that an increase in the expression of ACE2 receptor in cholangiocytes reveals that SARS-CoV-2 connects directly to positive ACE-2 cholangiocytes to impair the function of liver. However, the pathological analysis was done on patients who died of COID-19. This analysis on their liver tissue showed that there is not any viral infection in liver. The damage of liver tissue was the result of drug toxicity showing a wide variety of various categories. Moreover, immune inflammation including cytokine-induced pneumonia and hypoxia may be influential in the damage for liver or even liver failure in patients with COVI-2019(71, 72).

In the first months of pregnancy, vitamin D (often vitamin D3, the dominant form in the mother's blood) is involved in regulating cytokine metabolism and mediating the immune system, as well as helping to position the embryo and regulate the secretion of several hormones. The lack of Vitamin D and its insufficiency in the mothers and infants was seen for decades in northern European countries, especially in winter. Despite the uniformity of accurate absorption among different countries, vitamin D supplement is recommended for pregnant women at 600 units per day (15μg/day)(73) .

Prevention and treatment

10 percent of the total cost of medical care in developed countries was related to cancer, but the pandemic of Quaid 19 is higher than other medical causes (74). The best way to prevent the infection is to avoid exposure to the virus. However, with preventive health measures such as hand washing, not contacting the sick people, using a home moisturizer, not touching the eyes, nose and mouth, drinking plenty of fluids, not being in crowded covered places and performing the functions increasing the immune system can prevent the spread of respiratory viruses such as COVID-19 (75-79) .

Various drugs have been introduced to treat coronavirus. Ribavirin has been used as an antiviral agent with broad spectrum in the process of treating hepatitis C. Taking into account the drug reactions and dosage, the use of ribavirin in the medication process of COVID-19 has been seriously observed even in combination with other possible antiviral medications (72). Lopinavir/ritonavir is another drug that has been widely utilized as an enhanced protease inhibitor in eliminating HIV infection(80) . Kim and colleagues confirmed a successful medication for MERS-CoV treated with the triple

combination of LPV/RTV, ribavirin, and IFN-α2a in South Korea. Treatment with the triple combination of kim can be considered as an option in the treatment of the patient's initial level (81). Another important drug is remdisivir (RDV). This drug inhibits coronavirus in human and animal and tries to control ARDS (in SARS-CoV). However, RCTs are required to assure and specify safety and efficacy of RDV (82, 83). Nelfinavir is another drug that Yamamoto and colleagues found that it strongly inhibits SARS-CoV replication. Thus, nelfinavir can be taken into account as another option in COVID-19 medication (84, 85). Arbidol (ARB) is an indole-derived molecule used for the prophylaxis and influenza cure and possible viral infections in respiratory organs. It has been applied as a primary drug in corona patients (84). NO is defined as a gas with different biological activities and is the result of NO synthase from Argentina. NO inhalation can be used as an option for the treatment of COVID-19 patients (85).

CONCLUSION

Investigating the relationship between nutrition and safety can be considered as an interdisciplinary approach and it is required to extend because people consider these issues more than before. In addition, the impact of micronutrients on the functioning of the immune system has been extensively studied. Vitamin A has a remarkable effect on both the innate and adaptive immune system. Therefore, it can boost the immune system performance and provide an advanced defense opposed to different infections. Currently, the effect of vitamin A on the performance of the immune system at the molecular level has been studied, and more examination is being done on the medication effects of vitamin A in inhibiting and curing different infections. Providing intervention with vitamin D experimentally is a clinical approach that can be explained and defended by low serum levels and the risk of immune system disorders. As matter of fact, improving circulation at level of 25(OH)D makes it possible to slow the progression of the disease or even improve the survival of the patients. In general, research indicates that consuming vitamins improves the immune system performance, which increases the human body's ability to fight viruses. Fat-soluble vitamins can be applied in pregnant mothers. Vitamins are involved in regulating the secretion of hormones and metabolism in the body of the mothers, and this affects the health of the baby and the mother. It is hoped that this will be scientifically revealed by examining the clinical role of these vitamins in the mothers with corona.

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