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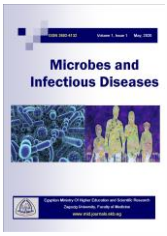

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Original article

Alpha-1 antitrypsin and vitamin D deficiency in COVID-19: Correlation with risk of disease in Iraqi patients

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ABSTRACT

Background: In our study we aimed to evaluate links of plasma alpha-1 antitrypsin and vitamin D with the risk COVID-19, and whether it explained the higher incidence of COVID-19. Background: The pandemic COVID-19 was generated by severe acute respiratory syndrome [SARS] coronavirus (CoV2). A fast viral broadcasting leads to an unexpected increase of the number of cases in the world. Like the SARS -CoV2 infection case report the italian alpha 1 antitrypsin registry conclusions demonstrated an adjacent geographic spreading of positive cases. The highest infected rates were demonstrated in peoples deficient with alpha-1 antitrypsin (AAT). **Methods:** One hundred and eight person with mean age 49 years, from them 54 patients (33.3% male and 66.6 female) had COVID-19 infection and 54 heathy person. alpha-1 antitrypsin (AAT), vitamin D and C-reactive protein (CRP) checks were done for all of them. **Results:** Regarding the AAT there was a highly significant difference($p<0.05$) among the groups where the average of the concentration in patients lower than that in healthy 0.99 (mg/dl) and 4.33(mg/dl) spontaneously, also there was a highly significant difference($p<0.05$) between the two groups regarding to vitamin D level that in patients 9.97 ng/ml lower that in healthy persons 34.22 ng/ml. While the average of CRP 119.43 µg/ml in infected persons and 6.33 µg/ml in non-infected persons with a highly significant difference ($p<0.05$). **Conclusion:** There was an association between COVID-19 infection with the levels of alpha-1 antitrypsin, vitamin D, CRP.

Introduction

From the first discovery of the SARS-CoV2 (severe acute respiratory syndrome coronavirus2) in the city of Wuhan, it has been famed for its elevated rates of mortality and infectivity because the failure of the respiratory system has led to rise in worldwide health emergencies [1]. Braccioni and Vianello showed that there was a possible relationship between the pre-existence of alpha-1 antitrypsin deficiency (AATD) and the high mortality of SARS-CoV2 [2], supported by a distinguished correlation amongst the geographical distribution of SARS-CoV2 infection and AATD cases. This proposed connotation between COVID-19and AATD may expose subtypes of COVID19-infected person that may benefit from the complementary treatment of alpha1-antitrypsin (AAT), so it merits additional importance [1]. The protein of AAT, made by the hepatocytes, is a serine protease inhibitor that has a

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chief role in the respiratory tract by providing most tissue defenses against the damaging action of the proteolytic proteases [3]. Additionally, this protein is known for being one of the most important players in the response against inflammation in the acute stage [4]. Thus, persons with low AAT concentrations were fail to regulate inflammatory mediators, like Tumor Necrosis Factor (TNF) alpha and interleukins (IL-1β, IL-8, IL-6), the higher rate of mortality in COVID-19 infected peoples is linked with the failure of respiratory system or multiorgan failure because of a cytokine storm[5], when stages of cytokines have gone through the top, adding to that the profuse inflammatory cells infiltration into the pulmonary tissue, provoking apoptosis of pneumocytes through cytokine induction [6]. Similarly, a nucleotide polymorphism of the *SERPINA1* gene that codes AAT associated with elevated hazard of acute respiratory distress syndrome and mortality [7].

C-reactive protein is a form of liver formed protein that acts as a precursor to inflammation and infection. Normal blood concentrations of CRP are fewer than 10 mg/L; however, as the illness begins, it increases speedily through 6-8 hours giving the maximum peak 48 hours later. Approximately its half life about nineteen hours, and when the infected person heals and its concentration declines, the inflammatory steps pass. Phosphocholine preferably binds to CRP expressed extremely on the surface of injured cells. That binding stimulates the complement pathway and alters the activity of phagocytic cells to eradicate microorganisms and injured cells. CRP is an appreciated measure for tracking the severity of the disease, where its concentration declines when tissue damage or inflammation is resolved [8].

Vitamin D has been documented as a significant cofactor in numerous functional processes related to calcium absorption and bone and also in miscellaneous non-skeletal results, like diabetes type 2, cardiovascular, autoimmune disease, overweight and infections [9]. Specifically, the noticeable effect of metabolites of vitamin D on the immune system's response, on the progress of COVID-19 infection by the new SARS_CoV2 virus [10,11]. Vitamin D deficiency has been documented as a universal sickness [12, 13]. Consequently, we aimed to determine relations among lower plasma vitamin D concentration and the hazard of COVID-19 infection.

Methods:

This is a case-control study carried out from September 2023 to January 2024, We enrolled 108 person of the age18 years and above; 54 of them covid-19 infected persons and the others were non infected persons who were looked healthy and on the other hand had comparable criteria to the patients, we get all the necessary information from patients and healthy people, and taking 5 ml of venous blood from them, then centrifuged at 1500 rpm for 5 minutes and only unhaemolyzed serum was used, the serum was placed in a plane tube and then labelled and freezed. Alpha-1 antitrypsin and CRP was determined using fully automated ELISA reader (Bio-Rad QX 200), Vitamin D concentration using Biochemical Analysis System, (Roche Cobas E411).

Results:

In this study, 54 patients with covid-19 infection, 33.3% male and 66.6 female with mean age 49 year, and control group of 54 people. Alpha-1 antitrypsin, CRP, vitamin D3 were compared between the two groups. The data are shown in table (1) that shown a highly significant statistical difference ($p<0.05$) was found between both groups.

Table 1. Comparison between alpha-1 antitrypsin, CRP, vitamin D3 results in both studied groups.

Variable	sample	N	Mean	S. D	P value
Alpha1(mg/dl)	patients	54	.99	.19	0.0001
	control	54	4.33	1.91	
CRP(µg/ml)	patients	54	119.43	117.32	0.0001
	control	54	6.33	2.47	
Vit D3(ng/ml)	patients	54	9.97	3.19	0.0001
	control	54	34.22	6.91	

P value is significant at the 0.05 level, highly significant at the 0.01 level

Table 2. Correlation between alpha-1 antitrypsin, CRP and vitamin D3 results in both studied groups.

Variable	Alpha1	CRP	Vit D3
Alpha1	1	-.447**	.760**
CRP	-.447**	1	-.558**
Vit D3	.760**	-.558**	1

**** Correlation is significant at the 0.01 level (2-tailed).**

Figure 1. Concentration mean of alpha-1 antitrypsin in patients and control.

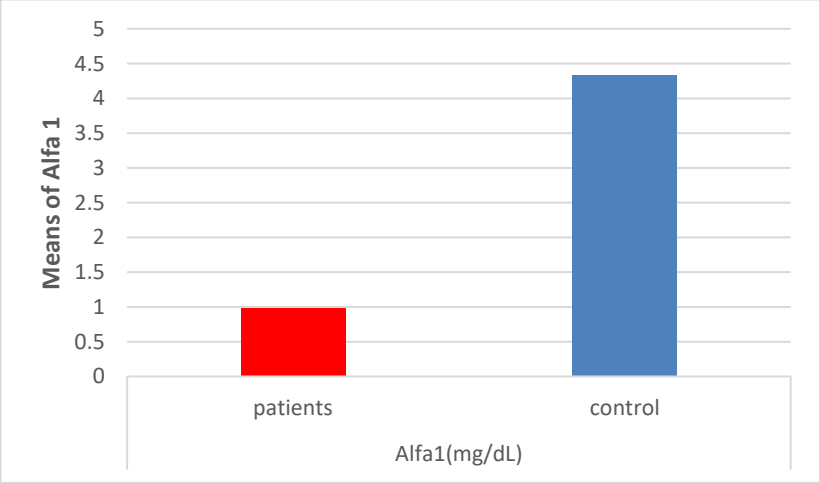


Figure 2. Concentration mean of CRP in patients and control.

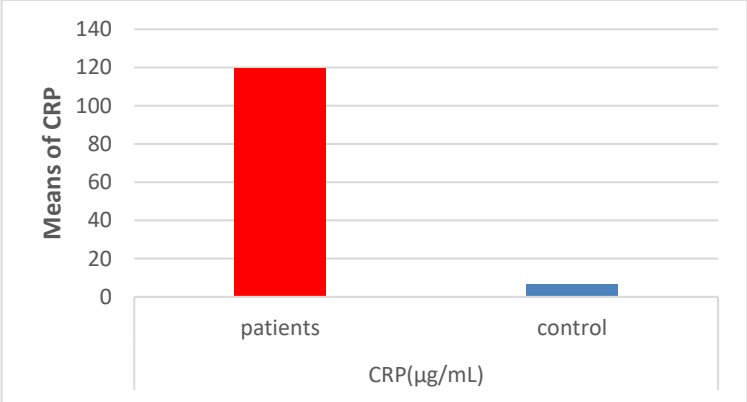
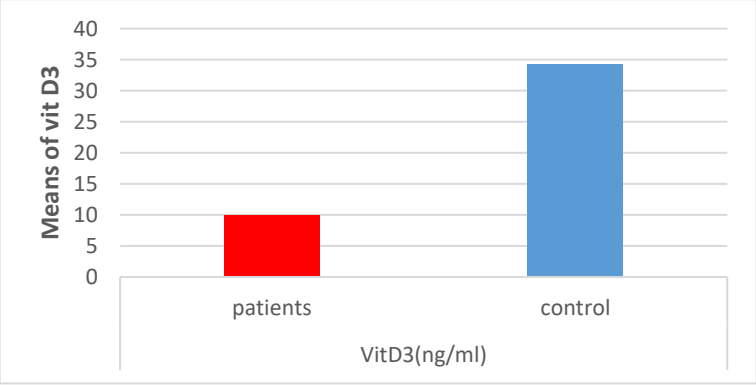


Figure 3. Concentration mean of vitamin D3 in patients and control.



Discussion

Relative to the table 1 the current study has revealed that there was a highly significant difference between patients and control regarding to alpha-1 antitrypsin concentration (*p*.value 0.0001) were the concentration mean in patients was 0.99 (mg/dl) while 4.33 (mg/dl) in control. Two clinical studies in Italy showed that AAT has been involved as one of the medical and biological foretellers of COVID19. Remarkably, serum AAT concentrations in SARS infected peoples were fewer compared to that in non-infected persons, also the truncated kinds of AAT were raised in patients with SARS. Decreased activity of AAT and reduced levels in patients with SARS are probably linked to pulmonary failure and an appearance of acute respiratory distress syndrome[14]. Iwata-

Yoshikawa and his assistants [15] mentioned that host transmembrane protease serine type 2 (TMPRSS2) makes it easer for viral S-protein to attach to the enzyme angiotensin converting enzyme 2(ACE2) situated on host cells. Mice that deficient with TMPRSS2 showed diminished viral spreading in the airways when infected by SARS_CoV. In a dose-dependent manner A1AT inhibits the proteolytic activity of TMPRSS2 [16], also Wettstein et al. [17] discovered AAT as a fixed inhibitor of SARS-CoV2 infection following screening a peptide / protein library resulting from human bronchoalveolar lavage fluids. Moreover, when its the main inhibitor of human serum protease, strongly restricts SARS-CoV2 protease-mediated cellular entering[18].

In present study the median CRP concentration was 119. 43 (µg/ml), a value above than that in control 6.33(µg/ml) with a highly significant difference between them (*p*.value 0.0001) , Similar to a study done by Smilowitz N R and *et al* [19]. Higher CRP levels also described in severe virus-related infections, such as H1N1 influenza and nowadays in SARS-CoV2 [20,21]. A previous work of (298) COVID-19 patients , individuals that deceased have CRP with ten-fold more than those of the survivors(100.0 vs. 9.7 mg/L, P < 0.001), recent studies also recognized an association amongst CRP levels and the failure of respiratory system needing machine driven ventilation, patients who had high sensitivity CRP more 5 mg/L have been shown to have 5 fold raised risk of acute respiratory distress syndrome (ARDS) compared to those with low CRP values [22,23]. Finally, CRP might chosen as a biomarker due to it is low-priced and commonly obtainable at various medical centers, helping quick application of regular biomarker testing into COVID-19 patients clinical treatment [19]. Elevated concentrations of CRP (median 76.5 mg/L) was detected in persons with poor saturation of oxygen compared with peoples who had high oxygen saturation (median 12.7mg/L) [24], representing that more severe patients with lung impairment had raised CRP concentrations. Subsequently elevated values of CRP elucidate too severe infection course linked to lung damage and wicked prognosis. Symptoms severity of patients with COVID-19 are correlated well with the level of CRP, thus might be a good indicator in evaluating a patient's situation composed with further clinical findings. The higher values of CRP may be related to inflammatory cytokines overproduction in worse COVID-19 infection. Microbes are fighted by cytokines but lung tissues may be damaged when the immune system becomes more active. Therefore, the of production CRP is stimulated by inflammatory cytokines and tissue damage in COVID-19 infected individuals [8].

Our study determines a correlation between vitamine D deficiency and COVID-19 severity were the level was 3 9.97 (ng/ml) in patients and 34.22 (ng/ml) in control with a high significant difference between them (*p*.value 0.0001), thus agreed with D'Avolio *et al*. presented that levels of 25(OH)D were less in an infected persons with confirmed SARS-CoV2 [25], also Radujkovic, *et al* 2020 [26] stated that Vit D-deficient patients had a high rate of hospitalization, require further oxygen treatment and invasive mechanical ventilation, so that according to their work deficiency of Vit D was related with a six-fold raised risk of the illness and a ~fivteen-fold higher risk of decease. Especially, Faul *et al* [27] with their work included 33 SARS-CoV2 infected person with related pneumonia described that deficiency of VitD (25(OH)D < 12 ng/mL) was correlated with a higher hazard for invasive mechanical ventilation. Vitamin D may fight against acute respiratory infections through its stimulation of innate immunity and modulation of acquired immunity. Vitamin D deficiency is very communal, specifically through cold seasons due to deficiency of sun light contact, containment at house will stop sun light exposure for various peoples in the world, even in spring or summer,we trust that supplementation of vitamin D must be supported, at least in any person with hazard of vitamin D deficiency like dark skin, oldness, overweightness, no sunshine contact, wearing covering clothes [28].

Conclusion

Our study found an important connection between COVID-19 infection and the low concentrations of AAT and vitamin D that may explain the higher incidence of COVID-19 and guide healthcare systems in recognizing peoples at risk, and contribute to interventions designed to decrease the danger of the COVID-19 infection. In addition, the higher concentration of CRP that might be beneficial primary indicator in foretell the likelihood of the disease development in unsevere COVID-19 cases, that may support health staffs to recognize that patients in the initial stage for primary treatment. Also these patients want monitoring and

treatment even though they don't progress signs to meet the criteria for the severity of the infection.

Disclosure of potential conflicts of interest

The authors report that there were no conflicts of interest.

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