

# Effectiveness of vitamin D<sub>3</sub> in severe persistent asthmatic patients: A double blind, randomized, clinical study

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## ABSTRACT

**Objective:** To assess the pulmonary function and quality of life in asthma patients receiving vitamin D<sub>3</sub> supplementation with inhaled budesonide and formoterol. **Materials and Methods:** This was a double blinded, randomized, comparative study. Patients were recruited as per the study criteria and randomized into two groups: usual care group ( $n = 69$ ) patients received budesonide (800  $\mu\text{g}$ ) with formoterol (24  $\mu\text{g}$ ) and intervention care group ( $n = 72$ ) patients received vitamin D<sub>3</sub> (1000 IU) supplementation along with budesonide (800  $\mu\text{g}$ ) plus formoterol (24  $\mu\text{g}$ ) for a period of 6 months. **Results:** A total of 140 patients completed the study. Significant within-group improvement and non-significant between-group improvement is observed with respect to FEV<sub>1</sub>. In terms of health-related quality of life, within-group comparison revealed a significant ( $P < 0.05$ ) improvement in all the domains of SGRQ. However, between-group comparisons showed statistically significant ( $P < 0.05$ ) improvement in symptom, impact and total scores. **Conclusion:** On the basis of our findings, we conclude that supplementation of vitamin D<sub>3</sub> is effective in improving the quality of life rather than pulmonary function in severe asthmatics. However, further studies are warranted to substantiate the present findings.

**Key words:** Asthma, budesonide, FEV<sub>1</sub>, formoterol, vitamin D<sub>3</sub>

## INTRODUCTION

In recent days, deficiency of vitamin D is found to be a major factor in the progress of diseases like cancer, depression,

cardiovascular diseases, diabetes, multiple sclerosis, osteoporosis, fertility, asthma, etc.<sup>[1]</sup> Thus, vitamin D<sub>3</sub> has brought an incredible amount of attention toward the health care professionals. Despite day to day foods are fortified with vitamin D, many studies have shown an absolute deficiency of vitamin D in many people.

The prevalence of asthma increases globally by 50% every decade. The pathophysiology of asthma is complicated.

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Vitamin D deficiency leads to increased bronchial hyper-responsiveness and reduced pulmonary function.<sup>[2]</sup> Nearly 5–15% of patients with asthma symptoms and exacerbation are uncontrolled despite of routine controller medications including corticosteroids. Therefore, they are more prone to have irreversible obstruction of airflow and also associated with airway remodeling.<sup>[3]</sup> If vitamin D plays either preventive or protective role against the development of asthma, then it could be the most effective therapy.

Very few studies have considered this point and evaluated the relationship between vitamin D<sub>3</sub> and pulmonary function<sup>[4,5]</sup> and there is no clinical study report from Indian adult population to explore the role of vitamin D<sub>3</sub> in asthma. Thus, the present study was undertaken to study whether or not vitamin D<sub>3</sub> can improve pulmonary function and health-related quality of life in severe persistent asthma patients.

## MATERIALS AND METHODS

### Study design

The study was approved by the Institutional Ethical Committee and it was conducted in the Department of Pulmonary Medicine, SRM Medical College hospital and research center, Kattankulathur, Tamil Nadu, India. The study was designed as a prospective, randomized, double blinded and parallel group study. A randomization list was generated using random allocation software and concealment of the randomization codes was done by serially numbered, opaque envelope model. Randomization and allocation details were known only to a third party.

### Study criteria

The study participants were 18 to 60 years of age, both sexes, were clinically diagnosed as having severe persistent asthma, had improvement in forced expiratory volume in 1 second (FEV<sub>1</sub>) >12% after bronchodilator inhalation and had given their written informed consent. Exclusion criteria included clinically significant renal, respiratory (other than asthma), cardiac, gastrointestinal, hepatic, endocrine, or hematologic disorders, cancer, unresolved upper respiratory tract infection within the past 3 weeks, suspected hypersensitivity to study therapy or excipients, pregnant or lactating mother.

### Study protocol

Patients satisfying above-mentioned study criteria were enrolled in the study. Enrolled patients were randomized by randomization chart generated by computer-assisted random allocation procedure. Patients were divided into two groups, namely usual care ( $n = 69$ ) and intervention care ( $n = 72$ ) groups. Clinical information relevant for the study was collected from the patients, healthcare professionals, necessary

records and as well as from patient's bystanders in few cases. Antiasthmatic drugs prescribed till date were stopped and the patients were asked to take salbutamol inhaler (i.e., rescue medication) whenever necessary for 7 days (run-in period) prior to the study. Patients were educated and counseled about the proper usage of inhalers. The usual care group patients received budesonide (800 µg) with formoterol (24 µg) daily. This is the fixed dose combination (FDC). The intervention care group patients received the same FDC plus vitamin D<sub>3</sub> tablet (1000 IU; once daily). All patients could take short-acting β-agonist in case of an asthmatic crisis. Commercially available brands of the study medications were used throughout the study period.

Spirometry was performed before the morning dose of trial medication at each visit and at least three spirometry maneuvers were performed, and the largest FEV<sub>1</sub> was recorded. Standard spirometer (Mini Wright flow meter, Clement Clarke International, London) was used in the study. The spirometry was performed by well-trained pulmonary technicians. The patients were assessed individually for the appropriate use of inhaler during baseline and at every follow up. The steps which the patients found difficult were identified for each patient and were educated and trained accordingly.

Health-related quality of life (HRQoL) was assessed by Saint George Respiratory Questionnaire (SGRQ). SGRQ is a disease-specific instrument designed to measure impact on overall health, daily life and perceived well-being. SGRQ was scored according to the developer's guidelines.<sup>[6]</sup>

Patient's compliance with the study medication was assessed with the help of medication compliance charts. Patients not obeying the study protocol were withdrawn from the study. All the patient's clinical symptoms, pulmonary function (% FEV<sub>1</sub> by spirometer) and health-related quality of life (SGRQ scores) were measured at the baseline and every follow up days, i.e. day 30, 60, 90, 120, 150 and 180. At each and every follow up, patient medication adherence and their inhaler usage technique were monitored.

### Sample size

Considering  $\alpha$  error at 0.05% and 80% power ( $1 - \beta = 0.8$ ) of study with an approximate 8.5% difference between two groups<sup>[7]</sup> for a significant increase in % FEV<sub>1</sub> with the standard deviation of 0.05 using 1:1 ratio of independent sample *t*-test, 66 patients must complete the study in each group. Considering 20% dropout, 79 patients should be included in each group.

### Statistical analysis

Data are expressed as mean  $\pm$  SD. The probability value less than 0.05 was considered for statistical significance.

Demographic characteristics like age and gender, baseline and final visit data were used to assess response rates by comparing usual care and intervention groups. Student's *t* test was used for comparison within the groups. One-way ANOVA followed by Bonferroni multiple comparison test was used for comparison between groups using GraphPad Software, Inc. (USA). Per protocol analysis (PPA) was performed.

## RESULTS

The study was conducted between June 2013 and April 2014. A total of 172 patients attended the screening phase for severe persistent asthma condition, out of which 161 patients met the study criteria. In the usual care group, out of 79 patients, 69 patients completed the study and in the intervention care group, out of 82 patients, 72 patients completed the study. Reasons for drop out in both the groups are mentioned in Figure 1. Baseline characteristics, including age, gender, education and BMI are given in Table 1. There were no significant differences in baseline characteristics among the groups ( $P > 0.05$ ).

The visit-wise changes in the FEV<sub>1</sub> values from baseline to final follow-up of the study are shown in Figure 2. It is evident from the Figure 2 that FEV<sub>1</sub> values are improved at every follow-up in both groups. However, between-group comparison of FEV<sub>1</sub> shows no significant difference ( $P > 0.05$ ) in any of the follow-up days [Table 2].

Statistically significant improvement is observed in symptom score, activity score, impact score and total scores of SGRQ in within-group comparison [Figure 3]. With respect to symptom score, between-group comparison showed statistically significant improvement ( $P < 0.001$ ) from day 30 onward. However, no significant difference was observed between the groups in terms of activity scores. Regarding impact score, a statistically significant difference was observed from day 30 till the end of final follow-up. Between-group comparison of total score has shown no statistically significant improvement from the baseline to day 150. However, on the final follow-up day, a statistically significant improvement ( $P < 0.05$ ) was observed [Table 3].

Physical examination, including oropharyngeal inspection, heart rate and blood pressure were monitored during the study period. There were no significant changes in such assessments recorded in all the clinical visits (Data are not shown). Asthma exacerbations which required hospitalization were considered as serious adverse events. There was no such critical situation faced by study patients of both groups.

## DISCUSSION

Asthma is a major public health problem. Although there is recent evidence of a modest further increase in asthma rates

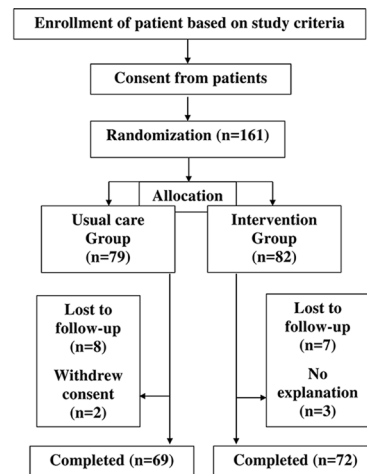


Figure 1: Flow of patients and CONSORT diagram

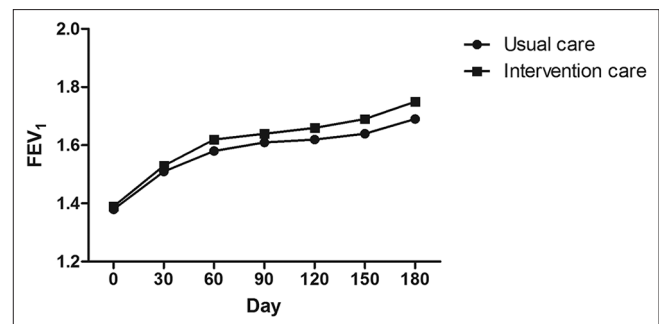


Figure 2: Visit-wise change in FEV<sub>1</sub> within the study groups

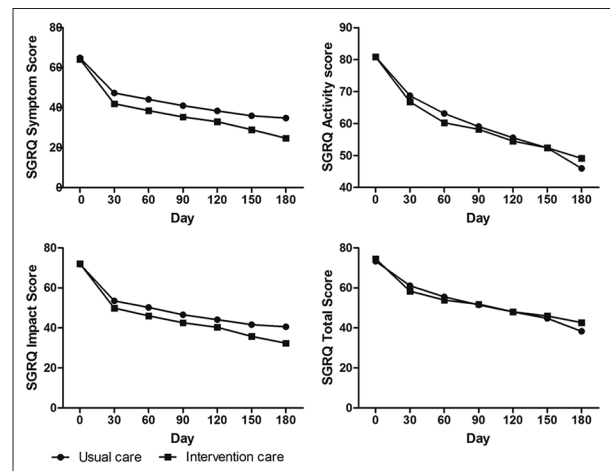


Figure 3: Visit-wise change in SGRQ scores within the study groups

in countries with high disease prevalence, the causes of the “asthma epidemic” are incompletely understood.<sup>[8]</sup> Various International and National guidelines have recommended inhaled corticosteroid as the first-line controller therapy for persistent asthma patients; however, not all the patients respond to inhaled corticosteroid and clinical studies demonstrated that up to 45% of patients do not have a clinical or physiological response to this agent. The component of this variability may be explained by vitamin D status, with studies

**Table 1: Baseline characteristics of the patients**

| Baseline characteristics                 | Usual care (n=69) | Intervention care (n=72) |
|--|-------------------|--------------------------|
| Age (mean±SD)                            | 57.18±9.2         | 58.46±8.6                |
| BMI (mean±SD)                            | 22.5±2.8          | 21.3±3.1                 |
| Gender % (n)                             |                   |                          |
| Male                                     | 49.27 (34)        | 49.29 (35)               |
| Female                                   | 50.72 (35)        | 50.70 (36)               |
| Educational status % (n)                 |                   |                          |
| Illiterate                               | 23.18 (16)        | 26.76 (19)               |
| 1 to 10                                  | 36.23 (25)        | 38.02 (27)               |
| 11 to degree                             | 34.78 (24)        | 30.98 (22)               |
| >Degree                                  | 5.79 (4)          | 4.22 (3)                 |
| Pulmonary function (mean±SD)             |                   |                          |
| FEV <sub>1</sub>                         | 1.38±0.26         | 1.39±0.26                |
| Health-related quality of life (mean±SD) |                   |                          |
| Symptom score                            | 64.83±6.93        | 64.16±6.01               |
| Activity score                           | 80.87±8.51        | 80.83±8.22               |
| Impact score                             | 71.84±6.91        | 72.11± 5.96              |
| Total score                              | 73.27±8.52        | 74.47±7.96               |

**Table 2: Comparison of FEV<sub>1</sub> between the study groups**

| Day     | Mean difference | t     | P     |
|---------|-----------------|-------|-------|
| Day 0   | 0.010           | 0.198 | >0.05 |
| Day 30  | 0.020           | 0.396 | >0.05 |
| Day 60  | 0.040           | 0.793 | >0.05 |
| Day 90  | 0.030           | 0.595 | >0.05 |
| Day 120 | 0.040           | 0.793 | >0.05 |
| Day 150 | 0.050           | 0.991 | >0.05 |
| Day 180 | 0.060           | 1.189 | >0.05 |

<sup>ns</sup>P>0.05

**Table 3: Comparison of mean differences in SGRQ scores between the study groups**

| Day     | Symptom score | Activity score | Impact score | Total score |
|---------|---------------|----------------|--------------|-------------|
| Day 0   | -0.670        | -0.040         | 0.270        | 1.200       |
| Day 30  | -5.400***     | -1.940         | -3.660*      | -2.720      |
| Day 60  | -5.560***     | -2.860         | -4.170**     | -1.640      |
| Day 90  | -5.660***     | -0.890         | -4.010**     | 0.320       |
| Day 120 | -5.420***     | -1.050         | -3.780*      | -0.020      |
| Day 150 | -6.980***     | 0.060          | -5.880***    | 1.150       |
| Day 180 | -10.080***    | 3.150ns        | -8.170***    | 4.310*      |

\*P<0.05, \*\*P<0.01, \*\*\*P<0.0001

suggesting that vitamin D may enhance the effects of inhaled corticosteroids.<sup>[9,10]</sup>

It has been hypothesized that vitamin D deficiency, as a result of westernized lifestyles that have led to sun avoidance

behaviors and more time indoors, has a role in the development and treatment of asthma and allergies.<sup>[11]</sup> Studies carried out in animal model reported that vitamin D<sub>3</sub> pre-treated groups enhanced the efficacy of allergen immunotherapy in a mouse allergic asthma model.<sup>[12]</sup> Bergman *et al.* studied the effect of vitamin D<sub>3</sub> supplementation to reduce the disease burden in patients with frequent respiratory tract infection.<sup>[13]</sup> Black and Seragg revealed a strong relationship between serum concentration of vitamin D<sub>3</sub> and pulmonary function parameters like FEV<sub>1</sub> and FVC.<sup>[14]</sup>

A possible relationship between asthma and polymorphisms in other genes involved in vitamin D synthesis, bioavailability and metabolism has been proposed. Higher prevalence, hospitalization and emergency visits along with decreased the pulmonary function and increased bronchial hyper-responsiveness has been demonstrated with low serum 25-hydroxy vitamin D in asthmatic pediatric patients.<sup>[15,16]</sup>

Iqbal and co-workers analyzed the various factors and the role of vitamin D<sub>3</sub> in asthma.<sup>[17]</sup> They concluded that vitamin D<sub>3</sub> acts on lung tissue and to improve immune function and reduce the inflammation. However, they did not give any ample evidence that vitamin D<sub>3</sub> has the potential to improve pulmonary function.

Studies carried out in pediatric population also not reported any definitive proof of improved clinical symptoms of asthma with the adjunctive therapy of vitamin D<sub>3</sub>.<sup>[18]</sup> Recently, Gergen *et al.* studied the relationship between serum vitamin D<sub>3</sub> concentration and prevalence of asthma with severity and response of asthma treatment.<sup>[19]</sup> The study concluded that overall vitamin D<sub>3</sub> concentrations were low in two samples of adolescents and they were not reliably linked with the presence of asthma or asthma morbidity.

From the above-mentioned contradictory statement, we could not come to a conclusion whether the vitamin D<sub>3</sub> has a role on asthma condition or not. Thus, the present study was undertaken. The finding of this study suggests that the addition of vitamin D<sub>3</sub> to the regular treatment regimen had no improvement in the pulmonary function. However, statistical as well as clinical improvement is seen with respect to health-related quality of life. This is in accordance with the study carried out by Castro *et al.* No significant reduction in the rate of first treatment failure or exacerbation was noticed in their study. There was also no significant reduction in the secondary endpoints related to asthma control, airway function or airway inflammation.<sup>[20]</sup>

## CONCLUSION

If the dietary intake of vitamin D fails to meet the recommended daily allowance, health care professionals may encourage the

asthma people to increase their intake of vitamin D, preferably through the consumption of healthy food sources rich in vitamin D or otherwise through the use of appropriate vitamin supplements. 25-hydroxy vitamin D<sub>3</sub> is the best biomarker of vitamin D metabolic status and reflects contributions from all sources (diet and sun exposure). Further studies may be carried out by serum estimation of serum 25-hydroxy vitamin D<sub>3</sub> to substantiate the current findings.

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Nil.

#### Conflicts of interest

There are no conflicts of interest.

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