Role of Vitamin D in the Length of Hospital Stay of Covid 19 Positive Patients

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ABSTRACT

Introduction: Vitamin D has an immunomodulatory and therapeutic role in reducing hospital stay in SARS-CoV-2 infected patients. Study objective was to know the effect of oral cholecalciferol supplementation on SARS-CoV-2 viral clearance.

Material and methods: Asymptomatic or mildly symptomatic SARS-CoV-2 positive vitamin D deficient (25(OH) D<20 ng/ml) individuals were included in the study .A total of 60 patients were selected, out of which 5 were excluded due to ventilator support, 2 due to co morbid condition and 3 for denial of consent.Therefore,50 patients were divided into 2 groups.First, the Intervention Participants ,were given 3 doses of 60000 IU of cholecalciferol on alternate days with therapeutic target 25(OHD>30ng/ml (intervention group) or placebo (control group). SARS-CoV-2 RNA and inflammatory markers fibrinogen, D-dimer and (CRP) were measured periodically. Outcome measures proportion of patients with SARSCoV-2 RNA negative and change in inflammatory markers.

Results: Fifty SARS-CoV-2 RNA positive individuals were randomised to intervention (n=25) or control (n=25) group. Baseline serum 25(OH) D was 12.4 for male and 8.1 for female in intervention group and 32 for male and 31.75 in female in control group. 03 out of 25 patients could achieve 25(OH)D>20 ng/ml first dose, 06 patients by second dose and another 11 patients by third dose could achieve 32.2 ng/ml. 22 participants in the intervention group and 18 participants in the control arm became SARS-CoV-2 RNA negative. Levels of other inflammatory markers significantly decreased with cholecalciferol supplementation.

Conclusion: Greater proportion of vitamin D-deficient individuals with SARS-CoV-2 infection turned SARS-CoV-2 RNA negative with a significant decrease in inflammatory markers on cholecalciferol supplementation.

Keywords: SARS-CoV-2, Vitamin D, Inflammatory Markers

INTRODUCTION

Coronavirus-2019 (COVID-19) caused by severe acute respiratory syndrome-associated coronavirus-2 (SARS-CoV-2) has affected the lives of millions. Presymptomatic and asymptomatic SARS-CoV-2 positive individuals are on a rise than symptomatic ones.[1,2] The transmission potential of SARS CoV-2 is potentially greater than earlier viral outbreaks of SARS-CoV and MERS-CoV because of its high transmissibility even from asymptomatic SARSCoV-2 RNA positive individuals.[3] Routine measures of social distancing, personal hand hygiene and limited outdoor contact activities have shown benefits to limit corona virus infection.But identification of asymptomatic carriers ofSARS-CoV-2 infection is paramount to containviral infection.It has been observed that vitamin D-deficient individuals have increased COVID-19 risk and mortality.[4–6] The role of vitamin D in SARSCoV-2 infection is still under study despite the knowledge of an immunomodulatory and protective effect against other viral infections.[7] Anintervention study with calcifediol shows reduced length of ICU stay in patients of COVID19.[9,7] However, the immuno-modulatory effect of vitamin D is likely to be observed at 25(OH)D levels, which are considered higher than that required for its skeletal effects.[8–10] The role of therapeutic vitamin D supplementation in asymptomatic individuals with vitamin-D deficiency and SARS-CoV-2 infection is yet under study. Therefore, we hypothesise that high-dose cholecalciferol supplementation in patients with SARS-CoV-2 infection and vitamin D deficiency may lead to SARS-CoV-2 negativity in greater proportions of patients with a decrease in serological markers of inflammation.

MATERIAL AND METHODS

Individuals with SARS-CoV-2 infection who were mildly symptomatic or asymptomatic without comorbidities (hypertension, diabetes mellitus, chronic obstructive airway disease, chronic liver disease, and chronic kidney disease) admitted to tertiary care hospital were included in the study. A total of 60 patients were selected, out of which 5 were excluded due to ventilator support, 2 due to co morbid condition and 3 for denial of consent. Therefore, 50 patients were divided into 2 groups. First, the Intervention Participants, were given 3 doses of 60 000 IU of cholecalciferol on alternate days with the therapeutic target of >30ng/ml (intervention group) or placebo (control group). SARS-CoV-2 RNA and inflammatory markers were measured periodically. Outcome measures Proportion of patients with SARS CoV-2 RNA negative. Subsequently,

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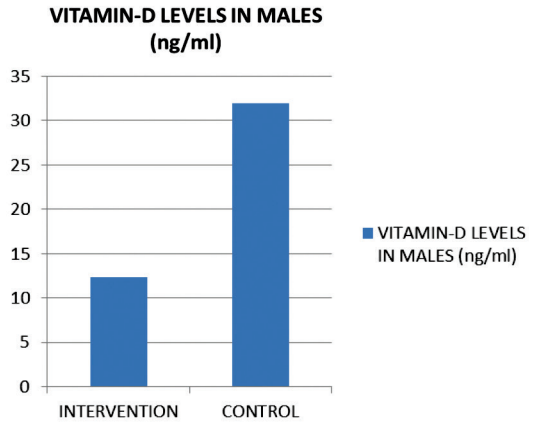
25(OH) D levels were assessed at day 7 in the intervention group. No cholecalciferol supplementation was provided in the control arm.. Oro-pharyngeal swabs were obtained for SARS-CoV-2 RNA and detection was performed by real-time PCR (RTPCR). The primary outcome measure was proportions of participants who turn SARS-CoV-2 negative.

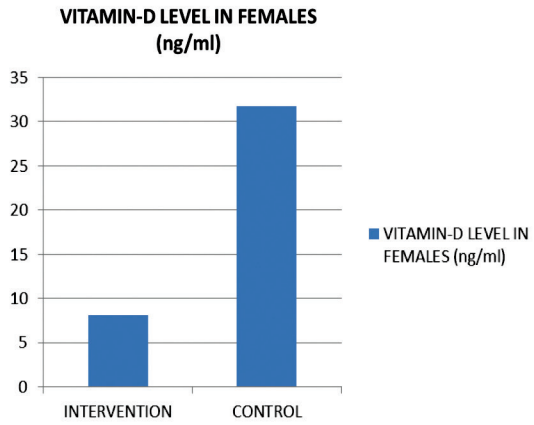
RESULT

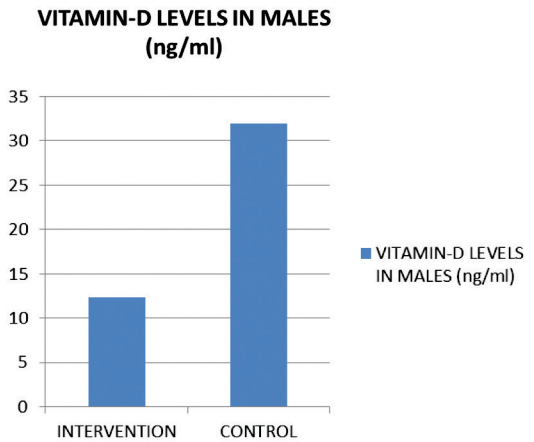
50 participants were subsequently randomised (25 in intervention arm and 25 to the control arm).

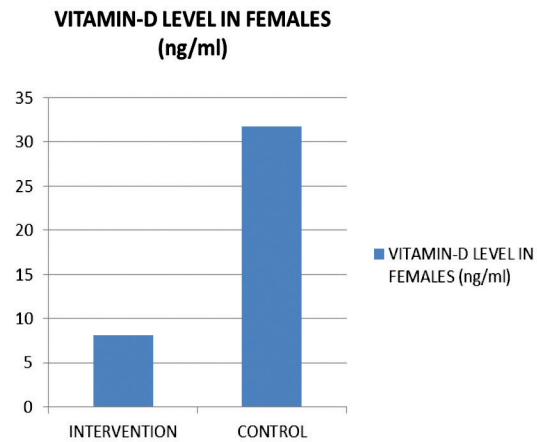
The mean age of males (38.3 yrs) and females (41.1 yrs) in the intervention group was compared with the mean age of males (33.93 yrs) and females (36.6) in the control group, indicating that female patients of higher age group are more prone to the deficiency of vitamin d and its adverse effects than the male patients.

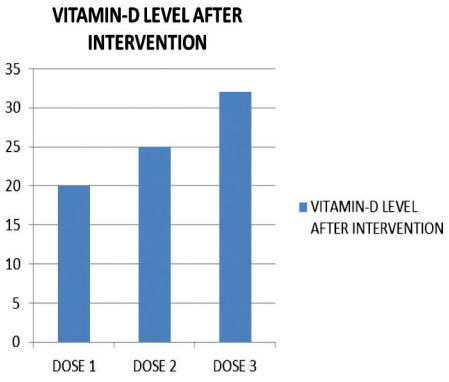
Mean values of 25(OH)D levels and inflammatory parameters in the two groups at study were evaluated . Three participants in intervention arm could achieve 25(OH) D levels >20 ng/ml at first dose of intervention, six more participants achieved 25(OH)D levels >25 ng/ml at second dose. The 25(OH)D levels at day-7 i.e. the third dose was >32 was achieved by 13 patients . 22 out of 25participants in the intervention group achieved SARS-CoV-2 negativity compared to 18 out of 25 participants (p=0.018) in the control arm.. However, not much difference was seen in the control group .











DEMOGRAPHIC AND BIOCHEMICAL PARAMETERS

Parameters	Intervention (n=25)		Control (n=25)	
	Male	Female	Male	Female
No.	15	10	16	09
Mean Age(years)	38	41.1	33.93	36.6
Vitamin-D (ng/ml)	12.4	8.1	32	31.75
Mean Fibrinogen (g/dl)	5.10		4.30	
Mean D-dimer (ng/ml)	382		250	
Mean CRP (mg/L)	2.1		2.4	

CHANGE IN THE LEVEL OF INFLAMMATORY MARKERS DURING THE INTERVENTION

Parameters (Mean Values)	Intervention (n=25)	Control (n=25)
Fibrinogen (g/dl)	2.1	3.90
D-dimer(ng/ml)	280	200
CRP (mg/L)	0.4	2.0

IMPROVEMENT AFTER GIVING VITAMIN-D SUPPLEMENTATION

Dose	No. of Patients	Vitamin- D level (ng/ml)
Dose 1	3	>20
Dose 2	6	>25
Dose 3	13	>30

DISCUSSION

In this cholecalciferol intervention study for asymptomatic and mildly symptomatic SARS-CoV-2 positive individuals, we found that a greater proportion of patients could attain SARS CoV-2 RNA negativity on vitamin D supplementation at 25(OH)D >30 ng/ml. The newer recommendations by CDC and ICMR do not mandate repeat testing to document SARS CoV-2 negative before discharge of asymptomatic individuals, hence achieving SARSCoV-2 negativity in greater proportions is likely to beneficial. Vitamin D influences various genes involved in the immune system and the downstream inflammatory cascade, thus affecting the susceptibility and severity of infections.[11] In SARS-CoV-2 infection vitamin D deficiency leads to a proinflammatory cytokine storm, augmenting the severity of disease. [12] SARS CoV-2 is known to bind to ACE-2 receptor on the cell surface and subsequently enters into the cell. Vitamin D down regulates the ACE2 expression and prevent the viral entry into cell.[13,14] It is plausible that vitamin D supplementation may decrease the likelihood of SARS CoV-2 infection or cause an early viral clearance. It is noticed that vitamin D levels>30 ng/ml are associated with a significant decrease in the SARS-CoV-2 infection severity and mortality.[15] There remain two concerns regarding vitamin D supplementation and disease outcomes. First, the appropriate levels of 25 (OH) D for its immunomodulatory effects. Secondly, these effects may not be observed on bolus administration and may be more pronounced only on long-term maintenance of higher levels of 25 (OH) D levels. Therefore, we chose an arbitrary cut-off of 25 (OH) D levels>30 ng/ml to render immunomodulatory effect. Moreover, it was imperative to achieve the desired levels [25 (OH) D levels>30 ng/ml] early, considering the outcome measure of SARS CoV-2 negativity.

CONCLUSION

Concluding with the role of vitamin D in immune function, and the impact of supplementation on vitamin D-deficient patients with COVID-19, and the favourable safety profile (and low cost) of vitamin D, we recommend:

Health guidelines for optimising vitamin D status and its benefits in the prevention of respiratory infections and improvement of pulmonary infection when supplemented with vitamin D.

The optimal vitamin D status of the host may contribute by down regulating overly exuberant cytokine responses (as higher vitamin D levels correlate with lower IL-6 levels).

Patients with COVID-19 who are hospitalised should have baseline serum 25(OH) D concentrations measured and should be supplemented to a level >30 ng/mL.

In COVID-19 patients with 25(OH) D serum concentrations under 20 ng/mL the recommended correction dose is 6000–7000 oral IU/day for 6–8 weeks. Maintenance dose varies from 2000 to 3000 oral IU/day.

If it is not possible to measure baseline 25(OH) D concentrations in COVID-19 patients, supplementing with 2000–3000 oral IU per day is recommended.

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