Vitamin D Supplementation as an Adjunct Treatment for Asthma

Robert Marshall
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Abstract
Background: Asthma is a significant health problem that is trending up in prevalence and cost. The pathophysiology of asthma has been shown to be multi-factorial. In recent years vitamin D has demonstrated potential therapeutic benefit. Vitamin D is thought to have an effect on immune function decreasing inflammation; as a result vitamin D may have a role in asthma management. Despite many studies linking vitamin D with asthma very few studies have looked at treatment response following supplementation. This review attempts to look at the effects of using oral vitamin D, in addition to standard therapy, to gain better control of asthma.

Method: An exhaustive search was performed using Medline-Ovid, Medline-Pub-Med, Web of Science, and Google Scholar. Keywords included were as follows: asthma, vitamin D, supplementation or dietary supplements, and airway functions or respiratory functions. Relevant articles were assessed for quality using GRADE.

Results: Two randomized, open-label studies and one randomized, blinded study met inclusion criteria. All three studies demonstrated a benefit in measured airway functions and outcomes specific to each study were all shown to confirm vitamin D’s role in asthma management. Overall the qualities of the study were moderate to low warranting further study with a greater amount of participants and a focus on correlating serum vitamin D levels with therapeutic benefit.

Conclusion: Vitamin D has the potential to play a significant role in the overall management of a patient with asthma. These studies have laid the groundwork and strengthened the hypothesis that standard treatment with supplementation of vitamin D may reduce morbidity. Despite the need for stronger, more complete studies vitamin D is a safe adjunct therapy for asthma patients.

Keywords: Asthma, vitamin D, supplementation, dietary supplements, airway function, and respiratory functions tests.

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First Advisor
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Keywords
Asthma, vitamin D, supplementation, dietary supplements, airway function, and respiratory functions tests.

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Vitamin D Supplementation as an Adjunct Treatment for Asthma

Robert Marshall

A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
Pacific University
Hillsboro, OR
For the Masters of Science Degree, August 2015

Faculty Advisor: David Keene, PA-C
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

[Redacted for privacy]
Abstract

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**Conclusion:** Vitamin D has the potential to play a significant role in the overall management of a patient with asthma. These studies have laid the groundwork and strengthened the hypothesis that standard treatment with supplementation of vitamin D may reduce morbidity. Despite the need for stronger, more complete studies vitamin D is a safe adjunct therapy for asthma patients.

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List of Abbreviations

BMI Body Mass Index
COPD Chronic Obstructive Pulmonary Disease
CI Confidence Interval
FEV<sub>1</sub> Forced Expiratory Volume in 1 second
FVC Forced Vital Capacity
GINA Global Initiative for Asthma
GRADE Grading of Recommendations, Assessment, Development and Evaluations
PEFR Peak Expiratory Flow Rate
Vitamin D Supplementation as an Adjunct Treatment for Asthma

BACKGROUND

Asthma is a major health problem in the United States, affecting over 25 million people in 2012, according to the Center for Disease Control and Prevention.\textsuperscript{1} It is estimated that asthma accounts for over 14 million outpatient visits and 500 000 hospitalizations yearly in the U.S. Of the 2 million emergency room visits in the U.S. yearly, asthma is responsible for 25% and in 2007 was estimated to cost over 56 billion in medical costs, lost work, missed school, and early deaths.\textsuperscript{1,2} Globally, evidence has shown asthma prevalence to be greatest in developed countries, such as the UK, Australia, North, and South America.\textsuperscript{3,4} However, as developing countries begin to become more westernized and urbanized, the problem of asthma is beginning to increase in many of these regions.\textsuperscript{5,6} Despite medical advancements made towards more effective treatments, the problem of asthma continues to increase in prevalence.\textsuperscript{7} In recent years epidemiologic studies\textsuperscript{8,9} have linked vitamin D deficiency with an increase of asthma symptoms.

According to the Global Initiative for Asthma (GINA),\textsuperscript{10} asthma is defined as a chronic inflammatory disease of the airways resulting in bronchial constriction, hyper-responsiveness, and excessive mucus formation.\textsuperscript{10} Anti-inflammatory medications (eg, corticosteroids) are the mainstay of treatment against asthma considering inflammation is the key element in the pathophysiology of the disease. Vitamin D has demonstrated anti-inflammatory properties in many tissues, including lung tissue. It is theorized that vitamin D decreases certain proinflammatory molecules and mediators that attract and recruit various immune cells.\textsuperscript{11} Also, there is a study\textsuperscript{12} suggesting low vitamin D levels might
inhibit corticosteroid signaling pathways; therefore playing a critical role in corticosteroid resistance and overall control of asthma.

There has been numerous studies\textsuperscript{13-16} correlating lower serum 25-hydroxy-vitamin D with worse asthma control, decreased lung function, reduced corticosteroid response, more frequent exacerbations, and increased corticosteroid use, suggesting that supplementation of vitamin D levels in patients with asthma may improve several factors of asthma severity and treatment response. One prospective prebirth cohort study\textsuperscript{17} looking at higher maternal intake of vitamin D during pregnancy found that those with higher intake of vitamin D during pregnancy decreased the risk of wheezing in early childhood. Despite adequate epidemiologic studies linking vitamin D and asthma, there are few studies evaluating the affect of vitamin D supplementation on asthmatic patients. If vitamin D has the potential to play either a preventative or protective role against asthma, then supplementation could become part of standard therapy. This systematic review looks to answer the question; in asthmatic patients does the supplementation of oral vitamin D as an adjunct to standard therapy improve lung function when compared to standard therapy alone?

**METHODS**

An exhaustive search of available literature was performed using Medline-OVID, Medline-Pub-Med, Web of Science, and Google Scholar. Keywords used included: asthma, vitamin D, supplementation or dietary supplements, and airway function or respiratory functions tests. Additionally, the bibliographies of the studies were searched further for other pertinent sources. The search was then limited to include only studies done on humans and in the English language. Using the Grading of Recommendations,
Assessment, Development, and Evaluation (GRADE),\textsuperscript{18} all relevant articles were assessed for quality.

**RESULTS**

A total of 11 articles were reviewed for relevancy. After this review, three articles were shown to meet inclusion criteria. These articles included one double-blinded, randomized trial\textsuperscript{19} and two open-labeled, randomized comparative trials.\textsuperscript{20, 21} See Table I.

**Yadav et al**

In this randomized, double blinded, placebo-controlled trial\textsuperscript{19} researchers sought to investigate the therapeutic role of vitamin D supplementation in children with moderate to severe asthma in addition to standard therapy. Children were recruited from the respiratory and asthma clinic at Sharma University of Health Sciences in Rohtak, India. To be included in the study children had to have a diagnosis of moderate to severe asthma and be between 3-14 years in age. Children were excluded if they were currently on immunotherapy or anti IgE, had a history of premature birth (ie, <36 weeks gestation), required home oxygen use, had non-wheezy asthma, or showed clinical signs of vitamin D deficiency (eg, bony deformities or hypocalcemic symptoms).\textsuperscript{19}

A total of 100 asthmatic children who met the above criteria were randomized into two groups: the placebo group (n = 50) and the vitamin D group (n = 50). In addition to standard therapy, the placebo group received placebo powder in the form of glucose sachet and the vitamin D group received 60 000 IU of oral vitamin D3 per month for 6 months. Out of the 100 recruited patients, 10 from the placebo group and 8 from the vitamin D group were lost to follow up. Therefore, 82 patients completed the study. Overall, the groups were prognostically balanced with exception to the mean age of onset.
of asthma, which was much higher in the placebo group.\textsuperscript{19}

Randomization was done using sealed opaque envelope method. This was a double-blinded study, so both the researchers and the participants did not know which treatment group they were in. The primary outcome of the study was to measure the change in the level of severity of asthma according to GINA guidelines. Secondary outcomes measured were as follows: number of exacerbations during treatment period, change in the peak expiratory flow rate (PEFR), change in the steroid dosage, change in level of control, and number of emergency visits. Patients were required to follow up every month for 6 months in order to record the necessary outcomes.\textsuperscript{19}

For the following results a P value < 0.05 represents statistical significance. After 5 months there was no increase in asthma severity seen in the vitamin D group, while there was a small increase in asthma severity seen in the placebo group; this difference was not statistically significant. However, at 6 months the vitamin D group showed improvement in asthma severity that was statistically significant (P = 0.016). See Table II. There was statistically significant reduction in acute exacerbations seen in the vitamin D group compared to the placebo group (P = 0.011). See Table III. Significant improvement in the PEFR can be seen in both groups at all follow up visits up to 6 months, however the improvement made by the vitamin D group was significantly higher than the placebo group (P = 0.000). See Fig. I. Regarding change in steroid dosage, a statistically significant decrease in steroid dosing can be seen in the vitamin D group when compared to the placebo group (P = 0.013). See Fig. II. When looking at asthma control, both groups achieved control after 4 months of treatment, however at one month 35 patients in the vitamin D group were well controlled compared to 21 in the placebo
group (relative risk of 1.67 and a number-needed-to-treat of 4, \( P = 0.005 \)). See Table IV.

Lastly, in the first 3 months of treatment the number of emergency room visits demonstrated a statistically significant difference in favor of the vitamin D group (\( P = 0.015 \)). After the first 3 months of treatment no patients in either group were seen in the emergency room for asthma.\(^{19}\) See Table V.

The authors discussed two limitations. Firstly, not including measurements of serum vitamin D levels prior, during, and after the study was a major limitation to this study. Next, following the patients for a longer period of time would increase the significance of their findings.\(^{19}\)

**Nageswari et al**

This open labeled, randomized comparative trial\(^{20}\) investigated the effect of vitamin D3 supplementation in patients with mild to moderate persistent asthma by measuring the improvement in forced expiratory volume in 1 second (FEV\(_1\)). Patients were recruited from SRM Medical College Hospital and Research center in Tamil Nadu, India. Patients were required to be between 35-65 years old without comorbidities and have a diagnosis of mild to moderate persistent asthma at the time of the study. Patients were excluded from the study if they had a history of cardiac disorders, chronic obstructive pulmonary disease (COPD), hepatic or renal dysfunction, intolerance to vitamin D supplementation, or were currently pregnant or lactating. There were 63 patients who satisfied the above study criteria and were randomized into two groups: the usual care group (n=31) and the intervention care group (n=32). The groups were prognostically balanced with respect to age, BMI, gender, and education. Seven days prior to the study all patients were asked to stop using their prescribed anti-asthmatic
medications and use a salbutamol inhaler as rescue medication during that seven days. The usual care group patients received 400 \( \mu \)g of budesonide with 24 \( \mu \)g of formoterol daily by inhaler. The intervention care group received the same medications as the usual care group plus were instructed to take one 1000 IU vitamin D3 tablet orally every day. Patients in both groups were given permission to use a short acting \( \beta \)-agonist if having an acute asthma exacerbation.\(^{20}\)

Randomization was done using a computerized system. This was an open-label study, so both the researchers and the participants knew which treatment they were being administered. The primary outcome of the study was to measure pulmonary function by spirometry, specifically looking at the FEV\(_1\). This was measured at baseline and each scheduled follow-up: day 30, 60, and 90.\(^{20}\)

Significant improvement in the FEV\(_1\) was noted at every follow up visit for both treatment groups. However, in the intervention group there was significant improvement in percentage predicted FEV\(_1\) when compared to the usual care group. In the usual care group the percentage improvement in FEV\(_1\) after 90 days was 4.95 with a confidence interval (CI) of 0.2755-9.624. In the intervention group the percentage improvement in FEV\(_1\) after 90 days was 7.07 with a CI of 2.469-11.67.\(^{20}\) This difference was not statistically significant when comparing the two groups.

The authors discussed several limitations to this study; the first being the short duration. With the study lasting only 90 days they were unable to account for asthma exacerbations in the long-term control. Secondly, the study being open-label instead of blinded could be seen as a weakness, however the authors were not convinced this was a significant limitation. Not measuring the serum level of vitamin D3 prior to the study,
throughout, and after completion of the study was potentially the most significant
limitation to this study.\textsuperscript{20}

\textbf{Arshi et al}

This was a prospective, randomized, open-label study\textsuperscript{21} looking at airway function
in patients with mild to moderate persistent asthma following supplementation of vitamin
D in addition to standard therapy. Patients were enrolled from Rasool-e-Akram Hospital
in Tehran. To be included in the study patients needed to have a current diagnosis of
mild-moderate persistent asthma and between 10-50 years in age. Patients were excluded
from the study if they had a history of COPD, sarcoidosis, hyperparathyroidism,
nephrolithiasis, active tuberculosis, intolerance to vitamin D, liver failure, renal failure,
lymphoma, malignant tumors not in remission for more than 2 years; on current treatment
with anticonvulsants, vitamin D, systemic corticosteroid therapy up to 3 months before
the study; were pregnant or lactating; had baseline serum calcium level > 2.65 mmol/L;
had an asthma exacerbation up to 3 months prior to beginning of study; were actively
smoking; or demonstrated inappropriate use of asthma medication during the study. In an
effort to control outcomes only native Fars, patients living in Tehran were selected, to
eliminate known factors of vitamin D metabolism, such as skin color, diet, and exposure
to sun.\textsuperscript{21}

A total of 130 patients that met the above study criteria participated in the study.
These patients were randomized into two groups; the control group (n=66) and the
intervention group (n=64). Based on stage of asthma, the control group either was given
budesonide alone or budesonide plus formoterol, both in the form of dry powder inhaler.
The intervention group received the same medications as the control group plus a bolus
dose of 100 000 U of vitamin D intramuscularly followed by 50 000 U of oral vitamin D pearls weekly. There were 22 patients who were lost to follow up; therefore, a total of 108 patients completed the study. 

Randomization was done using consecutive random selection. Prior to randomization variables considered were as follows; age, sex, body mass index (BMI), stage of asthma, history of atopic dermatitis, allergic rhinitis, food allergy, serum IgE, FEV$_1$, ratio of FEV$_1$ to FVC, and serum vitamin D. There was no significant difference between the two groups with respect to these variables. This was an open-label study, so both researchers and participants knew which treatment they were being administered. The primary outcome of the study was to measure airway function by spirometry, using the FEV$_1$ and the ratio of FEV$_1$ to forced vital capacity (FVC). They also looked at the correlation between serum 25-hydroxy-vitamin D levels and the FEV$_1$ and the correlation between Δ vitamin D and Δ FEV$_1$. All outcomes were measured at baseline, 8, and 24 weeks. 

For the following results a P value < 0.05 represents statistical significance. After 8 weeks, the FEV$_1$ had a significant improvement in both groups (P = 0.001 in the control group and P < 0.001 in the intervention group), but when comparing the two groups there was no significant difference (P = 0.16). After 24 weeks, only the intervention group had a significant improvement in FEV$_1$ (P < 0.001 in the intervention group and P = 0.64 in the control group), so when comparing the two groups the FEV$_1$ was significantly higher in the intervention group (P < 0.001). When looking at the FEV$_1$/FVC ratio, the intervention group had significant improvement after 8 and 24 weeks (P = 0.002 after 8 weeks and P = 0.001 after 24 weeks). The control group only had significant
improvement in the FEV₁/FVC ratio after 24 weeks (P = 0.48 after 8 weeks and P = 0.001 after 24 weeks). This reveals no significant difference between the two groups with respect to FEV₁/FVC ratio (P = 0.73 after 8 weeks and P = 0.06 after 24 weeks). Lastly, in looking at the correlation between serum vitamin D and FEV₁, it can be seen there was a positive correlation between the two prior to the study beginning (P = 0.001, r = 0.272). Then, after 8 weeks of treatment, a negative correlation is seen between vitamin D and FEV₁ without any significant difference (P = 0.25, r = -0.063). However, after 24 weeks the data shows again a positive correlation between the two with a significant difference (P < 0.001, r = 0.336). Also, the researchers decided to look at the correlation between Δ serum vitamin D and Δ FEV₁ after 8 and 24 weeks. The results show a positive correlation after both 8 and 24 weeks with only a significant difference seen after 24 weeks (P=0.33, r = 0.092 after 8 weeks and P < 0.001, r = 0.543 after 24 weeks).²¹

The authors found the most important limitations of this study to be the small sample size and the high mean BMI of the patients included in the study. However, there was not a significant difference between the two groups with respect to BMI. Another limitation discussed was not using a placebo for parallel control.²¹

DISCUSSION

There are approximately 300 million people worldwide currently living with asthma and if current trends continue, it is estimated this number may increase to 400 million by the year 2025.² The United States along with other countries is bound to feel the increasing burden in providing care for asthmatic patients. Today, evidence suggests that inhaled corticosteroids are the best treatment option for asthmatics,²² however evidence also shows that this current recommended pharmacotherapy for asthma is not
achieving optimal asthma control.\textsuperscript{23,24} There have been numerous studies\textsuperscript{14-16,25-29} linking low levels of serum vitamin D with negative outcomes for patients with asthma. Despite sufficient evidence linking vitamin D with asthma, there is a limited amount of studies actually looking at the therapeutic role of vitamin D supplementation as an adjunct to asthma treatment.

This systematic review attempted to uncover three such studies\textsuperscript{19-21} that measured lung function following administration of vitamin D supplementation to standard therapy. Despite differences in length of study conducted and outcomes measured between the three studies, all three studies provided support that overall lung function improved with the addition of vitamin D to standard therapy. The articles when looked at collectively further supported each other’s findings, but also confirmed certain limitations to each study.

All three studies had limitations related to the lack of diversity in regard to the participants. Specifically, when looking at the age of included participants in these three studies, only one\textsuperscript{19} had included young children. Yadav et al\textsuperscript{19} looked solely at the effects of vitamin D supplementation in children, aged 3-14 years old. While Nageswari et al\textsuperscript{20} included patients ranging from 35-65 years old, and Arshi et al\textsuperscript{21} included patients ranging from 10-50 years old. This clearly is a limitation for both of these studies. Separating groups based on age would benefit future studies to determine what effect age may play in response to vitamin D supplementation. Also, a limitation that all three of these studies share is a lack of ethnic diversity among participants. Two studies\textsuperscript{19,20} included only patients from India and one study\textsuperscript{21} included only native Fars from Tehran. On a global scale, future studies would prove more beneficial if including a wide variety
of ethnic backgrounds to determine the differences in response to treatment based on ethnicity.

While the study conducted by Nageswari et al reported a greater improvement in the FEV₁ in the intervention group compared to the usual care group (7.07% increase vs. 4.95% increase) after 3 months, this improvement was not statistically significant.²⁰ After reviewing the other two articles,¹⁹,²¹ it can be seen that this study running a duration of 3 months was a major limitation. Arshi et al reported no difference between the two groups after 8 weeks, with respect to FEV₁ and correlation between serum 25-hydroxy-vitamin D levels and the FEV₁. It was only after 24 weeks that a significant difference can be seen between the two groups.²¹ Likewise, the Yadav et al study showed similar findings. Outcomes of asthma severity, change in PEFR, and change in steroid dosage all began to show statistical significance in improvement after 5 months of treatment when compared to the control group.¹⁹ Various studies³⁰-³² have demonstrated that different functions of vitamin D begin having their effect at different serum levels and looking at evidence from these three studies¹⁹-²¹ it is easy to hypothesize that it may take time for the body to reach a therapeutic level to see the desired effects of vitamin D. For this reason the Nageswari et al study and future studies would benefit from a longer treatment period.

Only one study²¹ measured the serum vitamin D levels prior to administration and at follow-ups. This was a major limitation for both the Yadav et al and Nageswari et al studies. Arshi et al reported positive and significant correlation after 24 weeks between serum vitamin D and FEV₁, as well Δ vitamin D and Δ FEV₁. Measurements of serum vitamin D levels allows for better control of variability within the study and provides evidence as to the appropriate serum vitamin D level to see the positive impact. Future
studies would be strengthened by measuring serum vitamin D levels throughout, as well as giving different doses of vitamin D to each group to determine the best effective dose of vitamin D.

Despite the limitations discussed previously and the need for stronger future studies, clinicians would not be taking any great risks, along as toxic levels of vitamin D are avoided, in applying the information gathered in these studies to their patients. Based upon the information gathered from all three studies it seems reasonable to supplement asthmatic patients with vitamin D at a starting dose greater than the recommended 600-800 IU daily\textsuperscript{33} and to assume that benefit is most likely noted after 6 months of therapy. Care should be taken prior to supplementation in that the patient vitamin D levels should be assessed, risk factors should be reviewed, and toxic doses should be avoided. Supplementation with vitamin D as adjunct to standard therapy is a safe and inexpensive option.\textsuperscript{34} For this reason, clinicians could enter into discussion with certain patients that may benefit from vitamin D supplementation as an adjunct to standard therapy.

**CONCLUSION**

Vitamin D has been demonstrated to have a significant role in the management of mild to severe asthma as an adjunct to standard treatment. Supplementing asthmatics with vitamin D has the potential to impact overall morbidity in a positive way. Despite the promising evidence established by these three studies, they were unable to assist in setting clear treatment guidelines that can be implemented in clinic practice today. These studies only further supported the need for improved future studies that include larger, randomized, placebo controlled trials. However, due to the low cost, low risk, and potential benefits of vitamin D supplementation as an adjunct treatment, it could be
considered for patients who are willing.
References


8. Litonjua AA, Weiss ST. Is vitamin D deficiency to blame for the asthma epidemic?


TABLE I: Grade evidence profile: Vitamin D supplementation as an adjunct treatment for asthmatics

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>Downgrade Criteria</th>
<th>Quality</th>
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<tr>
<td></td>
<td>Design  Limitations Indirectness Imprecision Inconsistency Publication bias likely</td>
<td></td>
</tr>
<tr>
<td>Yadav et al\textsuperscript{19}</td>
<td>RCT Serious\textsuperscript{a,b} Not Serious Not serious Not serious No bias likely</td>
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<tr>
<td>Nageswari et al\textsuperscript{20}</td>
<td>RCT Very Serious\textsuperscript{a,b,c,d,e} Not serious Not serious Not serious No bias likely</td>
<td>Low</td>
</tr>
<tr>
<td>Arshi et al\textsuperscript{21}</td>
<td>RCT Very Serious\textsuperscript{a,b,c,d,e} Not serious Not serious Not serious No bias likely</td>
<td>Low</td>
</tr>
</tbody>
</table>

a. Did not assess vitamin D levels  
b: Lack of allocation concealment  
c: Lack of blinding  
d: Length of study is less than 6 months  
e: Lack of representation of diverse ethnicities
Summary of Findings

Table II: Level of severity of the patients in the two groups (Yadav et al19)

<table>
<thead>
<tr>
<th>Level of severity</th>
<th>Placebo group (n = 50)</th>
<th>Vitamin D group (n = 50)</th>
<th>P value</th>
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<td></td>
<td>Mild</td>
<td>Moderate persistent</td>
<td>Severe persistent</td>
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<tr>
<td>0 mo</td>
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<tr>
<td>1 mo</td>
<td>0</td>
<td>41</td>
<td>9</td>
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<tr>
<td>2 mo</td>
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<td>4 mo</td>
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<td>5 mo</td>
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<tr>
<td>6 mo</td>
<td>9</td>
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Table III: Number of exacerbations during treatment period (Yadav et al19)

<table>
<thead>
<tr>
<th>Number of exacerbations during treatment period</th>
<th>Placebo group (n = 50) (%)</th>
<th>Vitamin D group (n = 50) (%)</th>
<th>P value</th>
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</thead>
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<tr>
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<td>36 (72.0)</td>
<td>0.011 (S)</td>
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<td>8 (16.0)</td>
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<tr>
<td>4</td>
<td>1 (2.0)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

Fig. I: Mean PEFR in the two groups (Yadav et al19)
Fig. II: Mean steroid dose in the patients of the two treatment groups (Yadav et al19)

Table IV: Level of control of the patients in the two groups (Yadav et al19)

<table>
<thead>
<tr>
<th>Level of control</th>
<th>Placebo group (n=50)</th>
<th>Vitamin D group (n=50)</th>
<th>P value</th>
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<tr>
<td></td>
<td>Well controlled</td>
<td>Not well controlled</td>
<td></td>
</tr>
<tr>
<td>1 mo</td>
<td>21</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>2 mo</td>
<td>37</td>
<td>13</td>
<td>0.005 (S)</td>
</tr>
<tr>
<td>3 mo</td>
<td>43</td>
<td>7</td>
<td>0.220 (NS)</td>
</tr>
<tr>
<td>4 mo</td>
<td>50</td>
<td>0</td>
<td>0.538 (NS)</td>
</tr>
<tr>
<td>5 mo</td>
<td>50</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6 mo</td>
<td>50</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Table V: Mean number of emergency visits of the patients in the two groups (Yadav et al19)

<table>
<thead>
<tr>
<th>Follow up</th>
<th>Placebo group (n=50)</th>
<th>Vitamin D group (n=50)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of emergency visits</td>
<td>1 mo 0.70±0.564</td>
<td>0.31±0.517</td>
<td>0.015 (S)</td>
</tr>
<tr>
<td></td>
<td>2 mo 0.30±0.516</td>
<td>0.14±0.354</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 mo 0.18±0.446</td>
<td>0.10±0.297</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 mo 0.00±0.000</td>
<td>0.00±0.000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 mo 0.00±0.000</td>
<td>0.00±0.000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 mo 0.00±0.000</td>
<td>0.00±0.000</td>
<td></td>
</tr>
</tbody>
</table>