ORIGINAL ARTICLE

Role of Vitamin D in Pathogenesis and Severity of Coronavirus Disease 2019 (COVID-19) Infection

AMIR HAMZA[1], MAQBOOL AHMED[2], KHALIL AHMED[3], *ABDUL BAQI DURRANI*[4]
[1]Assistant Professor, [3]Senior Registrar, [4]Professor, Department of Medicine, Bolan Medical College/Bolan University of Medical & Health Sciences Quetta
[2]Assistant Professor, Department of Pulmonology, Bolan Medical College/Bolan University of Medical and Health Sciences Quetta
Correspondence to Dr. Amir Hamza hamza4170@gmail.com Cell 0333-7805128

ABTRACT

Aim: To determine the vitamin D deficiency in COVID-19 infection and its association with the severity and fatality of COVID-19 disease.

Study Design: Descriptive cross sectional study

Place and duration of study: Department of Internal Medicine Bolan Medical College Hospital Quetta from 1st March to 30th April 2020.

Methods: A total of 168 patients diagnosed with COVID-19 infection, age ranged from 30 to 80 years of either gender were included. The brief medical history was taken and clinical examination were done. Nasopharyngeal and oropharyngeal swabs samples of patient for severe acute respiratory syndrome coronavirus 2 were collected and sent to the hospital medical laboratory to detect COVID-19 infection by using real-time polymerase chain reaction(RT-PCR). Blood sample of each patient were also collected to detect the vitamin D3 levels.

Results: Mean age of patients was 42.26±13.69 years, 94(56%) were males, while 74(44%) were females. Most of the patients were with age group of 31-50 years 80(47.6%). Regarding COVID-19 asymptomatic subjects were 139(82.73%), while 22(13.09%), 5(2.97%), 2(1.19%) cases were respectively suffering from mild, moderate and severe disease. Vit D deficiency was significantly associated with both asymptomatic and symptomatic cases.

Conclusion: Vitamin D is having protective role in respiratory tract infections. Its administration in deficient individuals suffering from COVID-19 infection may boost the immune system and reduces the severity of COVID-19 infection Vitamin D supplementation might boost the immune system of COVID-19 patients and reduce severity of the disease in vitamin D deficient individuals.

Keywords: Severe acute respiratory syndrome coronavirus 2, Coronavirus disease 19, Real-time polymerase chain reaction, Vitamin D; Angiotensin-converting enzyme 2, Pneumonia; Acute respiratory distress syndrome

INTRODUCTION

The name coronavirus (CoV) is derived from Latin word corona, meaning crown[1]. It is a large family of RNA viruses, ranging from common viruses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] It was first discovered in chickens in the 1930,while in human in the 1960. It causes diseases in animals, birds and humans.[2] It causes mild to lethal illness in human beings. The mild illnesses is characterized as common cold, while the lethal illnesses were reported are Severe Acute Respiratory Syndrome *(*SARS*)* and Middle East Respiratory Syndrome *(*MERS*)*. The most recent infection is called Coronavirus disease 2019 (COVID-19)[3].

The COVID-19 is caused by 2019 novel coronavirus (2019-nCoV), now given name severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] It was first identified and reported as an outbreak of respiratory illness in Wuhan City, Hubei Province, China. It was initially reported to the WHO on 31st December 2019. The World Health Organization (WHO) declared the COVID-19 outbreak a global health emergency on 30th January 2020 and a global pandemic on March 11, 2020[3]. The disease is currently spreading worldwide. Pakistan got its first two positive cases on February 25, 2020[2].

The COVID-19 is an infectious disease and according to current evidences, it is primarily transmitted between

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people through respiratory droplets and contact routes. The incubation period is 2-14 days, by average of 5 days[4]. The clinical presentations ranged from asymptomatic carriers to severe illness and mortality[5]. The common symptoms were malaise, fatigue, fever, cough and breathlessness. The other symptoms were respiratory distress and diarrhea. All these features are due to, either by direct viral or secondary superimposed bacterial infection[6].

The chronic medical conditions such as diabetes, pulmonary, cardiovascular, liver, kidney diseases as well as the vitamin D deficiency are associated with the increased risk of lung injury and acute respiratory distress syndrome (ARDS)[7].

It has been observed that, the main entry point of SARS-CoV-2 into the human cells is via angiotensin converting enzyme 2 (ACE2). It is an enzyme attached to the outer surface of cell membranes of cells in the lungs[8]. It has been identified as a functional receptor as well as cellular binding site for SARS-COV-2 in animals and humans. It has been observed, that increased concentrations of ACE2 is associate with pathogenesis and increased severity of COVID-19[9]. Increased concentrations of ACE2 is found in patients taking antihypertensive in the form of angiotensin converting enzyme (ACE) inhibitors angiotensin receptors blockers (ARBs) and those suffering from vitamin D deficiency.

The protective role of the vitamin D is through inhibition of Renin Angiotensin System (RAS)[6]. It also boost the immune system of patients by regulating innate and

adaptive immunity.[7] It has been considered, that vitamin D supplementation in those patients suffering from vitamin D deficiency may boost the immunity of COVID-19 patients and reduce severity of the COVID-19 infection[7].

Hypovitaminosis D is defined as a vitamin D level that is below normal. It is a major public health problem worldwide[6]. It most commonly occurs in people having inadequate sunlight exposure, inadequate intake of nutritional vitamin D and gastrointestinal disorders, which may cause decreased absorption. The conditions impairing vitamin D conversion into active form such as liver and kidney diseases or disorders also play a prime role in deficient levels of active vitamin D[9,10].

The globally prevalence of vitamin D deficiency is approximately between 30–50%[12]. The circulating levels of Vitamin D were categorized as optimal when it is >30ng/mL, insufficient when it is 20–30ng/mL and deficient when it is <20ng/mL[12].

MATERIALS AND METHODS

This randomized controlled trial study was started after taking approval from the hospital ethical committee. The participants in the study were selected from medical inpatient departments of Internal Medicine Bolan Medical College Hospital Quetta. The study duration was two months from 1st March 2020 to 30th April 2020.Patients more than 15 years of the age, both genders were included, having clinical history of covid-19 infection and diagnosed by RT-PCR. Subjects unwilling to participate in this study and diagnosed cases of chronic medical conditions were excluded from study. Brief medical history was taken and clinical examination was done. Nasopharyngeal and oropharyngeal swabs samples of patient for SARS-CoV-2 were collected and sent to the appropriately equipped hospital medical laboratory to detect incidence of COVID-19 infection by using RT-PCR. Blood sample of each patient were also collected and sent to laboratory to detect the vitamin D3 levels. All the laboratory samples were taken by trained staff in the relevant technical field with safety procedures. Standard operating procedures (SOPs) were adequately and appropriately ensured during specimen collection, storage, packaging, and transport. All specimens collected for laboratory investigations were considered potentially infectious. In certain suspected and confirmed cases Chest X-Ray and computed tomography (CT) scan was also taken. The COVID-19 patients were categorized into asymptomatic and symptomatic, while the symptomatic patients were categorized into mild, moderate and severe disease as according to questioner. The Vitamin D levels were categorized as optimal, insufficient and deficient. All the data was recorded in the proforma, which was specially made for COVID-19 infection. All the collected data was entered and analyzed with SPSS 25. Relationship of the COVID-19 with vitamin D was computed through Chi-square test. P-value < 0.05 will be considered significant.

RESULTS

There were total 168 adult subjects studied in present research. Mean age of participants was 42.26+13.69 years, 94 (56%) were males and 80 (47.6%) were females. Most of the patients 80(47.6%) were with age group of 31-50 years. The mean duration of COVID-19 was 14±7 days (Table 1).

Table 1: Demographic information of the patients (n=168)

Variable	No.	%
Age (years)		
15-30	38	22.6
31-50	80	47.6
≥51	50	29.8
Gender		
Male	94	56.0
Female	74	44.0
Marital status		
Single	59	35.1
Married	101	60.1
Separated/divorced	8	4.8
Occupation		
Office worker	30	17.9
Labourworker	30	17.9
House wife	108	64.2
Residence		
Rural	90	53.6
Urban	78	46.4
Socioeconomic status		
Lower Class	90	53.6
Middle Class	49	92.2
Upper Class	29	17.3
Education		
Primary	40	23.8
Middle	20	11.9
Matriculation	30	17.9
Intermediate	10	6.0
Graduate	4	2.4
Uneducated	64	38.1

Table 2: Clinical features and investigations

Variable	No.	%
Symptoms		
Malaise	22	13.1
Fever	29	17.3
Body ache	29	17.3
Rhinorrhea	22	13.1
Cough	29	17.3
Chest pain	7	4.2
Breathlessness	7	4.2
Signs		
Pallor	7	4.2
Cyanosis	7	4.2
Respiratory system		
Normal vesicular breathing	161	95.8
Bronchial breathing	5	3.0
Coarse crepitation's	2	1.2
Chest X-ray/CT scan chest		
Note done	111	66.1
Normal	50	29.8
Consolidation	5	3.0
Ground glass appearance	2	1.2
Presentation of COVID-19		
Asymptomatic	139	82.73
Mild	22	13.09
Moderate	5	2.97
Severe	2	1.19
Vitamin D3 Levels		
Optimal	22	13.1
Insufficiency	47	28.0
Deficiency	98	58.3

Regarding COVID-19 asymptomatic subjects were 139(82.73%), while 22(13.09%), 5(2.97%), 2(1.19%) cases were respectively suffering from mild, moderate and severe disease. During this study one patient died (0.59%). He was suffering from severe disease and diagnosed as ARDS. A large proportion of the patients 98 (58.33%) had vitamin D deficiency. Vitamin D insufficiency was found in 47 (28.0%), while optimal vitamin D was found in 22 (n=80, 13.1%) patients. Vitamin D Deficiency was significantly associated with both asymptomatic and symptomatic cases (Table 2).

DISCUSSION

The renin angiotensin system is a complex network. It contains angiotensin Converting Enzyme (ACE) and angiotensin converting enzyme 2 (ACE2), which have key role in various biological functions.[11-13] The angiotensinogen is converted into angiotensin I in the liver by ACE, while the angiotensin I is converted into angiotensin II in the lungs ACE2[14]. The RAS regulates the blood pressure through peripheral vascular resistance and the fluid and electrolyte balance. Renin angiotensin system regulates the fluid and electrolyte balance, predominantly by homeostasis of electrolytes such as sodium (Na) and potassium (K), which take place with the help of aldosteron.

It has been observed that, the main entry point of SARS-CoV-2 into the human cells is via ACE2, which is expressed in human airway epithelia.

Vitamin D3 regulates and inhibits renin-angiotensin system and helps in prevention of severe respiratory illnesses.[7,10] Vitamin D also act as an immune modulator factor and enhances the immunity, which play an important role against all forms of bacterial and viral infections such as covid-19[7,13].

The patients suffering from chronic diseases with associated co-morbidities have significantly higher risk of death from severe respiratory tract infections.[16] The vitamin D deficiency, when present with chronic diseases with associated co-morbidities further increase the death from severe respiratory tract infections.[17] SARS-CoV-2 is a new disease and its fatality rate is mild in isolated cases, while it fatality increases with associated co-morbidities. When SARS-CoV-2 is present vitamin D deficiency, it increase the fatality and death rate[18]. According to study of Grant WB, et al, that Vitamin D administration to deficient subjects can prevent and treat the respiratory tract viral infections, specially influenza and coronavirus infections[7].

Vitamin D is a fat soluble vitamin. It is mostly (90%) synthesized endogenously by dietary cholesterol, when ultraviolet rays from sunlight strike the skin. It is naturally present in very few foods[6]. It is also present as added vitamin in all commercially available oil and ghee. It is also available as a dietary supplement and mostly prescribed by medical practitioners[6,14]. Vitamin D obtained from food, dietary supplements or sun exposure is biologically inert and must undergo to liver and kidney for activation. The liver converts the vitamin D into 25-hydroxyvitamin D, also known as the calcidiol, while the kidney converts the 25-hydroxyvitamin D into the physiologically active the 1,25-dihydroxyvitamin D, also known as the calcitriol.[15] Vitamin D promotes calcium absorption from the gut and maintains adequate serum calcium and phosphorus concentrations,

which is essential for normal mineralization. Vitamin plays many key roles in the body, including regulation of cell growth, neuromuscular and immune function, and reduction of inflammation.[16] The optimal vitamin D concentrations reduce the risk of many chronic diseases, such as cardiovascular disease, diabetes mellitus, and hypertension[20].

Most of the clinical studies suggest that serum Vitamin D concentrations are generally low in many populations, especially in the elderly.[19,20] According to Chapuy et al study in France vitamin D deficiency is 61%.[13] According to Burnand et al study in Switzerland vitamin D deficiency is 50%.[14] According to van der Meeret al study in Nether-land vitamin D deficiency is 27%.[15] According to Meddeb et al[16] study in Tunisia vitamin D deficiency is 40.3%. According to Arya et al[17] study in India vitamin D deficiency is 30%. According to Ho-Pham et al[18] study in Vietnam vitamin D deficiency is 91.8%. According to Chailurkit et al[19] study in Thailand vitamin D deficiency is 64.8%.

It has been proved, that having comorbid conditions, such as cardiovascular, pulmonary, renal and hepatic diseases, diabetes mellitus or hypertension, when associated with vitamin D deficiency increase the case fatality rate significantly with increasing age.[21] This may be due to compromised adaptive immune response. It has been observed by many researchers that, hypovitaminosis D with aging, affects the immune system.[21,22] Vitamin D has various immune modulatory effects to decrease viral infections, which include strengthening of epithelial cell junction integrity.[21] It has been proved, that vitamin D may help prevent dryness of epithelium by producing a protein called cathelicid, which up-regulate the effect on the anti-microbial in family of peptides, which is started by the innate and adaptive immune response.[23]

CONCLUSION

It has been proved, that vitamin D is having protective role in respiratory tract viral infections. Its administration in deficient individuals suffering from COVID-19 infection may boost the immune system and reduces the severity of COVID-19 infection, especially with chronic associated co-morbidities.

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