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ORIGINAL ARTICLE

Effect of Rapid Correction of Serum Cholecalciferol Deficiency on Protection against Clinical Manifest COVID-19 Infection.

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ABSTRACT

Background and Aim: Vitamin D has anti-viral, anti-inflammatory, and metabolic effects. The goal of this study was to evaluate the link between vitamin D level and COVID-19 incidence and to identify the result of short-term vitamin D deficiency correction in decrease the risk of COVID-19 infection.

Patients and Methods: A prospective open-label controlled trial was carried out on 897 enrolled subjects who had contact with relatives infected by COVID-19 disease randomized into two arms according to baseline vitamin D level; the first arm of which 816 subjects (90.97% vitamin D deficiency) received 200,000 IU cholecalciferol/vitamin D3 every other day with a total of 3 doses, whereas the second arm, 81 subjects (9.03% normal vitamin D) didn't receive vitamin D supplementation. Serum calcium and serum vitamin D were measured at baseline and 2 weeks after treatment. CBC, ESR, CRP, ferritin, and D-dimer were performed in suspected cases.

Results: Symptoms compatible with COVID-19 were 17.3% in the second arm and 16.4% in the first arm, Laboratory-confirmed diagnosis were 3.7% in the second arm and 5.4% in the first arm. Hospitalization was 1.2% in the second arm and 0.4% in the first arm. Deficient vitamin D levels increased the risk of symptoms compatible with COVID-19 disease by 1.66 folds.correlation was detected between P300 amplitude with IQ or language age ($P > 0.05$).

Conclusion: Rapid correction of vitamin D deficiency decrease the risk of COVID-19 infection.

Keywords: COVID-19, Vitamin D, Inflammatory markers.

INTRODUCTION:

Vitamin D (Vit D) deficiency is distinct as a 25-hydroxyvitamin D level under 20 ng/mL. Vit D insufficiency or deficiency has been described to be very public in all age groups [1]. The plasma Vit D level was considerably lower in persons who confirmed positive for COVID-19 than negative [2]. There is evidence that Vit D has immune modulatory, anti-inflammatory, and antiviral actions [3]. Moreover, to this, Vit D augments innate immunity by increasing the formation of antimicrobial peptides in respiratory epithelial cells [4]. The outbreak of COVID-19 looks to occur largely in the cold wintertime, when serum Vit D concentrations are the lowest [5].
Active metabolite of Vit D is 1, 25 dihydroxy Vit D, goes in the blood and achieves its hormone regulatory role through the particular receptor Vit D, also named (Nuclear Receptor). Vit D together with its nuclear receptor, doings

as a transcription factor, thus control courses by genomic action [6]. Vit D receptor is greatly expressed in immune cells such as dendritic cells, macrophages, and T cells. Responsible for inflammatory reactions, immune modulation, immune response, and reactions to microbial infections [7].

There are numerous probable mechanisms by which Vit D may diminish the risk of COVID-19 infection. They include the stimulation of the transcription of the defensin and cathelicidin genes coding for anti-microbial peptides stimulating chemotaxis of macrophages and further immune cells to the locations of inflammation and preventing viral replication and reduce the risk of COVID-19 infection [8]. Vit D and closely linked molecules, like lumisterol, they may display potent action against SARS-CoV-2 [9]. Lately, Qayyum et al. had revealed that this non-genomic effect of Vit D and lumisterol comprise of active prevention of SARS-CoV-2 replication. Therefore, the inhibitory effect of Vit D and lumisterol show a major role in vigorous fight with SARS-CoV-2 infection and consequently weaken the severity of COVID-19 progression [10]. Vit D prevents cytokine storm (one of the methods of damage to lung tissue by SARS-CoV-2) by switching the pro-inflammatory Th17 and Th1 to the anti-inflammatory Th2 [11].

A meta-analysis of randomized clinical studies has also recommended that regular oral Vit D consumption (in doses up to 2000 IU/d) is defending against acute respiratory tract infection, particularly in Vit D deficient persons [12]. Numerous loading doses have been considered for reaching a 25(OH) D concentration of 30ng/ml. For example, a weekly dose totaling 100000–200000IU [13]. Certain studies just focus on single high Vit D doses for prevention and treatment of COVID-19 cases [14]. There is a shortage of cohort studies and clinical trials identifying the inhibiting role of Vit D in COVID-19 infections [15]. Vit D supplements are safe, and their toxicity is a rare occurrence caused by excessively high amounts of Vit D supplementation, many studies suggest that the blood levels should be over 150 ng/mL before there is any worry [1].

This study aimed to assess the association between COVID-19 and Vit D level incidence and to notice the impact of short-term vitamin D deficiency correction in decline the risk of COVID-19 infection.

METHODS:

Study design:

A prospective open-label controlled trial was carried out on 897 enrolled subjects who had contact with relatives infected by COVID-19 disease and randomized into two arms according to baseline vitamin D level; the first arm, of which 816 subjects (90.97% Vit D deficiency) received a single intramuscular dosage of 200,000 IU vitamin D3 every other day with a total of 3 doses, whereas in the second arm, 81 subjects (9.03% normal Vit D) didn't receive Vit D supplementation. The study subjects were recruited from outpatient clinics in Sharkia Governorate. Zagazig University Institutional Review Board accepted the study (ZU-IRB#:6959/13-1-2021). The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

The time of the study was prolonged from April 2021 to October 2021. Informed consent will be obtained from individuals included in the study. A contact can be anyone who survives in the same household as another person who has COVID-19 symptoms or has confirmed positive for COVID-19 (any time from 2 days before the subject who confirmed positive developed their symptoms and up to 10 days after) [16].

Patients Selection and Data Collection:

To be authorized for this study, subjects must fulfil the following:

Inclusion criteria: Age > 16 years old and have had contact with relatives infected by the COVID-19 infection, normal daily activity with sun exposure.

Exclusion criteria: subjects on calcium or Vit D supplementation in the previous two months, relatives were vaccinated for COVID-19, patients with kidney disease and pregnant women were excluded.

The flowchart is illustrated in (figure 1).

Laboratory determinations and clinical assessments:

The following information's were collected for each subject authorized for this study at the baseline [full history taking and general examination with special consideration of sex, age, body mass index, body temperature, respiratory rate, heart rate, oxygen saturation, and blood pressure]. Baseline laboratory tests

including fasting blood glucose, renal function, and liver function. Serum 25(OH) D level, serum calcium, and serum phosphorus were measured at baseline.

Follow up: Serum Vit D levels and serum calcium was measured 2 weeks after treatment, as well as clinical manifestations. The complete blood count (CBC) and the inflammatory markers as (ferritin, CRP, and D-dimer) performed if needed in suspected cases.

Assessment procedures:

In BD Vacutainer (Franklin Lakes, Becton, NJ, Dickinson and Company) the blood samples were acquired. The plain vacutainer was permitted to coagulate for 30 minutes after collection, then was centrifugation at 1200 x g for ten minutes to separate serum. At baseline and after 2 weeks, serum was used to assess Vit D and calcium levels.

In suspected cases, EDTA tube was collected for CBC. The citrate tubes directly was centrifuged at 2000 x g for fifteen minutes to measure D-Dimer. The plain vacutainer was collected and centrifuged to separate serum in order to measure ferrtin and CRP.

The CBC was achieved by the XS500i analyzer. The differential cell count were calculated by the blood film. Serum calcium and ferrtin were assessed using the Cobas 8000 Modular Analyzer. CRP, D-Dimer and Vit D were measured by Cobas 6000 Modular Analyzer.

STATISTICAL ANALYSIS:

A non-parametrically distributed data was found by the Shapiro–Wilk test. Mann-Whitney U test, Wilcoxon test and Chi-Square test were utilized when appropriate. The Spearman Correlation Analysis estimate the degree of association between different variables. The Binary Logistic Regression Analysis was performed to detect the odds ratio (OR) and its 95% confidence interval (CI). The statistically significant point was a p-value below 0.05. The SPSS 20.0 (SPSS Inc., Chicago, IL, USA) was the utilized software.

RESULTS:

A total of 897 enrolled subjects were contacted with relatives infected by COVID-19 disease and participated in being randomized into two arms according to baseline Vit D level; the first arm of which 816 subjects (90.97% Vit D deficiency) received Vit D, whereas the second arm of 81 subjects (9.03% normal Vit D) didn't receive vitamin D supplementation (figure 1).

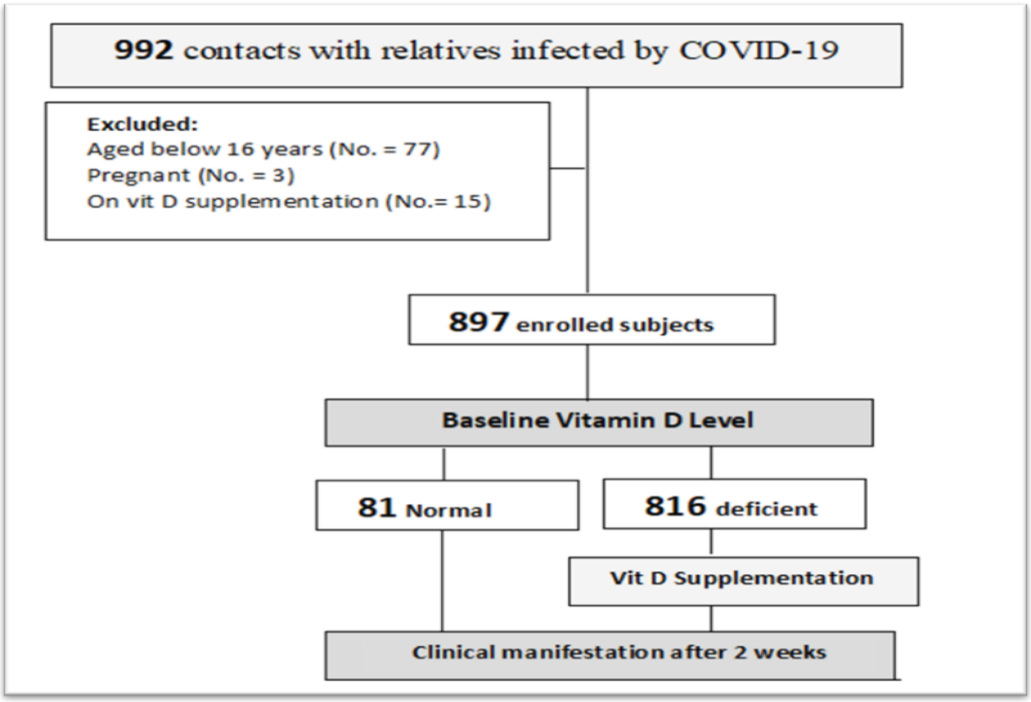

Figure 1: Study flowchart

Demographic, clinical, and laboratory characteristics of the patients were presented in (table 1).

Table 1: Baseline demographic, clinical, and laboratory characteristics of the patients.

Parameters	Normal Vit D (second arm group) (No.: 81)	Deficient Vit D < 20 ng/mL. received vitamin D (first arm group) (No.: 816)	*p*
Age, Years	47 [17-75]	44 [17-90]	0.37
Sex, Male	36 (44.5)	409 (50.1)	0.33
Smoking, current	9 (11.1)	138 (16.9)	0.24
BMI, Kg/m^2	26.9 [21.1-44.9]	26.7 [18.3-51.9]	0.48
Co-morbidities			
• Diabetes	31 (38.3)	243 (29.8)	0.11
• Hypertension	25 (30.9)	251 (30.8)	0.98
• Heart disease	0 (0)	10 (1.2)	0.32
• Chest diseases	0 (0)	5 (0.6)	0.48
• Thyroid diseases	2 (2.5)	26 (3.2)	0.72
• Liver diseases	1 (1.2)	9 (1.1)	0.91
• Rheumatic diseases	0 (0)	4 (0.5)	0.53
• HCV treatment	6 (7.4)	29 (3.6)	0.09
Baseline laboratory parameters			
• Vit D, ng/mL	32.8 [30.7-48]	12.8 [4.6-27.5]	<0.0001*
• Calcium, mg/dL	9.4 [8-11.1]	8.6 [7.8-9.1]	<0.0001*
Outcome			
• Symptoms compatible with COVID-19	14 (17.3)	134 (16.4)	0.84
• Laboratory-confirmed diagnosis	3 (3.7)	44 (5.4)	0.69
• Hospitalization	1 (1.2)	3 (0.4)	0.26
• Death	0 (0)	0 (0)	

Data are expressed as median [range] or number (%)

Vit D: Vitamin D; BMI: Body mass index; HCV: Hepatitis C virus; COVID-19: Coronavirus disease 2019.

*: Significant

Symptoms compatible with COVID-19 were 17.3% in the second arm and 16.4% in the first arm. Laboratory-confirmed diagnosis were 3.7% in the second arm and 5.4% in the first arm. Hospitalization was 1.2% in the second arm and 0.4% in the first arm (table 1). At baseline,

there was significant difference between two arms patients regards Vit D and serum calcium levels ($p<0.0001$). The levels of Vit D and calcium levels after correction were illustrated in (figure 2).

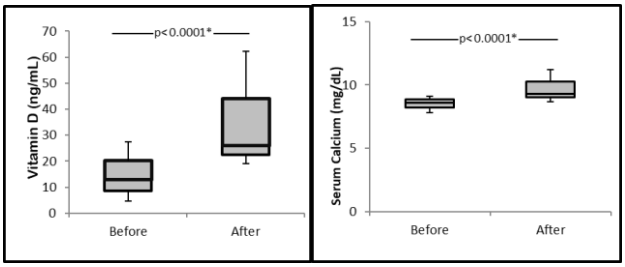

Figure 2: Effect of rapid correction of Vitamin D in deficient group

The data of laboratory markers of symptomatic patients presented in (table 2).

Table 2: The laboratory markers of symptomatic patients.

Parameters	Normal Vit D (No.: 14)	Corrected Vit D (No.:134)	*p*
CRP, mg/L	16.9 [11.2-30.7]	15.7 [8.7-44.4]	0.83
Ferritin, ng/mL	263 [80-432]	274 [83-412]	0.96
D Dimer, µg FEU/mL	0.95 [0.4-1.9]	0.9 [0.2-2.9]	0.48

Data are expressed as median [range]
Vit D: Vitamin D; CRP: C-reactive protein; FEU: fibrinogen equivalent.
**: Significant*

Correlations between corrected Vit D levels and laboratory markers in the symptomatic patients were evaluated. There were significant negative correlations (figure 3).

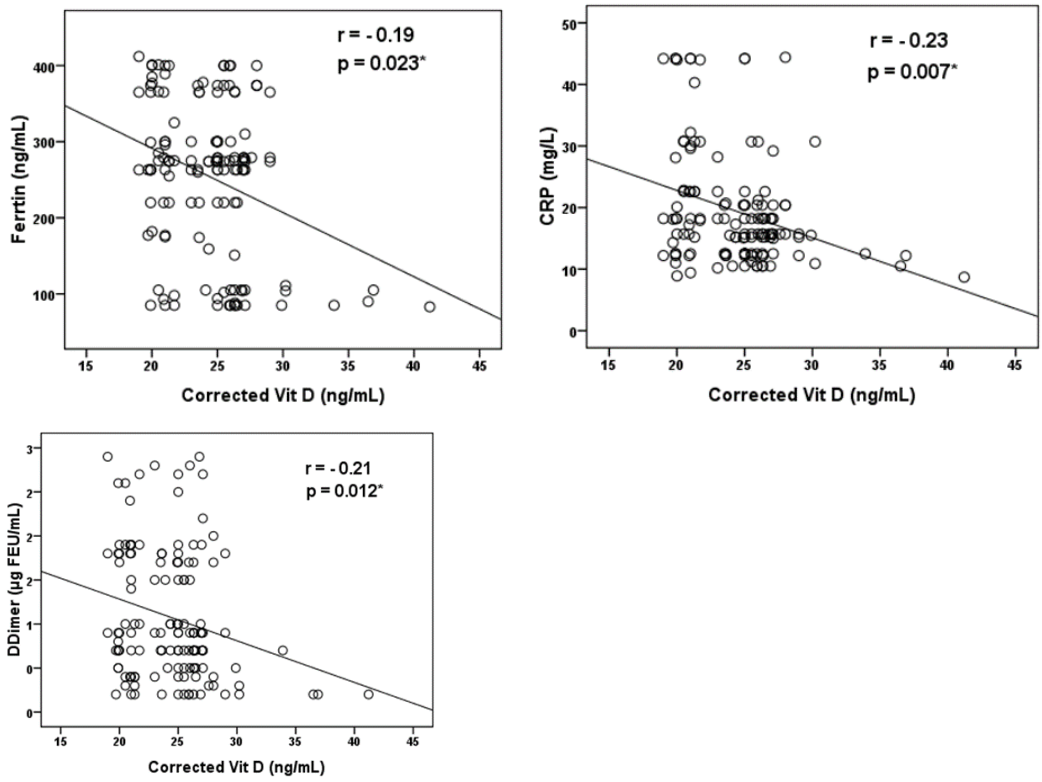

Figure 3: Correlation between corrected Vitamin D levels and laboratory markers in the symptomatic patients.
Vit D: Vitamin D; CRP: C-reactive protein; FEU: fibrinogen equivalent.
**: Significant*

Logistic regression analysis for Vit D level as a prophylaxis of COVID-19 was performed. Deficient Vit D levels increase the risk of symptoms well-matched with COVID-19 by 1.66 folds (table 3).

Table 3: Vitamin D status as a prophylaxis of COVID-19

Vitamin D	Odds ratio	95% Confidence interval	*p*
Normal level	0.6	0.37 – 0.99	0.049 *
Deficient level	1.66	1 – 2.74	

**: Significant*

DISCUSSION:

Despite the richness of sunshine in the Middle East allowing Vit D production all the year, the region shows some of the lowest levels of Vit D worldwide [17]. Vit D deficiency is a public health problem amongst the world and touching all ages, sexes and races [18]. In a study directed on 90 healthy Egyptian adults aged 20-60 years, the prevalence of Vit D deficiency was 77% [19]. That come consistent with our results (figure 1, table 1). Other studies reported different prevalence of Vit D deficiency as 42.5% in Beijing, 47% in Greece, and 59.4% in Turkey [20].

According to our study (9.03% of subjects with normal Vit D, 44.5% male) and (90.97% of subjects was vitamin D deficiency, 50.1%male) incompatible with Laila et al., who showed that the prevalence of Vit D deficiency was 142 out of 180 (78.9%) which was significantly higher among females [21].

In our study: Symptoms compatible with COVID-19 were 17.3% in second arm and 16.4% in first arm, Laboratory-confirmed diagnosis were 3.7% in 2nd arm group and 5.4% in 1st arm group, hospitalization were 1.2% in 2nd group and 0.4% in 1st group (table 1,2). That come agreeing with Mustafa et al., who showed that the individuals with Vit D levels above 30 ng/ml had considerably lower CRP and D-dimer levels, number levels, amount of affected lung segments and decrease hospital stays. Higher Vit D levels can reduce COVID-19 positivity, CRP and D-dimer levels and the total of affected lung segments in positive COVID-19 cases [22]. And compatible with Jolliffe et al., Meta-analysis of randomized controlled trials comprising 10 933 persons measured the result of Vit D therapy on the danger of viral respiratory infections. This revealed a decrease, from 42.2% to 40.3%, in danger of one or more infections with preceding Vit D therapy [23]. And also consistent with Afaghi et al., retrospective study on 646 persons COVID-19 confirmed positive who were admitted in Shahid Modarres Hospital, Iran. Vit D deficiency is a strong risk factor for SARS-CoV-2 infection. Vit D supplementation capable of prevent COVID-19 during this pandemic [24]. And also compatible with prospective study by Pizzini et al. studied the linking of Vit D with the clinical picture and the progression of COVID-19. In his study, 109 cases infested with SARS-CoV-2 were joined and exposed to eight week follow-up. Vit D deficiency has been revealed to be common amongst cases [25]. Parallel results are obtainable by Hernandez et al. The study concerning 216 COVID-19 cases and 197 healthy control. In the study group, Vit D deficiency was present in 84% of cases, and 47% in the control group only [26]. And similar to a meta-analysis directed by Pereira et al. detected that the Vit D deficiency in COVID-19 cases was connected with a greater danger of hospitalization. This time, a positive relationship has also been verified between the severity of symptoms and Vit D level [27]. But opposite to Vanessa et al., No significant differences were present in serum Vit D level at the period of hospital admission between cases with COVID-19 positive and COVID-19 negative inpatients [28].

As regard our results (Figure 3): Correlation between corrected Vitamin D levels and laboratory markers in the symptomatic cases. Reliable with Anshul et al., who showed that Vit D deficiency rises the occurrence of having severe disease after SARS Cov-2 infection. The strength of inflammatory reaction is moreover higher in Vit D deficient COVID-19 cases, author's approved mass administration of Vit D supplements to persons at threat for COVID-19 [29].

As regard our results in (table 3): Deficient vitamin D levels rise the risk of symptoms compatible with COVID-19 by 1.66 folds. That come compatible with Nanyang et al., revealed that Vit D deficiency was connected with an increased possibility of COVID-19, moreover, COVID-19 positive cases had lesser Vit D levels than COVID-19 negative cases [30]. And come compatible with a study by D'Avolio et al. revealed a clear link between Vit D level in the blood and the threat of COVID-19. It has been established that cases with COVID-19 had lower levels of Vit D as compared to cases negative for SARS-CoV-2 [31]. Parallel remarks were made by Kaufman et al. The study was carried out on 191,779 cases who confirmed positive for SARS-CoV-2 infection. There was a solid inverse link between Vit D level in the blood and the COVID-19 infection. Cases with Vit D level < 20 ng/ml displayed a 54% higher test positive index [32].

The strengths of our study: the availability of an adequate sample size to draw meaningful conclusion about the importance of rapid correction of Vit D deficiency in the era of COVID-19 pandemic, and yet being in a developing country like Egypt restrictions access to more expensive recent therapies for COVID-19 infection. Limitations of our study: short period of follow up so cannot reveal long time protection against COVID-19 infection after correction of Vit D deficiency. So more studies needed to detect efficacy of rapid correction of Vit D deficiency on the risk of COVID-19 infection for long duration.

Conclusion:

Short-term Vit D deficiency correction by one intramuscular dose of 200,000 IU cholecalciferol/vitamin D3 every other day, with a total of 3 doses, decrease the risk of COVID-19 infection.

Declaration of Competing Interest:

This study received no specific donation from any funding support.

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