Original research

Effect of vitamin D supplementation on asthma control in patients with vitamin D deficiency: the ACVID randomised clinical trial

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ABSTRACT

Background The relationship between asthma and vitamin D deficiency has been known for some time. However, interventional studies conducted in this regard have shown conflicting results.

Objective To evaluate the efficacy of vitamin D supplementation in asthmatic patients in improving the degree of control of asthma.

Methods Randomised, triple-blind, placebo-controlled, parallel-group study in adult asthmatic patients with serum 25-hydroxyvitamin-D_3 <30 ng/mL. The intervention group received oral supplementation with 16 000 IU of calcifediol per week, and the control group had placebo added to their usual asthma treatment. The study period was 6 months. The primary endpoint was the degree of asthma control as determined by the asthma control test (ACT). Secondary endpoints included quality of life measured using the mini Asthma Quality of Life Questionnaire, the number of asthma attacks, oral corticosteroid cycles, the dose of inhaled corticosteroids, number of emergency visits, unscheduled consultations with the primary care physician and hospitalisations for asthma.

Results One hundred and twelve patients were randomised (mean age 55 years, with 87 (78%) being women). Of the 112 patients, 106 (95%) completed the trial. Half the patients (56) were assigned to the intervention group and the other half to the control group. A statistically significant clinical improvement was observed in the intervention group (+3.09) compared with the control group (−0.57) (difference 3.66 (95% CI 0.89 to 5.43); p<0.001) as measured using ACT scores. Among the secondary endpoints, a significant improvement in the quality of life was found in the intervention group (5.34), compared with the control group (4.64) (difference 0.7 (95% CI 0.15 to 1.25); p=0.01).

Conclusion Among adults with asthma and vitamin D deficiency, supplementation with weekly oral calcifediol compared with placebo improved asthma control over 6 months. Further research is needed to assess long-term efficacy and safety.

Trial registration number NCT02805907.

Key messages

What is the key question?

► The key question is whether calcifediol supplementation in asthmatic patients who have serum vitamin D deficiency improves asthma control.

What is the bottom line?

► In adults with asthma and vitamin D deficiency, weekly oral calcifediol supplementation improves asthma control when compared with placebo.

Why read on?

► There are no randomised clinical trials to evaluate calcifediol supplementation in which all asthmatic patients have serum vitamin D deficiency. In this work, all asthmatic patients included have such a deficiency, and this group could benefit from supplementation with calcifediol.

INTRODUCTION

There are several studies of children and adults indicating that low vitamin D serum levels in asthmatic patients correlate with poorer asthma control, poorer lung function, decreased response to glucocorticoids and frequent exacerbations.[1–4]

Specific vitamin D receptors are distributed in a variety of tissues and immune cells, including the respiratory tract.[5] In addition, other molecular discoveries that have been appearing over the last few years support several possible mechanisms by which vitamin D could influence asthma, including its influence on innate immunity,[6] adaptive immunity,[7] regulatory T cells,[8 9] improving the response to treatment with corticosteroids[7 9 10] and decreasing airway remodelling.[11]

However, there are not many randomised clinical trials (RCTs) in this field, especially in adults, and the outcomes of those that exist show different results. Nevertheless, a Cochrane review of vitamin D and asthma trials was found showing great heterogeneity in the methods, using different population samples, objectives, protocols and highly variable vitamin D supplementation guidelines.[12]

Having properly designed clinical trials would clarify whether there is a causal relationship between vitamin D supplementation and improvement in asthmatic patients. For this reason, we conducted a study with a triple-blind RCT design, the results of which could help to

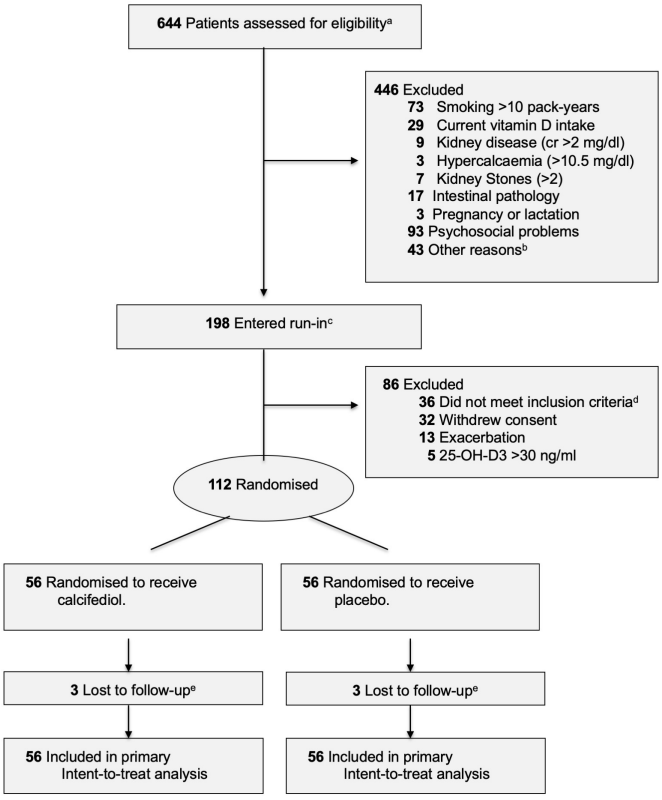

Figure 1 [a]Patients selected from list of patients (hospitalised o consulted in emergency department in 2013–2014). [b]Not possible to contact patients. [c]Patients contacted by phone, requested informed consent orally and sent blood test. [d]Most common reasons were not finding a diagnosis of asthma in the documented medical history either through reversibility in the bronchodilator test (forced expiratory volume in the first second (FEV_1) ≥12% following 400 µg (four puffs) of salbutamol) or airway hyperresponsiveness (provocative concentration of methacholine, decreasing FEV_1 by 20% (PC20)* <8 mg/mL if not receiving inhaled corticosteroids or ≤16 mg/mL if receiving inhaled corticosteroids). [e]Causes of loss of patients during follow-up and after randomisation was unknown: it was no possible to contact patients by phone, nor did they go to the final visit. *PC20: provocative concentration of methacholine causing a 20% fall in FEV_1. 25-OH-D_3, 25-hydroxyvitamin-D_3.

determine whether vitamin D supplementation may be beneficial for asthma control.

METHODS

Trial design and participants

Our trial design was a prospective randomised, placebo-controlled, triple-blind study conducted at Hospital Morales Meseguer in Murcia, Spain. The aim was to study the degree of improvement in asthma control using vitamin D as an adjuvant treatment added to the usual asthma treatment. The patient enrolment period began in June 2016 and continued until February 2017. Before inclusion, qualifying patients provided signed informed consent.

Patients were selected from lists of patients who had been hospitalised at Morales Meseguer Hospital or who consulted in the emergency department at this hospital in 2013 and 2014 with bronchial asthma as a primary or secondary diagnosis. Subsequently, the clinical histories and reports of these patients were reviewed to detect exclusion criteria (figure 1).

The patients included were aged 18 or older. Exclusion criteria included smoking more than 10 packs a year (defined packets per year as the number of cigarettes smoked per day times number of years smoked divided by 20), current use of vitamin D supplements, the prevalence of kidney disease (defined as serum creatinine >2 mg/dL), hypercalcaemia (defined as serum calcium corrected with proteins >10.5 mg/dL), history of recurrent kidney stones (three or more episodes), presence of pathologies affecting the intestinal capacity to absorb vitamin D, pregnancy, breast feeding or severe psychosocial problems (such as dementia, alcoholism or other drug addictions, psychiatric disorders such as major active depression or schizophrenia).

After excluding patients who met any of these criteria, we telephoned all possible participants, explaining the objective and processes of the trial, inviting them to participate, and asking them for their informed consent orally at first. A request was then sent to have blood drawn during an in-person visit to the hospital medical office. During that visit, the participants signed a written informed consent.

The blood serum levels were measured using chemiluminescence (Siemens). Based on the results of the blood tests (excluding patients with serum levels 25-hydroxyvitamin-D_3 (25-OH-D_3) >30 ng/mL), the next step was to make sure that the patients met the criteria for a medical diagnosis of asthma. This includes evidence of either bronchodilator reversibility (forced expiratory volume in 1 s (FEV1) ≥12% following 400 µg—four puffs—of Salbutamol) or airway hyperresponsiveness (provocative concentration of methacholine, decreasing FEV1 by 20% (PC_{20}) <8 mg/mL if not receiving inhaled corticosteroids (ICS) or ≤16 mg/mL if receiving ICS).

Randomisation and blinding

For randomisation, numbers were generated by computer. The assignment of each patient to one of the groups was done by a system of opaque and numbered envelopes, safeguarded by the researchers. After opening the envelopes, the participants were assigned to group A or B without knowing which group would receive the placebo and which would receive vitamin D. The next step was to collect the initial data (baseline characteristics and parameters) and schedule a new appointment. Patients were assigned to each group using this method by the investigator on the randomisation visit. The visits were made by an endocrinologist and a pulmonologist.

To avoid errors associated with inadequate basic treatment, patients from both groups continued with their regular asthma treatment. The study's pulmonologist (who was blinded to the group assignment) reviewed and adjusted the patients' basal medication at the first visit, if necessary. Later, the patients continued to follow up with their usual doctor.

Intervention

The vitamin D supplement was a presentation of 16 000 IU of oral calcifediol in one ampoule per week (Hidroferol 266 µg, 1.5 mL). This dosage was chosen based on the guidelines from the Endocrine Society.[13] The placebo, also presented as one ampoule per week, was designed with the same internal consistency, flavour and with the same external appearance as the supplements. The laboratory that provided the ampoules labelled them A or B so that neither patients nor researchers knew whether they contained calcifediol or the placebo.

Study visits

All patients were observed for 6 months. During that time, the patients visited the hospital three times: for the randomisation visit and inclusion in the study, a baseline visit and a final follow-up visit after 6 months. Every month, they were also interviewed by phone during which time they were asked about therapeutic compliance, adverse events, asthma attacks, hospitalisations or unscheduled medical consultations for asthma. In addition, they were provided a phone number where they could directly contact the researchers if they had any questions or incidents.

Outcomes

The primary objective of the study was to monitor any changes in the asthma control scores between baseline to 6 months. These measurements are based on the asthma control test (ACT) which had been developed by Nathan *et al*[14] and validated in different populations[15] and with different measurement criteria. The ACT is a five-question survey self-administered by the patient. Answers are scored on a scale ranging from 1 (worst) to 5 (best), and adding up the scores ranges from 5 (poor control) to 25 (excellent control).

Cut-off scores were studied to establish a relationship with the global initiative for asthma (GINA) degrees of control and other criteria such as the expired fraction of nitric oxide) or spirometric function tests, concluding that a score equal to or greater than 20 is consistent with well-controlled asthma, a score between 16 and 19 with partially controlled asthma, and scores equal to or less than 15 with poorly controlled asthma.[16]

Likewise, a minimally significant difference was established, defined as the smallest difference in the test score that represents a clinically significant change in the patients whose value is equal to or greater than 3 points.[17]

Secondary endpoints included changes in 6 months prior to study vs the study period in average quality of life, measured with the validated Spanish version of the Mini Asthma Quality of Life Questionnaire (AQLQ),[18 19] self-administered by patients. The questionnaire evaluates four dimensions (symptoms, limitation of activities, emotional sphere and environmental stimulation) based on 15 questions rated 1 (always, worst) to 7 (never, better quality of life). A test score difference of 0.5 is considered of minimal importance, equal to or greater than 1 point as moderately significant, and equal or greater to 1.5 points as significant.[20]

Other secondary objectives were changes in the 6 months prior to the study vs the study period based on the following variables: dose of ICSs (classified as low, medium or high doses according to the GINA criteria), number of oral corticosteroid cycles, number of asthma attacks (defined according to GEMA as requiring an increased treatment dose for at least 3 days[21]), number of unscheduled visits with the primary care physician for asthma-related causes, number of emergency visits and number of hospitalisations due to asthma.

The information was extracted from the hospital's computerised medical records as well as what was self-reported by the patients.

Statistical analysis

The data analysis was performed based on intent to treat. To calculate the sample size, accepting an alpha risk of 0.05 and a beta risk of 0.2 (80% power), a total of 100 participants (ie, 50 patients in each group) was required to detect an absolute difference of 3 points in the ACT, considering the mean of 19 and an SD of±5. A loss rate of 7% of patients was estimated.

The baseline characteristics and results were expressed as percentages (%) for qualitative variables, while for quantitative variables results were expressed as mean (SD) or median IQR, depending on their distribution. The 95% CIs were calculated for the outcome endpoints.

To compare the means for paired data, the comparison between qualitative variables was performed using Pearson's χ^2 test or Fisher's exact test (two tailed). The comparison between quantitative and qualitative variables was performed using the Student's t-test or the Mann-Whitney U test, depending on whether the qualitative variable was distributed normally or not.

The final ACT score and Mini-AQLQ scores were compared between groups by analysing the covariance (ANCOVA) using the initial ACT score and the initial Mini-AQLQ score as a covariate, respectively. For the correlations between quantitative variables, Spearman's r was used, expressing it with the correlation coefficient and statistical significance. All tests were two sided and based on a significance criterion of $p<0.05$. Without formal adjustment for the number of secondary analyses that were performed, the secondary results should be considered exploratory. IBM's SPSS V.15.0 was used for the analysis.

Once these analyses were carried out and given the results obtained, a post hoc analysis was performed to assess the number of patients who achieved a significant improvement in their ACT score within each of the study groups (ie, achieving an increase of 3 or more points[17]). Similarly, the possible relationship between serum vitamin D levels and the ACT score was investigated, both at the beginning and the end of the study (see online supplemental 1).

RESULTS

Recruitment

Of the 644 total evaluated patients with the bronchial asthma diagnosis (obtained from the lists of patients hospitalised or with consultations in the emergency department in the previous 2 years), 198 possible participants were identified. After checking all the inclusion and exclusion criteria, 112 patients agreed to participate in the trial. These were randomised into two groups with 56 patients each. In each group, three patients were lost to follow-up. The reason for not continuing in the study after randomisation was lost to follow-up in all lost patients (figure 1). The researchers tried to contact with the patients by phone without success.

Baseline variables

At the start of the study, there were no differences in the characteristics of the patients belonging to each group. The mean age (SD) was 55 years (15.4), and 87 (78%) were women. The ACT score was 17.71 (4.54) points in the intervention group compared with 19.02 (4.59) points in the control group. Serum 25-OH-D_3 levels were 16.71 (6.71) ng/mL in the intervention group and 17.48 (5.72) ng/ml in the control group. The main baseline characteristics of patients are summarised in table 1.

Primary objective

After the 6-month follow-up period, with the addition of vitamin D or placebo to their specific asthma treatments, the primary results regarding the ACT score were as follows (table 2):

In control group the final mean score was 18.23 points and in the intervention group was 20.49 points (difference 2.26 (95% CI 0.35 to 4.18); p=0.02). The difference between the

Table 1 Baseline characteristics of randomised patients

	Calcifediol N=56	Placebo N=56
Age, mean (SD)	54.57 (15.83)	56.61 (15.00)
Women	40 (71.4%)	47 (83.9%)
BMI (kg/m^2)	28.21 (5.23)	29.83 (7.41)
Current smokers	3 (5.5%)	4 (7.1%)
Former smokers	11 (19.6%)	9 (16.1%)
No packets/year*	1.02 (2.13)	0.82 (1.69)
Degree of dyspnoea (MRC)†	1.43 (0.89)	1.34 (0.75)
Evolution of asthma (years)	21.29 (11.30)	18.61 (9.25)
Extrinsic asthma	39 (69.6%)	38 (67.9%)
Severity of asthma - no (%)		
Intermittent	5 (8.9%)	12 (21.4%)
Mild persistent	9 (16.1%)	11 (19.6%)
Moderate persistent	29 (51.8%)	27 (48.2%)
Severe persistent	13 (23.2%)	6 (10.7%)
Asthma control: ACT‡	17.71 (4.54)	19.02 (4.59)
Quality of life: Mini-AQLQ§	4.38 (1.62)	4.85 (1.96)
ICS dose¶ - no (%)		
Low	12 (21.4%)	18 (32.1%)
Medium	25 (44.6%)	26 (46.4%)
High	19 (33.9%)	12 (21.4%)
Oral corticosteroid cycles	1.02 (1.27)	1.02 (1.33)
No asthma attacks	1.18 (1.55)	1.14 (2.70)
No unscheduled visits primary care due to asthma	0.55 (1.03)	0.46 (1.55)
No emergency visits due to asthma	0.45 (0.81)	0.59 (1.30)
No hospitalisations due to asthma	0.11 (0.31)	0.13 (0.33)
25-OH-D$_3$ (ng/mL)	16.71 (6.71)	17.48 (5.72)
Protein corrected calcium (mg/dL)**	9.13 (0.36)	9.20 (0.25)
Ig E (ku/L), mean (SD)	259.75 (527.53)	243.54 (550.93)
FEV$_1$ (mL) (%)††	2524.93 (1046.66)‡‡ 88.50±16.25	2316.54 (778.00)§§ 90.17±11.21
FVC (mL) (%)††	3264.85 (1173.88)‡‡ 89.41±13.37	2954.04 (933.16)§§ 86.54±11.64
FEV$_1$/FVC (%)	76.99 (7.84)‡‡	78.40 (7.73)§§

*No packets/year=number cigarettes smoked per dayxNumber of years smoked/20.
†MRC (Medical Research Council) Dyspnoea scale=grade 0: 'I only get breathless with strenuous exercise'; grade 1: 'I get short of breath when hurrying on the level or walking up a slight hill'; grade 2: 'I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level'; grade 3: 'I stop for breath after walking about 100 yards or after a few minutes on the level'; grade 4: 'I am too breathless to leave the house' or 'I am breathless when dressing.
‡ACT (Asthma Control Test): Resulting score can oscillate between 5 (poor control) and 25 (excellent control). A score equal to or greater than 20 is very consistent with well-controlled asthma, a score between 16 and 19 with partially controlled asthma, and scores equal to or less than 15 with poorly controlled asthma.
§Mini-AQLQ (reduced version of the AQLQ): consists of 15 questions with a score of 1 (worst, very limited) to 7 (better, no limited), that evaluates four dimensions: symptoms, limitation of activities, emotional sphere and environmental stimulation.
¶ICS dose: according to the criteria defined by the global initiative for asthma. Available from: www.ginasthma.com
**Protein corrected calcium (mg/dL): total measured calcium/(0.6+(proteins/18.5)).
††The reference values of FEV1 and FVC were indexed by height and age, according to the reference values of the European Respiratory Society.
‡‡For the calcifediol group, the total number of patients reporting data were 53 for respiratory function tests (FEV1, FVC, FEV1/FVC). For other categories, the number of patients was 56.
§§For the placebo group, the total number of patients reporting data were 54 for respiratory function tests (FEV1, FVC, FEV1/FVC). For other categories, the number of patients was 56.
AQLQ, Asthma Quality of Life Questionnaire; BMI, body mass index; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; ICS, inhaled corticosteroids; 25-OH-D$_3$, 25-hydroxyvitamin-D$_3$.

initial and final ACT scores in each of the groups was analysed, with −0.57 in the control group and 3.09 in the intervention group (difference 3.66 (95% CI 0.89 to 5.43); (p<0.001). These results were significant after adjusting with the initial ACT score as covariate by ANCOVA (p<0001).

The number of patients needed to treat (NNT) with vitamin D to achieve a clinically significant improvement (increase ≥3 points in the ACT) was 3.73 (95% CI 2.25 to 10.88).

Table 2 Primary outcome asthma control test (ACT) scores among groups receiving placebo or calcifediol, at the beginning and end of the study

ACT scores				
	Calcifediol	Placebo	Mean difference, % (95% CI)	P value
Initial ACT (points)	17.71	19.02	−1.30 (−3.01 to 0.41)	0.13
Final ACT* (points)	20.49	18.23	2.26 (0.35 to 4.18)	0.02
ACT variation (points)	+3.09	−0.57	3.66 (0.89 to 5.43)	<0.001

*These results were significant after adjusting with the initial ACT score as covariate by ANCOVA (p<0001).
ANCOVA, analysing the covariance.

A post hoc analysis was conducted to investigate the number of patients who achieved a clinically significant improvement in the ACT (increase ≥3 points[17]) in each group, and it was significantly higher in the intervention group, with 31 patients (58.5%) than in the control group with 16 patients (32%) (p=0.003).

Secondary objectives

The main secondary endpoint results were as follows (table 3):

Serum level of 25-OH-D$_3$ in the intervention group was 58.72 ng/mL vs 17.38 ng/mL in the control group (difference 41.34 (95% CI 33.29 to 49.39); p<0.001). Within the intervention group, there were seven patients (13%) who did not achieve plasma levels of 25-OH-D$_3$ >30 ng/mL, and two patients (4%) in the control group who achieved levels >30 ng/mL.

With regard to the quality of life measured using the Mini-AQLQ, a statistically significant improvement was observed in the group receiving calcifediol supplementation compared with the placebo group. The mean value in the Mini-AQLQ at the end of the study was 5.34 in the intervention group and 4.64 points in the control group (difference 0.70 (95% CI 0.15 to 1.25); p=0.01). The mean variation between the total initial and final scores in the Mini-AQLQ was 1.05 in the intervention group and −0.09 points in the control group (difference 1.14 (95% CI 0.63 to 1.64); p<0.001). These results were significant after adjusting with the initial Mini-AQLQ score as covariate by ANCOVA (p<0001).

In some endpoints, a small but statistically significant difference was detected in favour of the group receiving vitamin D supplementation vs placebo. These endpoints were the number of oral corticosteroid cycles in the last 6 months (0.28 in intervention group vs 0.66 in the control group; difference −0.38 (95% CI −0.71 to −0.05); p=0.02); number of asthma attacks (0.34 in the intervention group vs 0.70 in the control group; difference −0.36 (95% CI −0.70 to −0.02); p=0.04); and the number of unscheduled visits with the doctor due to asthma-related causes (0.23 in the intervention group vs 0.62 in the control group; difference −0.40 (95% CI −0.73 to −0.07); p=0.02).

There was no significant difference in the final dose of ICSs: the number of patients with a low dose of ICS was 24 (45.3%) in the control group and 18 (34%) in the intervention group, with intermediate doses of 23 (43.4%) in the control group and 30 (56, 3%) in the intervention group, and with high doses of ICS for 6 (11.3%) in the control group and 5 (9.4%) in the intervention group (p=0.34). There were also no significant differences in the number of the emergency room visits (0.19 in control group vs 0.08 in intervention group; difference −0.11 (95% CI −0.26 to −0.04]; p=0.14) or hospitalisations for asthma (0.04

Table 3 Final endpoints of the groups receiving calcifediol and placebo

	Calcifediol N=53	Placebo N=53	Mean difference, % (95% CI)	P value
Mini-AQLQ*, mean (SD)	5.34 (1.29)	4.64 (1.56)	0.70 (0.15 to 1.25)	0.01
ICS dose† - no (%)				0.39
Low	18 (34%)	24 (45.3%)		
Medium	30 (56.6%)	23 (43.4%)		
High	5 (9.4%)	6 (11.3%)		
Oral corticosteroid cycles	0.28 (0.6)	0.66 (1.04)	−0.38 (−0.71 to −0.05)	0.02
No asthma attacks	0.34 (0.65)	0.70 (1.07)	−0.36 (−0.70 to 0.02)	0.04
No unscheduled visits primary care due to asthma	0.23 (0.54)	0.62 (1.08)	−0.40 (−0.73 to 0.07)	0.02
No emergency visits due to asthma	0.08 (0.27)	0.19 (0.48)	−0.11 (−0.26 to 0.04)	0.14
No hospitalisations due to asthma	0.04 (1.92)	0.04 (1.92)	0.0 (−0.07 to 0 to 07)	>0.99
25-OH-D_3 (ng/mL)	58.72 (28.69)	17.38 (6.83)	41.34 (33.29 to 49.39)	<0.001
Protein corrected calcium (mg/dL)‡	9.18 (0.40)	9.27 (0.33)	0.93 (−0.52 to 0.24)	0.21
Ig E (ku/L), mean (SD)	297.02 (562.40)	353.12 (964.45)	56.10 (−258.86 to 371.06)	0.72
FEV_1 (mL) (%)	2516.35 (1013.21)§ 89.70±16.61	2313.60 (792.78)¶ 89.70±10.90	202.75 (−561.08 to 155.59) 0.00 (−5.52 to 5.53)	0.26
FVC (mL) (%)	3272.31 (1177.63)§ 90.66±13.13	3000.80 (945.61)¶ 87.22±13.17	271.51 (−692.07 to 149.06) 3.44 (−8.58 to 1.70)	0.20
FEV_1/FVC (%)	87.06 (7.89)§	77.62 (7.14)¶	9.44 (31.67 to 12.79)	0.40

*Mini-AQLQ (reduced version of AQLQ): Consists of 15 questions with a score of 1 (worst, very limited) to 7 (better, no limited), that evaluates four dimensions: symptoms, limitation of activities, emotional sphere and environmental stimulation.
†ICS dose: according to the criteria defined by the Global Initiative for Asthma. Available from: www.ginasthma.com.
‡Protein corrected calcium (mg/dL): Total measured calcium/(0.6+(proteins/18.5)).
§For the calcifediol group, the total number of patients reporting data were 52 for respiratory function tests (FEV_1, FVC, FEV_1/FVC). For other categories, the number of patients was 53.
¶For the placebo group, the total number of patients reporting data were 51 for respiratory function tests (FEV_1, FVC, FEV_1/FVC). For other categories, the number of patients was 53.
AQLQ, Asthma Quality of Life Questionnaire; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; ICS, inhaled corticosteroids; 25-OH-D_3, 25-hydroxyvitamin-D_3.

in control group vs 0.04 in intervention group; difference 0.0 (95% CI −0.07 to −0.07); p>0.99).

A post hoc analysis was performed to assess the possible relationship between serum vitamin D levels and the ACT score, both at the beginning and the end of the study (figure 2); observing that the worse the level of control, the lower the levels of vitamin D. Thus, the group of patients with poor initial control (ACT <16) presented a 25-OH-D_3 mean (SD) value of 14.83 (4.80) ng/mL, while the partially controlled patients (ACT 16–19) had a mean plasma vitamin D level of 16.88 (5.90) ng/mL and patients with good control (ACT >20) had a mean level of 18.48 (6.80) ng/mL, this being statistically significant (p=0.04). At the start of the study, a moderate correlation was observed between asthma control and 25-OH-D_3 levels (r=0.45; p=0.01).

Similarly, at the end of the study, patients with poor control (ACT <16) had a 25-OH-D_3 mean value of 18.62 (10.59) ng/dl, partially controlled patients (ACT 16–19) had a value of 37.10 (29.59) ng/dl and patients with good final control (ACT >20) had a value of 44.72 (30.80) ng/dl; (p=0.001). At the end of the study, a moderate correlation was also observed between serum 25-OH-D_3 levels and ACT (r=0.31, p=0.01).

It is important to highlight that there was no loss of data in either of the two groups, neither in the main variable nor in the secondary ones. Although there were some data losses concerning respiratory function tests, it is not relevant to report those.

Adverse events

No serious side effects were observed during the trial. The type of adverse reaction most frequently reported by the patients was of a gastrointestinal nature, although there were no significant differences between patients receiving placebo (two patients, 3.8%) and those receiving vitamin D (three patients, 5.7%) (p=0.65).

There were no cases of confirmed hypercalcaemia, renal colic or death in either group during the study.

DISCUSSION

Among adults with asthma and vitamin D deficiency, supplementation with oral calcifediol compared with placebo, improved asthma control at 6 months of follow-up. To our knowledge, only a few RCTs have been conducted among adults regarding this issue. We reviewed four of those that we found most interesting,[22–25] of which three were double blind and one had an open design.[22] In all of these studies, within the primary or secondary objectives, some beneficial association was observed in the group of patients receiving vitamin D compared with the placebo group.

In the VIDA study,[23] although the researchers did not find significant differences in their main outcomes (reduction of the rate of first treatment failure or exacerbation by adding vitamin D to ICS), they described a small but significant association in the decrease of the overall dose of ciclesonide required to

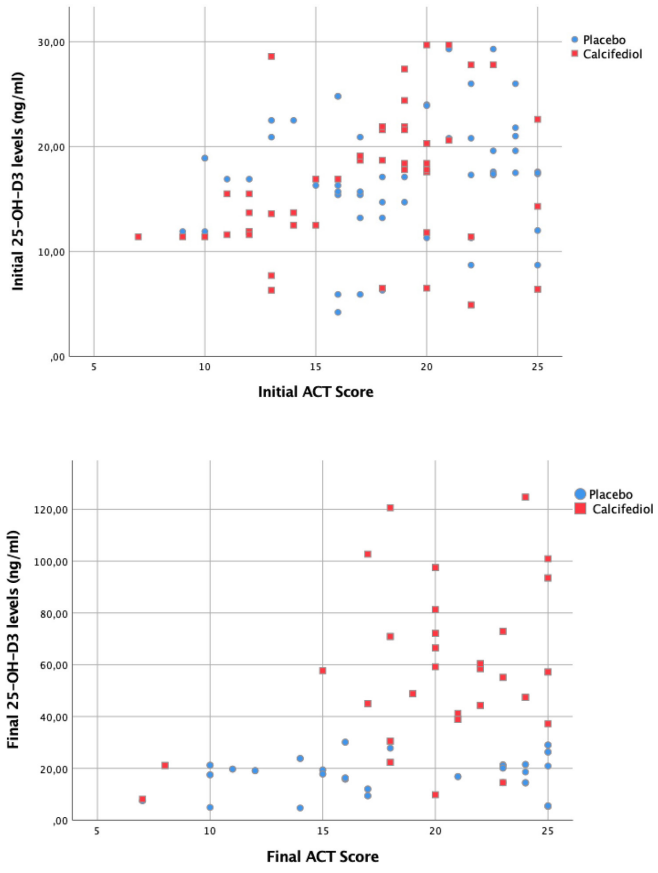

Figure 2 Serum 25-OH-D_3 according to the degree of asthma control, at the start of the study (A) and the end of the study (B). (A) At the start of the study, a moderate correlation was observed between asthma control and 25-OH-D_3 levels (r=0.45; p=0.01). (B) At the end of the study, a moderate correlation was also observed between serum vitamin D levels and asthma control (r=0.31, p=0.01). 25-OH-D_3, 25-hydroxyvitamin-D_3.

maintain asthma control in the vitamin D group (111.3 μg/day) vs in the placebo group (126.2 μg/day).

In the ViDiAs study,[25] researchers also found no significant difference in the reduction of asthma attacks nor of viral upper-respiratory infections (coprimary outcomes) associated with the use of vitamin D. However, within the secondary objectives they found a significant association in improving quality of life, measured with the St George Respiratory Questionnaire.[26] In the study by Arshi *et al*,[22] an improvement was observed in pulmonary function tests (primary endpoint). Meanwhile, in the work of de Groot *et al*,[24] a reduction was found in the percentage of eosinophils in sputum induced in patients with higher eosinophilic proportions in the sputum, as their primary objective.[27]

The data shown in table 1 could suggest an imbalance in the characteristics of each group, but no significant differences were found between the groups. However, the data show slightly worse control as measured by ACT, worse quality of life as measured by Mini-AQLQ, greater severity of patients, and therefore use of higher doses of corticosteroids in the group that received calcifediol. However, the results obtained were better in the intervention group, wich could support the efficacy obtained with calcifediol.

The inclusion criteria regarding serum vitamin D deficiency were different in the RCTs discussed. Only in the VIDA study[23] did all patients selected have serum vitamin D deficiency (<30 ng/mL), while in the other three studies[22 24 25] patients with and without vitamin D deficiency were selected.

In the design of our study—and since the primary endpoint was to assess the efficacy of vitamin D_3 supplementation in the control of asthma measured with the ACT—we considered it essential that all patients enrolled had serum vitamin D deficiency.

To achieve clinically significant improvement in the ACT, the NNT with vitamin D supplements was 3.73 patients. In a disease like bronchial asthma with moderate prevalence in adults and some very important clinical and economic consequences, we consider the NNT of 3.73 to be excellent efficacy data, also keeping in mind the low cost of vitamin D supplements, in addition to its convenient administration and the scarcity of adverse effects.

As secondary objectives, although they should be considered exploratory, they would serve to support the result obtained in our main objective of improving asthma control by adding calcifediol supplements. And so, a statistically significant association was observed between vitamin D supplementation and the majority of quality of life assessed with the Mini-AQLQ, these results match those described recently in ViDiAs study (25).

We also found a minimal but statistically significant difference in the number of asthmatic exacerbations presented in both groups throughout the study in favour of the group supplemented with calcifediol and in the number of unscheduled consultations with the primary care physician for asthma. These results are not clinically significant, partly due to the short time of the follow-up period.

Keeping in mind that the degree of control of asthma determines the current situation and conditions the future risk of exacerbation, it would be logical to think that with the significant improvement of the control that we found, a greater reduction in the number of exacerbations could be observed in the long term. This would probably require a larger sample size and a longer follow-up period since our study had a follow-up period of 6 months, which is often insufficient to demonstrate differences in the number of exacerbations in the studies.

No significant differences were found in the final ICS dose between the two groups at the end of the study. This was probably related to the design of our study, which had an initial and a final visit, without intermediate reviews to be able to give patients indications to reduce the ICS dose in the event of good control of the disease.

In contrast, we found a small but significant difference in the number of oral corticosteroid cycles that would support our final outcome as, by improving asthma control, patients would require fewer oral corticosteroids cycles to remain asymptomatic.

The supplementation of vitamin D used was calcifediol, as opposed to cholecalciferol used in most published RCTs with vitamin D. This is due to calcifediol being the most widely prescribed in our setting with which we have more experience in our daily clinical practice, and due to the existence of some studies supporting its greater efficacy inducing a more rapid and sustained increase of serum 25-OH-D_3 levels.[28] It is not possible to know if the results could have vary according to the type of vitamin D used.

As previously commented, in a post hoc analysis carried out, we found a statistically significant relationship between the degree of asthma control and serum 25-OH-D_3 levels in that the better the degree of disease control, the higher the plasma vitamin D level. This was confirmed at both the beginning and the end of the study (figure 2). These results are similar to those of other published studies.[29 30] This post hoc analysis could suggest

that, despite achieving 25-OH-D_3 levels higher than 30 ng/dL, the patients only have partial control of asthma according to the ACT score. Vitamin D levels could play an important role in asthma control in patients with serum deficiency. However, vitamin D is not the only factor that determines asthma control. For this reason, patients with poor control despite adequate vitamin D levels should be evaluated individually to determine the cause of poor asthma control.

There are many doubts still unresolved in published studies on vitamin D and asthma, so further research should be conducted. In addition, the published studies present very different designs, objectives, follow-up periods and guidelines for vitamin D, which makes it difficult to compare the studies and to carry out future systematic reviews and meta-analyses. It would be useful to standardise the studies to obtain reliable conclusions and to be able to determine whether vitamin D supplementation improves the results related to asthma in adults. It would be interesting to define if there are subpopulations of asthmatic patients that would benefit the most and to establish the most adequate supplementatnio guidelines.

Limitations

This study had several limitations. First, the short follow-up period which, although similar to other clinical trials described, was limited. Its length could not be extended due to limitations imposed by the hospital's ethics committee. With a longer follow-up period, we might have had different results, and it would have allowed us to create a design in which the ICS dose could have been reduced in patients who had achieved good asthma control. A follow-up period of 12 months would also have reduced the influence of the seasons of the year, especially in patients with extrinsic asthma.

Second, the number of participants represents a small sample from a single hospital in Spain, which could imply a lower external validity of the results.

Third, we selected asthmatic patients with any degree of severity. Probably, if we had only selected patients with moderate or severe asthma, the differences would have been greater, because the percentage of poorly controlled patients would be higher. However, the inclusion of all stages of severity in a proportion similar to those existing in routine clinical practice approximates the results that could be obtained when using vitamin D supplementation in all patients with serum vitamin D <30 ng/mL.

Fourth, there is a possible recall bias by patients, because intermediate data, such as an electronic diary, were not collected, also due to the use of self-administered questionnaires. Even so, the follow-up period was not very long and the patients had a contact telephone number available during the follow-up period.

Fifth, data on dietary intake of vitamin D and the patients' number of hours of sun exposure was not collected, which may have influenced the final value of plasma 25-OH-D_3, as two patients in the placebo group obtained serum 25-OH-D_3 >30 ng/mL levels at the end of the trial. However, it is more similar to what occurs in daily clinical practice, as it is usually difficult to measure and collect it.

CONCLUSION

Among adults with asthma and vitamin D deficiency, supplementation with weekly oral calcifediol compared with placebo improved asthma control at 6 months. Further research is needed to assess long-term efficacy and safety.

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