Short term, high-dose vitamin D supplementation for COVID-19 disease: a randomised, placebo-controlled, study (SHADE study)

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ABSTRACT

Background Vitamin D has an immunomodulatory role but the effect of therapeutic vitamin D supplementation in SARS-CoV-2 infection is not known.

Aim Effect of high dose, oral cholecalciferol supplementation on SARS-CoV-2 viral clearance.

Design Randomised, placebo-controlled.

Participants Asymptomatic or mildly symptomatic SARS-CoV-2 RNA positive vitamin D deficient (25(OH) D<20 ng/ml) individuals.

Intervention Participants were randomised to receive daily 60 000 IU of cholecalciferol (oral nano-liquid droplets) for 7 days with therapeutic target 25(OH) D>50 ng/ml (intervention group) or placebo (control group). Patients requiring invasive ventilation or with significant comorbidities were excluded. 25(OH)D levels were assessed at day 7, and cholecalciferol supplementation was continued for those with 25(OH)D <50 ng/ml in the intervention arm. SARS-CoV-2 RNA and inflammatory markers fibrinogen, D-dimer, procalcitonin and (CRP), ferritin were measured periodically.

Outcome measure Proportion of patients with SARS-CoV-2 RNA negative before day-21 and change in inflammatory markers.

Results Forty SARS-CoV-2 RNA positive individuals were randomised to intervention (n=16) or control (n=24) group. Baseline serum 25(OH)D was 8.6 (7.1 to 13.1) and 9.54 (8.1 to 12.5) ng/ml (p=0.730), in the intervention and control group, respectively. 10 out of 16 patients could achieve 25(OH)D>50 ng/ml by day-7 and another two by day-14 [day-14 25(OH)D levels 51.7 (48.9 to 59.5) ng/ml and 15.2 (12.7 to 19.5) ng/ml (p<0.001) in intervention and control group, respectively]. 10 (62.5%) participants in the intervention group and 5 (20.8%) participants in the control arm (p<0.018) became SARS-CoV-2 RNA negative. Fibrinogen levels significantly decreased with cholecalciferol supplementation (intergroup difference 0.70 ng/ml; P=0.007) unlike other inflammatory biomarkers.

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

Trial register number NCT04459247.

INTRODUCTION

Coronavirus-2019 (COVID-19) caused by severe acute respiratory syndrome-associated coronavirus-2 (SARS-CoV-2) has affected the lives of millions of individuals globally and severely strained the medical community. Pre-symptomatic and asymptomatic SARS-CoV-2 positive individuals far outnumber the symptomatic ones or those with severe disease.[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 SARS-CoV-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 of SARS-CoV-2 infection is paramount to contain viral infection.[2] Anti-viral, anti-inflammatory drugs and convalescent plasma therapy have been used for COVID-19 with variable results.[4]

It has been observed that vitamin D-deficient individuals have increased COVID-19 risk and mortality.[5–7] The role of vitamin D in SARS-CoV-2 infection is not explored in intervention studies despite the knowledge of an immunomodulatory role and protective effect of vitamin D against other viral infections.[8] An intervention study with calcifediol noticed a reduction in requirement for intensive care among hospitalised patients for COVID19.[9] However, vitamin D levels were neither available at baseline nor during follow up in the study. It is noticed that those receiving vitamin D supplementation have fewer respiratory tract infections.[8] However, the immune-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.[10–12]

The role of therapeutic vitamin D supplementation in asymptomatic individuals with vitamin-D deficiency and SARS-CoV-2 infection is not known. A PCR-confirmed SARS-COV-2 infection from nasopharyngeal swab pertains to relevant clinical outcome in intervention trials[10] especially for asymptomatic individuals as an earlier SARS-CoV-2 negativity would have significant public health benefits in limiting the spread of the disease. 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.

METHODS

Consecutive individuals with SARS-CoV-2 infection who were mildly symptomatic or asymptomaticwithor without co-morbidities (hypertension, diabetes mellitus, chronic obstructive airway disease, chronic liver disease, chronic kidney disease) admitted to tertiary care hospital in north India were invited for the study. A written consent was obtained from all patients included in the study and protocol was approved by the Institute Ethics Committee.

Patients with vitamin D deficiency defined as 25 (OH)D level<20 ng/ml were randomised to receive daily 60000 IU of cholecalciferol (5 ml oral solution in nano droplet form)for 7 days in the 'intervention arm' with the aim to achieve 25 (OH)D level>50 ng/ml or placebo (5 ml distilled water) for 7 days (control group). Patients unable to take oral supplementation like those requiring invasive ventilation or with significant comorbidities like uncontrolled hyperglycaemia or hypertension were excluded. Subsequently, 25(OH)D levels were assessed at day 7 and a weekly supplementation of 60000IU provided to those with 25(OH)D >50 ng/ml or else continued on daily vitamin D 60,000 IU supplementation for another 7 days up until day-14 in participants with 25(OH)D <50 ng/ml in the intervention arm. No cholecalciferol supplementation was provided in the control arm.

25 (OH)D, serum calcium, phosphorus, fibrinogen, D-dimer,, ferritin, procalcitonin, renal and liver function tests were performed periodically up until day-21 or virus negativity, whichever occurred earlier. Oro-pharyngeal swabs were obtained for SARS-CoV-2 RNA detection at day-5, 7, 10, 14, 18 and 21 and detection was performed by real-time PCR (RT-PCR), CFX-96 IVD, Bio-Rad. 25 (OH)D was analysed by electrochemiluminescence immunoassay (ECLIA) (Roche Cobas E 801 Analyser; Roche Diagnostics), using the kit supplied by the same manufacturer (Elecsys Total Vitamin D, version 2.0). Serum calcium(N, 8.5–10.2 mg/dl) and C-reactive protein (N, 0–5 mg/l) were processed by ECLIA method using Roche Cobas 8000, Roche Diagnostics. D dimer (N, 0–240 ng/ml) & fibrinogen (N, 2–4 g/l) were analyzed using StagoCompact/StagoSTA R model, DiagnosticaStago, Inc, USA, respectively.

All the participants received standard care for the SARS-CoV-2 infection and pre-existing co-morbidities as per institute protocol. The primary outcome measure was proportions of participants who turn SARS-CoV-2 negative(confirmed twice at 24-hour interval) before week 3 in the two groups. Other outcome measure was the change in the level of inflammatory markers with treatment.

Sample size estimation

Serum level of inflammatory marker decrease with the duration of SARS-CoV-2 infection.[13] An anticipated additional decline in level of inflammatory marker by 20% with intervention was used for sample size calculation. Sample size came to be 16 participants in each group with power of 80% (beta error 0.2) and at 95% level of significance (alpha error 0.05).

Statistical analysis

A modified intention-to-treat analysis was performed. Normality of the data was assessed by Kolmogorov–Smirnov test and mean ± SD is used to depict data following normal gaussian pattern and median and inter-quartile range for skewed data. Student T-test was used to compare the means of two groups for parametric variables and Mann–Whitney U-test for non-parametric variables. Proportion of participants achieving SARS-CoV-2 RNA negativity in the two groups was compared with Fischer Exact (2 by 2 tailed) test. SPSS version 22 was used for data analysis and a p-value <0.05 was considered significant.

RESULTS

Eighty-nine SARS-CoV-2 RNA positive individuals were evaluated. Six patients requiring invasive ventilation, four with prior co-morbidities and four with 25(OH)D>20 ng/ml were excluded. Thirty-five individuals denied consent; therefore, 40 participants were subsequently randomised (16 in intervention arm and 24 to the control arm)as shown in CONSORT diagram (figure 1). Median 25(OH)D levels and other parameters in the two groups at study inclusion are shown in table 1. Ten participants in intervention arm could achieve 25(OH)D levels >50 ng/ml at day-7 of intervention and two more participants by day-14. The 25(OH)D levels at day-14 were 51.7 (48.9 to 59.5) ng/ml and 15.2 (12.7 to 19.5) ng/ml, p<0.001 with a median increase of 42.4 (39 to 48.8) ng/ml and 5.1 (0 to 12.3) ng/ml (p<0.01) in the intervention and control group, respectively (online supplemental table 1S). 10 out of 16 (62.5%) participants in the intervention group achieved SARS-CoV-2 negativity compared to 5 out of 24 (20.8%) participants (p=0.018) in the control arm. The mean duration to SARS-CoV-2 negativity was 17.6±6.1 and 17.6±6.4 days (p=0.283) in the intervention and control arm, respectively.

There was a significant decrease in fibrinogen (p<0.01) in the intervention arm compared to control arm as shown in table 2. However, no intergroup difference in the change in D-dimer, CRP, ferritin and procalcitonin were observed during follow up (online supplemental table 2S–6S). There was no significant difference in calcium and phosphorus level in the two groups during the study period (online supplemental table 7S).

Adverse events: No episodes of hypercalcaemia were observed in either group.

DISCUSSION

In this first 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 high-dose vitamin D supplementation at 25(OH)D >50 ng/ml compared to vitamin D-deficient individuals. The newer recommendations by CDC and other

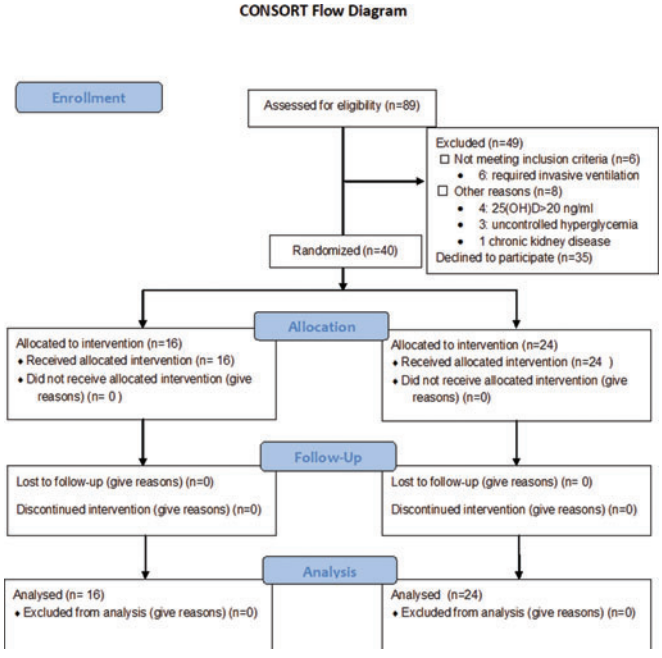

Figure 1 CONSORT diagram depicting participant inclusion, exclusion and flow during the study.

Table 1 Demographic and biochemical parameters at baseline in the two groups

Parameters	Intervention n=16	Control n=24	P-value
Age (years)	50.0 (36 to 51)	47.5 (39.3 to 49.2)	0.765
Gender (Male)	6	14	–
25 (OH) D3 (ng/ml)	8.6 (7.1 to 13.1)	9.54 (8.1 to 12.5)	0.730
Fibrinogen (g/L)	4.06 (3.7 to 5.12)	3.73 (3.40 to 4.30)	0.232
D-Dimer (ng/ml)	345 (219 to 860)	236.7 (224.8–384.4)	0.295
Procalcitonin (ng/ml)	0.02 (0.02–0.03)	0.03 (0.02–0.09)	0.411
C reactive protein (mg/L)	2.1 (0.8 to 20.4)	2.6 (0.7 to 14)	0.295
Calcium (mg/dl)	9.4 (9.2 to 9.7)	8.8 (8.0–9.2)	0.042*
Phosphorus	4.0 (2.1–6.2)	3.3 (3.1–3.8)	0.121

*p<0.05 is considered significant.
Data represented as median (Inter quartile range).

Table 2 Change in the levels of serum inflammatory markers in the two groups during follow up

	Intervention group (N=16)	Control group (N=24)	P-value
Δ Vitamin D (ng/ml)	42.4 (39 to 48.8)	5.1 (0 to 12.3)	<0.001*
Δ D-dimer(g/L)	−80.0 (−308.0 to 13.2)	−31.2 (−202 to 0)	0.241
Δ Fibrinogen (ng/ml)	−0.9 (−2.0 to −1.0)	−0.04 (−1.02 to 0.0)	0.001*
ΔCRP(ng/ml)	−0.3 (−1.4 to 0.2)	0.0 (−0.9 to 0.3)	0.507
Δ Procalcitonin (mg/L)	0.00 (−0.2 to 0.7)	−0.1 (−0.60 to 0.04)	0.260

*p<0.05 considered significant.
Data represented as median (Inter-quartile range).
Δ: Last available value-Baseline value.
CRP, C-reactive protein.

regulatory bodies including ICMR do not mandate repeat SARS CoV-2 RNA testing to document SARS CoV-2 negative before discharge of asymptomatic individuals, hence achieving SARS-CoV-2 negativity in greater proportions is likely to beneficial.

The immunomodulatory effect of vitamin D has been previously studied in bacterial as well as viral infections, but not in SARS-CoV-2 infection. Vitamin D influences the expression of various genes involved in the immune system (innate immunity, adaptive immunity) and the downstream inflammatory cascade, thus affecting the susceptibility to and severity of bacterial and viral infections.[14 15] Vitamin D can induce anti-microbial peptide cathelicidin (LL-37) in neutrophils, NK cells and monocytes to cause reduction of Herpes-Simplex virus titre.[11] In a recent meta-analysis of intervention trials, vitamin D supplementation was observed to reduce the incidence of acute respiratory tract infections [incidence rate ratio 0.96 (0.92–0.997), p=0.04].[8] Similarly in SARS-CoV-2 infection vitamin D deficiency may lead to a pro-inflammatory cytokine milieu, thus augmenting the disease severity.[7 12] SARS CoV-2 is known to bind to ubiquitously expressed ACE-2 (ACE-2) receptor on the cell surface and subsequent ingress into the cell. Vitamin D may downregulate the ACE-2 expression and prevent the viral entry into cell.[16 17] 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.[12] Therefore, we studied the effect of high doses of vitamin D supplementation on the likelihood of viral clearance in SARS CoV-2 positive individuals.

Though India is a subtropical country with adequate sunlight, vitamin D deficiency is prevalent.[18] However, there remain two concerns regarding vitamin D supplementation and disease outcomes. First, the appropriate levels of 25 (OH)D for its immunomodulatory effects are not known. Secondly, these effects may not be observed on bolus administration of vitamin D 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>50 ng/ml to render immunomodulatory effect unlike 30 ng/ml that are purported to be adequate for bone metabolism. Moreover, it was imperative to achieve the desired levels [25 (OH)D levels>50 ng/ml] early, considering the outcome measure of SARS CoV-2 negativity. It was observed that following a single bolus dose of 540 000 IU of vitamin D_3, mean serum 25(OH)D concentrations in those with vitamin D deficiency increased to >20 ng/mL by day 1 and peaked at 38.2 ±16.5 ng/mL at 1 week.[19] Also, in another study a single dose of 600 000 IU of vitamin D_3 raised serum 25(OH)D to >30 ng/mL early in elderly individuals and maintained for at least 4 weeks without any adverse event.[20] However, a systematic review regarding high dose of vitamin D supplementation in the doses of 1,00,000IU suggested an inability to increase 25(OH)D >30 ng/ml.[21] Therefore, we provided cholecalciferol supplementation of 60,000 IU daily (420 000 IU in the first week) in the present study that are higher than existing recommendations but were found to be safe as no episodes of hypercalcaemia were observed in the present study asserting the safety of short-term high doses of vitamin D supplementation.

COVID-19 is associated with a rise in the inflammatory markers like D-dimer, fibrinogen and pro-inflammatory cytokines. A serial evaluation of inflammatory markers might help in evaluating and monitoring the severity of COVID-19 disease. It is noticed that certain serological markers like IL-6, CRP, ferritin, ESR are increased to a greater extent in people with severe disease than those with less severe disease.[22] Also, D-dimer >1µg/l was an independent predictor of mortality in COVID-19 disease.[23] We found a significant difference in level of fibrinogen in patients achieving 25 (OH)D >50 ng/ml as compared to vitamin-D deficient individuals, suggesting a possible immuno-modulatory effect of vitamin D. However, the changes in the fibrinogen level though statistically significant was modest and may not be clinically meaningful; moreover, other inflammatory marker levels were not significantly different between the two groups. Inflammatory cytokines (IL-6, TNF-a, IL-1b) were not measured and any effect of vitamin D supplementation on cytokine levels could not be assessed in the present study.

The strengths include being the first study to demonstrate the role of therapeutic high dose, daily, oral vitamin D supplementation to attain 25(OH)D >50 ng/ml levels and its effect on COVID-19. We perceive certain limitations including that only mildly symptomatic and asymptomatic individuals were enrolled in the study which limits the generalisability of the results to symptomatic or severe cases of COVID-19. Placebo used in the study was not exactly matched with regards to the taste and consistency with the cholecalciferol nano formulation. Also, the dose of cholecalciferol used in the present study is high compared to conventional treatment, that warrants close follow up to look for vitamin D toxicity, though we did not observe the same. Clinical role of a decrease in inflammatory markers in the asymptomatic SARS-CoV-2-infected population with vitamin D supplementation as observed in the present study is contentious. Inflammatory cytokines (IL-6, TNF-a) were not measured in the present study. Parenteral vitamin D administration could be contemplated in future studies as four patients could not achieve 25 (OH)D >50 ng/ml after oral, high-dose vitamin D supplementation and malabsorption disorders could not be ruled out.

In conclusion, a high dose, oral vitamin D supplementation to augment 25(OH)D >50 ng/ml helped to achieve SARS-CoV-2 RNA negativity in greater proportion of asymptomatic vitamin D-deficient individuals with SARS-CoV-2 infection along with a significant decrease in inflammatory marker. SARS-CoV-2 RNA negativity by cholecalciferol supplementation may help in reducing transmission rates of the highly contagious SARS-CoV-2 infection. A reassurance for public health workers regarding greater likelihood of SARS CoV-2 RNA negativity in individuals receiving therapeutic cholecalciferol supplementation will be encouraging.

Current research questions

- What levels of 25 (OH)D3 have immunomodulatory functions in viral diseases particularly SARS-CoV-2 infection?
- Role of therapeutic vitamin D supplementation in severe COVID-19 disease for quantitative viral clearance?
- Vitamin D effect on 'cytokine storm' in patients with severe COVID-19 disease
- Can high-dose vitamin D reduce ICU/hospital stay and mortality in severe COVID-19 disease over and above standard care?

What is already known on the subject

- Vitamin-D has immunomodulatory effect and may reduce susceptibility and severity of viral infections but its role in SARS-CoV-2 infection is not known.

What we have found

- Daily cholecalciferol supplementation of 60,000 IU helps in achieving 25(OH)D>50 ng/ml in 75% of participants by day-14.
- Therapeutic, high-dose cholecalciferol supplementation led to SARS-CoV-2 RNA negative in additional 41.7% participants (p<0.001) and was useful for viral SARS-CoV-2 RNA clearance.

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