Chapter

Role of Vitamin D in Patients with Schizophrenia Suffering from COVID-19

Fatemeh Gholami, Saman Farshid, Parmida Soleimani and Rohollah Valizadeh

Abstract

People with schizophrenia are at high risk for vitamin D deficiency. There is more likely as association between vitamin D and COVID-19 development and even severe outcomes following SARS-CoV-2 infection. It should be noted that other factors except schizophrenia are also related to the severity of the COVID-19 such as heart conditions, respiratory disorders, overweight, and hypertension in which are prevalent in patients with schizophrenia linked with vitamin D deficiency. This book aimed to determine the relationship between the level of vitamin D and COVID-19 severity in patients with schizophrenia.

Keywords: schizophrenia, vitamin D, 25(OH) D, respiratory infection, COVID-19, coronavirus disease

1. Introduction

In December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, Hubei province, China. The World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) a pandemic on 11 March 2020. While it is estimated that 80% of those infected with COVID-19 are asymptomatic or have a self-limiting disease, the case fatality rate for those hospitalized with COVID-19 was 2.3%, increasing to 10.5% in those with cardiovascular disease, 7.3% in those with diabetes mellitus, 6% in those with hypertension and 5.6% for cancer [1]. COVID-19 was distributed worldwide and showed various symptoms, including lung involvement, liver and kidney damage, and conjunctivitis. COIVD-19 is considered a disease with multi-organ failure ability [2–7]. After declaring the Pandemic by WHO, researches were done further to find remedy and vaccines [8–10]. Vitamin D is one of the subjects that had controversial effects on the treatment or recovery process of patients with COVID-19. Now we elaborate on the details of vitamin D [11].

Vitamin D, a steroid hormone, plays the main role in the immune system [12, 13]. Vitamin D influences many reactions against the normal immune response to pathogens. Vitamin D can facilitate the recovery of COVID-19 because both cytokine storms and inflammation are related to severe outcomes in patients with COVID-19

who have high prevalence of pneumonia and lung failure, especially in older patients with lots of comorbidities results in high mortality rate. More than 70% of all schizophrenia (SCZ) patients also have one or more clinical conditions, including diabetes type II [14–16], chronic pulmonary disease [17], heart diseases, obesity, and hypertension, so the life span in these people decreases [18–20] and may be vulnerable to infection with SARA-CoV-2 [21].

People who have psychotic disorders are at high risk for vitamin D deficiency [22]. There is a close relationship between COVID-19 and SCZ. The results of a study showed that SCZ is associated with high mortality following COVID-19 development [23].

Low accessibility to suitable medical care aggravates this scenario [24]. Patients with SCZ and their home care providers may have problem seeking health services. Additionally, even if they want to ask for medical assistance, due to the stigma surrounding SCZ, there is more likely to not take proper assessment or treatment [25].

Patients with schizophrenia are prone to be infected with worse outcomes, especially if they are suffering from several comorbidities. They are vulnerable to worsening psychiatric symptoms and relapse due to fear of the disease, stress, and the boredom associated with compulsory isolation. Thus, health and care providers need more attention and support to prevent COVID-19 among in this group and should detect both psychiatric and respiratory problems as soon as possible.

In this chapter, we tried to describe the reason for high COVID-19 morbidity and mortality among individuals with SCZ through a literature review.

2. Development of vitamin D deficiency in patients with schizophrenia

Schizophrenia may be developed by environmental and genetic factors [26]. According to epidemiological research, schizophrenia is seen more in people: 1) born in the winter and spring seasons [27], 2) living in the urban area in childhood [28–31], and 3) living at high latitudes [32]. On the other hand, we know that dark skin needs much sunlight exposure to produce enough vitamin D, so children with dark skin who migrate to cold climates have more chance of developing SCZ due to low levels of vitamin D during gestation [33]. A Danish case–control study indicated that vitamin D deficiency in neonates is associated with an increased risk for SCZ in later life. People with 25OHD less than 20.4 nmol/L [34] had a 44% increased risk of SCZ compared to people over 40.1–53.5 nmol/L [22].

However, randomized clinical trials to investigate the effects of maternal vitamin D supplements on the development of SCZ in their children may never happen due to two reasons. First, there is no strong evidence suggesting high dose of 25OHD for

Study	Hypothesis
Finnish birth cohort	Lack of vitamin D supplements in the first year of life is associated with SCZ development in men [36].
Danish case–control study	Vitamin D deficiency in neonates is associated with SCZ development in later life [22].
KiGGS[1] study	The offspring of migrants with dark skin develop more SCZ [33].

[1]*The German National Health Interview and Examination Survey for Children and Adolescents.*

Table 1.
Summary of hypothesis related to vitamin D and SCZ.

health targets. Second, it is unethical to screen pregnant women for vitamin D deficiency and allocate this group to take vitamin D supplements or the placebo. Finally, it is hard to follow up on large mother-offspring samples for 2–3 decades to determine the risk of SCZ development [35]. A summary of the hypothesis related to vitamin D and SCZ is presented in **Table 1**.

3. Prevalence of vitamin D deficiency in schizophrenia

Vitamin D deficiency and insufficiency are in different people worldwide, but its burden, such that the prevalence of serum 25OHD < 25/30 nmol/L ranges from 5 to 18%, depends on the Food and Agriculture Organization (FAO) world region, varies from 24 to 49% in the case of serum 25OHD < 50 nmol/L [37]. It is not clear which dose of vitamin D levels are sufficient, insufficient, and deficient, and we showed typical thresholds in **Table 2**. The main circulating form of vitamin D is 25OHD which is usually taken as a proxy of vitamin D status in blood [39, 40]. Two prominent studies report an association between neonatal vitamin D deficiency and an increased risk of SCZ [26, 41]. A meta-analysis study including 31 studies showed that there were statistically significant differences in the mean 25OHD between SCZ and the control group in which; the control group in the case–control and cohort studies consisted of healthy subjects with no history of psychiatric disorders, while in the cross-sectional studies, psychiatric patients but non-schizophrenic were considered to be the control group. Consequently, it can be concluded that, compared with healthy people or other psychiatric patients, peripheral blood mean 25OHD is low in patients with SCZ [26].

Generally, patients suffering from SCZ have poor general health, poor nutrition, low activity, and more comorbidity. So it is important to be cautious in any causal interpretation for patients with SCZ [42]. Some studies have inconsistent results from existing vitamin D supplementation trials in patients with SCZ [43, 44]. We can conclude that vitamin D deficiency can increase the risk of SCZ development, and it is strongly recommended to do ongoing research.

4. Vitamin D deficiency and respiratory infection risk with SARS-CoV-2 virus

There are two critical questions emanating from the title of this part. The first is whether there is an association between susceptibility to develop COVID-19 and vitamin D deficiency or not. The second is whether vitamin D use in deficient people can prevent or improve infection with SARS-CoV-2 or change the course of its disease.

Serum 25(OH)D concentration, mean: nmol/L (ng/mL)	Prevalence, %	Classification
<25 (<10)	6.7	Deficiency
<50 (<20)	37	Insufficiency
>75 (>30)	11	Sufficiency

25(OH)D, 25-hydroxyvitamin D [38].

Table 2.
Vitamin D level and its prevalence worldwide.

Improvement of the immune system by correct nutrition is a considerable factor. Vitamin D as a nutrient plays a significant role in the immune system. However, there is little evidence about the role of vitamin D in preventing COVID-19 and its consequences [45].

COVID-19 pandemic has raised challenges in terms of the benefits of vitamin D used to prevent and even treat it. Sufficient blood vitamin D can help in a satisfactory cellular response and in protecting against the severity of infections caused by microorganisms such as SARS-CoV-2 [45]. Vitamin D deficiency is related to severe outcomes following COVID-19 [46]. In a systemic review and meta-analysis consisting of 14 studies, the effect of vitamin D supplementation in lowering the risk of non-COVID-19 respiratory tract infections in patients with lower vitamin D levels was found [47]. Moreover, a systematic review consisting of 7 meta-analyses on 30 clinical trials showed the same results [48]. Higher COVID-19 mortality rates in Europe have been identified in patients suffering from vitamin D deficiency [45].

There is still limited evidence in favor of the effect of vitamin D in people with COVID-19 in the treatment process [49]. A meta-analysis consisting of eight observational studies revealed that people with vitamin D < 50 nmol/l (i.e., <20 ng/ml) have 64% more risk of community-acquired pneumonia [50].

The results of the meta-analysis showed that vitamin D deficiency could result in the severe form of COVID-19, especially in the elder people [49], which is explained by both lower exposure to sunlight and lower 7-dehydrocholesterol values in the skin compromising the cutaneous synthesis of 25OHD in the elderly [51]. Moreover, aging is accompanied by lots of chronic diseases [52].

We recommend developing cohort studies, especially clinical trials on different age groups in various climatic conditions, to evaluate the causality between vitamin D and COVID-19.

4.1 Mechanism: vitamin D regulating inflammation

The association of vitamin D and C-reactive protein (CRP) level, an anti-inflammatory factor, is proposed. Vitamin D use is associated with a reduction in CRP level [53], while in patients with SCZ, an inverse relationship was found between CRP levels and vitamin D [54]. Low serum level of vitamin D seems to be associated with the inappropriate function of the immunomodulatory. Also, insufficient vitamin D levels result in less efficient antigen presentation and macrophage function. Low vitamin D may potentially contribute to a delayed response to the body's initial contact with the SARS-CoV-2 virus.

5. Schizophrenia and COVID-19

A large cohort study was carried out on 1092 patients with/without SCZ hospitalized due to COVID-19. Only 15 patients had SCZ. The overall in-hospital mortality rate was 9%. Patients with CSZ had more mortality compared to non-SCZ patients (26.7% vs. 8.7%) (Adjusted odds ratio: 4.36). We know that an adjusted odds ratio of more than one is considered a risk factor, while here, it is 4.36 [23]. Vitamin D deficiency is associated with higher risk of respiratory infection. There are more respiratory infections and deaths in patients with SCZ where vitamin D deficiency is prevalent. This potentially offers a modifiable risk factor to reduce the risk for and the severity of respiratory infection in people with SCZ [21].

5.1 Prognostic factors in developing COVID-19

5.1.1 Age and gender

In spite of the fact that females experience more morbidity (not mortality) than males [54], the relative risk of mortality following COVID-19 was higher for males than females in all regions and almost all age groups. The overall relative risk ranged from 1.11 in Portugal to 1.54 in France, showing the risk factor role of gender in COVID-19 consequences. In most regions, sex differences increase until 60–69 years [55]. Clinicians obviously noted that COVID-19 mortality rises with aging, unlike other respiratory diseases [56]. People ≥65 years have a strikingly higher mortality rate following COVID-19 compared to younger adults, and males have a higher mortality rate following COVID-19 compared to females. Over the 42-day period, there were 178,568 deaths following COVID-19 deaths. Mortality was influenced by age and sex in patients with COVID-19. Compared with individuals≤54 years, the incident rate ratio [57] was 8.1, indicating the high mortality rate following COVID-19, and also IRR was 62.1 for patients≥65 years or older. Totally mortality rate due to COVID-19 was 77% higher in males compared to females (IRR = 1.77) [58].

In addition, age may also have interaction with SCZ in respect of the mortality rate following SARS-CoV-2 infection. A retrospective case–control study showed that patients with SCZ >65 years had higher risk compared to the patients with SCZ aged 18–65 years (Adjusted odds ratio = 1.74) [59].

5.1.2 Ethnicity

In the general population, mortality following infection with SARS-CoV-2 among people from ethnic minorities is four times higher than in the white European population [60]. In an observational study, as compared to white patients, African-American people suffering from SCZ had higher prevalence of SARS-CoV-2 infection (adjusted odds ratio: 2.33) and higher mortality rate (6.2% vs. 3.7%), and men had higher mortality rate than women (6.6% vs. 3.4%) [61].

5.1.3 Comorbidities

The risk factors for severe SARS-CoV-2 infection, such as cardiovascular disease (CVD), chronic respiratory diseases such as chronic obstructive pulmonary disease (COPD) and diabetes mellitus (DM) [62–64], are frequent in patients with SCZ compared to the general people. More than 70% of all patients with SCZ have one or more comorbidity, including diabetes type II [15, 16], chronic pulmonary disease [17], hypertension, heart diseases, and obesity, so overall survival in these patients decreases [18–20] and is the vulnerable group to COVID-19 with high mortality [21]. Patients with SCZ and/or with other mental problems such as bipolar disorders had high risk of mortality following COVID-19. This can be justified by their immunological profile. Variation in the human leukocyte antigen complex is one of the most consistently replicated findings in genome-wide association studies in patients with SCZ and bipolar disorders [65]. In conclusion, the highest risk of mortality in individuals with SCZ and/or bipolar disorders is not far off [66].

5.2 Vitamin D deficiency in schizophrenia implications for COVID-19 infection

The global age-standardized prevalence of SCZ is 0.28% [67]. Among COVID-19 risk factors identified in patients with SCZ, the presence of comorbidities, stigma experience, poor insight into somatic symptoms, cognitive impairment, and delusions have been identified as factors that can lead to misperception of the risk related to the virus. Moreover, patients with SCZ are often heavy smokers with lower vitamin D levels, and it is unknown how it can affect their chance of COVID-19 survival. A case–control study on patients with COVID-19 in southern France showed that the mortality rate was 9.0%. The patients with SCZ had increased mortality compared to the non-SCZ patients (26.7% vs. 8.7%, respectively). In contrast, the patients with SCZ were admitted to the ICU less than those without SCZ. SCZ is associated with further COVID-19 mortality, confirming the existence of health disparities described in other somatic diseases [23].

Lack of vitamin D causes deterioration in the health of our body and thus increases the risk of mental disorders. Research is ongoing, but studies have shown that sunlight provides a significant protective effect for respiratory problems and inflammation disorders. In the context of the coronavirus pandemic, research has been conducted on the relationship between vitamin D, CZ, and increased rates of acute respiratory infection.

There is more respiratory infection and mortality in patients with SCZ whose vitamin D deficiency is prevalent [68]. A case series study including 14 elderly COVID-19 positive inpatients presenting with dementia or SCZ and other medical conditions was done. All patients received 800 IU daily vitamin D prior to the infection. Most of the patients were asymptomatic or with very few symptoms. There was no need for an intensive care unit, or deaths were not reported. But cognitive functioning of the patients was unchanged. It can be concluded pre-existing vitamin D use may reinforce the immune system and lower the severity of COVID-19 in elderly patients with psychiatric disorders [69].

6. Conclusions

It seems vitamin D deficiency is associated with an increased risk of acute respiratory infection and mortality after the development of COVID-19. There are further respiratory tract infections and mortality in patients with schizophrenia because vitamin D deficiency is prevalent in these patients. Patients with schizophrenia are prone to be infected with worse outcomes, especially if they suffer from several comorbidities. They are vulnerable to worsening psychiatric symptoms and relapse due to fear of the disease, stress, and the boredom associated with compulsory isolation. Thus, health and care providers need more attention and support to prevent COVID-19 in this group and should detect psychiatric and respiratory problems as soon as possible.

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Author details

Fatemeh Gholami[1,2], Saman Farshid[3], Parmida Soleimani[4] and Rohollah Valizadeh[5*]

1 Department of Epidemiology, School of Public Health, Iran University of Medical Sciences, Tehran, Iran

2 Social Determinants of Health Research Center, Research Institute for Health Development, Kurdistan University of Medical Sciences, Sanandaj, Iran

3 Nephrology and Kidney Transplant Research Center, Clinical Research Institute, Urmia University of Medical Sciences, Urmia, Iran

4 Department of Psychology, Roudehen Branch, Islamic Azad University, Tehran, Iran

5 Urmia University of Medical Sciences, Urmia, Iran

*Address all correspondence to: rohvali4@gmail.com

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