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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► Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2019-213936).

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Received 22 October 2019
Revised 6 October 2020
Accepted 10 October 2020
Published Online First 5 November 2020

To cite: Andújar-Espinosa R, Salinero-González L, Illán-Gómez F, *et al*. *Thorax* 2021;**76**:126–133.

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

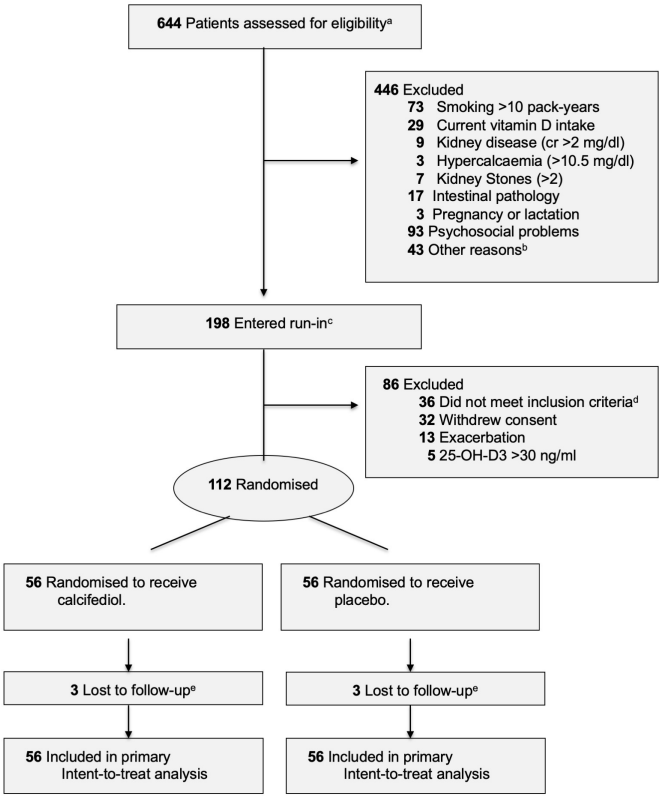

Figure 1 [a]Patients selected from list of patients (hospitalised o consulted in emergency department in 2013–2014). [b]Not possible to contact patients. [c]Patients contacted by phone, requested informed consent orally and sent blood test. [d]Most common reasons were not finding a diagnosis of asthma 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

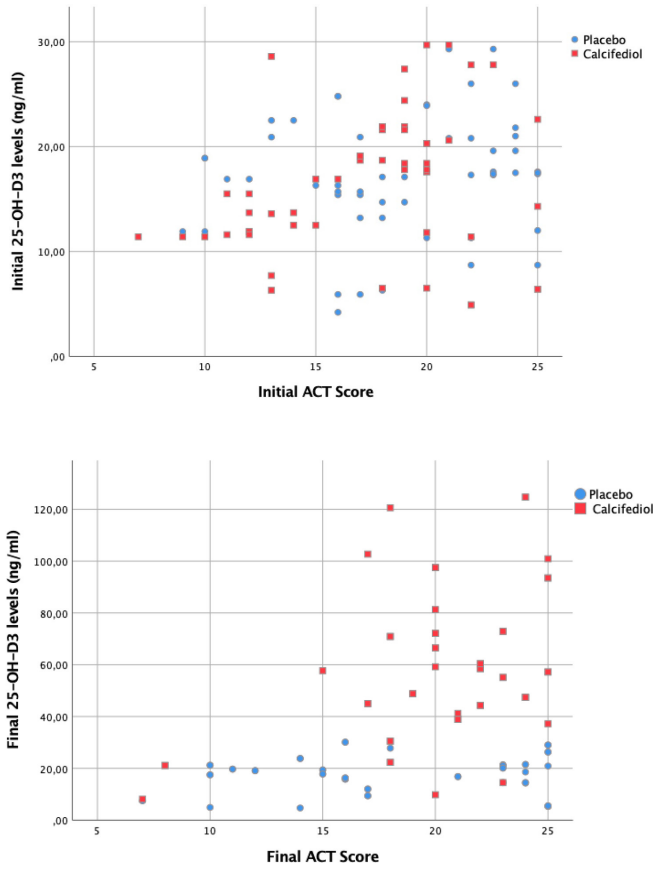

Figure 2 Serum 25-OH-D_3 according to the degree of asthma control, at the start of the study (A) and the end of the study (B). (A) At the start of the study, a moderate correlation was observed between asthma control and 25-OH-D_3 levels (r=0.45; p=0.01). (B) At the end of the study, a moderate correlation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

Acknowledgements We thank Andrés Carrillo, MD, PhD (Intensive Medicine, Hospital Morales Meseguer, Murcia, Spain) for his support and advice. Carrillo MD, PhD did not receive any compensation for his role in the study.

Contributors LS-G and RA-E had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: LS-G, RA-E and FI-G. Acquisition, analysis, or interpretation of data: LS-G, LS-G, FI-G and MC-M. Drafting of the manuscript: LS-G, RA-E and FI-G. Critical revision of the manuscript for important intellectual content: LS-G, RA-E and FI-G. Statistical analysis: LS-G and RA-E.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Disclaimer The researchers of the study have not received any funding. The only contribution has been made by the pharmaceutical company FAES FARMA, which provided the ampoules of vitamin D and placebo so that the study could be carried out without influencing the development or analysis of the results obtained from the study.

Competing interests All authors have completed and submitted the ICMJE for disclosure of potential conflict of interest. Outside the submitted work, RA-E reports personal fees and non-financial support from AstraZeneca, personal fees and non-financial support from Boehringer Ingelheim, personal fees and non-financial support from Chiesi, personal fees and non-financial support from Orion Pharma, personal fees and non-financial support from MundiPharma, personal fees and non-financial support from Novartis, personal fees and non-financial support from Menarini, personal fees and non-financial support from FAES Pharma, personal fees from Ferrer, personal fees and non-financial support from Zambon. Outside the submitted work, LS-G reports personal fees and non-financial support from Lilly, personal fees and non-financial support from Novo Nordisk, personal fees from AstraZeneca, personal fees and non-financial support from Sanofi, personal fees from Lacer, personal fees from Casen Recordati, personal fees and non-financial support from Jansen-Cilag, personal fees and non-financial support from Nutricia, personal fees and non-financial support from Nestlé, personal fees from Abbott and personal fees and non-financial support from Fresenius-Kabi. Outside the submitted work, FI-G reports non-financial support from Novo Nordisk, personal fees and non-financial support from Lilly, personal fees and non-financial support from Sanofi, personal fees from Abbott and personal fees from AstraZeneca. MC-M reports personal fees from AstraZeneca and Chiesi. CH-Y reports personal fees from Boehringer Ingelheim, outside the submitted work.

Patient consent for publication Not required.

Ethics approval The study was approved by Morales Meseguer Hospital's ethics committee for clinical research on 29 April 2015 (approval number 18/15).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information. The analysed data included the patients included in the study. All relevant data have been published in this article.

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eAppendix. ACVID Study Protocol

Salinero-González L, Andújar-Espinosa R, Illán-Gomez F, Hu-Yang C., Castilla-Martínez M, Ruiz-López FJ. Murcian Health Service, Murcia, Spain. Efficacy of vitamin D in the control of asthma in asthmatic patients with vitamin D deficiency: The ACVID randomized clinical trial.

ACVID (Asthma Control with Vitamin D Supplementation)

Study protocol

2015

A study to determine if the addition of vitamin D is superior to placebo in vitamin D insufficient asthma patients with persistent symptoms in improving the degree of asthma control

Table of Contents

1. Justification of the study.

Inhaled corticosteroids (ICS) are the main treatment for persistent asthma and a large part of patients are treated successfully with such therapeutic agents (1). However, there is a great variability in response to ICS, with a large group of subjects who do not get an adequate control of their respiratory disease (1-3).

For this purpose, different therapeutic alternatives have been searched, such as the possible role of vitamin D.
This theory initially emerged after finding that the specific receptors of vitamin D (VDR) were distributed in a variety of tissues and immune cells, including the airway. Later, numerous observational studies have emerged and showed an association between plasmatic 25-OH-D3 levels and asthma severity and the number of asthma exacerbations, both in children and adults.

Few randomized clinical trials (RCTs) have been carried out in this sense, and they found different results; which probably may due to the great heterogeneity in the design of the studies, using different sample populations, objectives, protocols and vitamin D preparations.

The availability of properly designed clinical trials would help to clarify whether there is a causal link between asthma and vitamin D. So, this is why we have designed this study, with which carry out a triple-blind RCT, whose results could provide good quality of evidence to determine if vitamin D supplementation may help in improving asthma control.

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2. Vitamin D: classical and nonclassical actions.

Vitamin D has been traditionally linked to phospho-calcium metabolism and maintenance of bone health, but for some years have aroused great interest in its possible extra-skeletal actions, such as potential role in promoting the immune system and participating in certain respiratory diseases, including asthma.

2.1. Classical actions of vitamin D.

In human, vitamin D comes from two main sources: orally, by eating vitamin D- enriched food, and by a cutaneous route, in which the hormone is synthesized from 7-dehydrocholesterol after exposure to UV rays.
This latter route has been considered the main way to get vitamin D, but in recent years and due to a variety of changes in lifestyle, such as the increased use of sunscreens and less sun exposure, have led to increasingly more important dietary sources of vitamin D. These sources are fortified cereals, dairy products, fish oils and egg yolks.

Regardless of origin, either digestive or skin, vitamin D enters the circulation bound to its binding protein (VDBP), a globulin that is synthesized in liver. About 88% of 25-OH-D3 circulates bound to VDBP, 0.03% is in free state and the rest circulates bound to albumin.

This complex (vitamin D-VDBP) travels to liver, where it undergoes a 25-hydroxylation by CYP27A1 enzyme, resulting in 25-hydroxyvitamin D (25-OH-D3), which is the main circulating and storage form of vitamin D.
The half-life of 25-OH-D3 is 2-3 weeks, but may be shortened as concentrations of VDBP are reduced, as may occur when increased urinary losses in nephrotic syndrome.

The second hydroxylation necessary for the active form of vitamin D, the 1,25-dihydroxyvitamin D (1,25-OH-D3) or calcitriol, occurs in kidney and is

conducted by the enzyme CYP27B1 or 25-OH-D3-1alfa hydroxylase. This enzyme is an oxidase which is tightly regulated in cells of the proximal renal tubule, being stimulated by parathyroid hormone (PTH), and inhibited by calcium and 1,25-OH-D3.

The main route of inactivating vitamin D metabolites is by hydroxylation, carried out by the vitamin D-24-hydroxylase or CYP24A1, an enzyme that is expressed in almost all tissues. This enzyme is induced by 1,25-OH-D3, thus promoting its own inactivation and thus limiting its biological effects.

Actions of 1,25-OH vitamin D.

This active form of vitamin D performs its biological effects by binding to a member of the superfamily of nuclear receptors, the vitamin D receptor (VDR).

As 1,25-OH-D3 enters into the cell, it binds to the nuclear VDR and forms a heterodimer with the retinoid X receptor (RXR). The complex vitamin D-VDR-RXR then binds to a response element vitamin D (VDRE) within the genome of the cell, and starts a large transcriptional complex that can activate or repress transcription of certain genes, depending on the composition of the transcriptional complex.

2.2. non-classical actions of vitamin D.

The discovery of VDR in numerous tissues (4), has suggested that this vitamin could play functions out of phospho-calcium metabolism and that receptors could be activated by different ligands (5).

It has also been described the CYP21B1 activity in numerous extra-renal cells, which facilitate the activation of 25-OH-D3, transforming into its active form 1,25-OH-D3 (6).

The binding of vitamin D to its specific receptor regulates transcription of 200 genes involved in numerous functions, such as regulation of cell growth and maturation, inhibiting the renin-angiotensin axis and angiogenesis, the secretion of insulin and the sensitivity to it.

Therefore, it has been studied the association of vitamin D with numerous pathologies, finding associations between that vitamin and certain neoplasms, and cardiovascular, pulmonary, metabolic and autoimmune diseases.

Within these extra-bone actions of vitamin D, and due to the objective of this work, we will focus on the major studies conducted between vitamin D and asthma (section 4).

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3. Vitamin D deficiency and supplementation.

3.1. Vitamin D deficiency

3.1.1. Definition of vitamin D deficiency

Nowadays there is no unanimous consensus on the optimal plasma levels of vitamin D and the definition of vitamin D deficiency (7, 8).

A large majority of experts believe that the level should be equal to or greater than 30ng/ml, to promote bone and extra-bone health (7, 9-12); although there is a great debate about this, considering even than for extra-bone health should probably be recommended higher values.

In 2011, the IOM (Institute Of Medicine) published the definition of vitamin D deficiency in serum levels of 25-OH-D_3 less than 20 ng/ml (13). And later in the same year, the US Endocrine Society (14) published their clinical guidelines about the management of vitamin D deficiency, using the cutoff value lower than 30 ng/ml.

The vast majority of scientific societies, including the IOF (International Osteoporosis Foundation) (15) also defines this deficit with plasma levels of 25-OH-D3 below 30ng/ml.

3.1.2. Epidemiology of vitamin D deficiency

It is believed that vitamin D deficiency is an "epidemic" worldwide, affecting more than half of the population (16, 17) and including children, youth, adults, and elderly people; especially if they have osteoporotic fractures, where the prevalence of low 25-OH-D3 reaches almost 100%.

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In a systematic review published in 2014 (18) that included 195 studies about the prevalence of vitamin D deficiency in 44 countries around the world (belonging to Europe, Asia, North and South America, and Oceania), found that 88% of the samples tested had serum levels 25-OH-D3 below 30ng/ml, 37% had average values below 20 ng/ml and 7% had lower average values at 10 ng/ml (18). The great heterogeneity of the studies made it difficult to generalize the results, without having allowed significant differences between countries or continents, nor in terms of age or sex.

3.1.3. Etiology of vitamin D deficiency

The vitamin D deficiency may be due to low skin production, because of lack of sun exposure or increased use of sunscreens preventing penetration of UV light on skin. Similarly, it could be due to low dietary intake.

Elderly have particularly high risk for this deficiency because of a lower efficiency in the cutaneous synthesis and intestinal absorption of vitamin D.

Also, there are several conditions that may increase the risk of such vitamin deficiency, as accelerated loss of vitamin in nephrotic syndrome; resistance to its biological effects, as in the case of mutation of VDR; intestinal disturbances that reduce fat absorption, such as celiac disease, inflammatory bowel disease (IBD) or bariatric surgery; alterations in activating vitamin D, such as kidney failure, hypoparathyroidism, certain drugs like ketoconazole, mutations in the 1αhydroxylase, oncogenic osteomalacia and the hypophosphatemic rickets X-linked (19).

There are some drugs, such as barbiturates, phenytoin and rifampicin, which induce liver oxidases, and thereby accelerate inactivation of metabolites of vitamin D.

3.2. Supplementation with vitamin D preparations

In numerous studies conducted in the US use a vitamin D2 preparation (ergocalciferol), however this formulation is not available in our country (Spain), where we have only available vitamin D3 supplements.

It has been described that vitamin D2 is less effective than vitamin D3 (20), so the triple dose of the first one would be required to achieve similar effectiveness. Heaney et al (21) conducted a study with various formulations of vitamin D, concluding that vitamin D3 was 87% more potent than vitamin D2 in raising and maintaining desired levels of 25-OH-D3 in plasma.

3.2.1. Vitamin D3 preparations marketed in Spain:

- Vitamin D3, calciferol or cholecalciferol.

They are liposoluble prepared with long half-life (approximately 1 to 3 months), which are deposited in adipose tissue, from where they are released slowly.

To develop its action, liver and kidney must work properly, to carry out the two hydroxylation to transform it into the active form of vitamin D.

There are two preparations available in our country: Deltius® (oral solution containing 10.000UI per ml, in vials with 2.5 ml) and vitamin D Kern Pharma® (oily solution containing 2,000 IU/ml, in vials of 10ml).

- 25-OH-D3 or calcifediol.

It is a derivative of vitamin D hydroxylation at position 25, such as the produced by hepatic metabolism, but still precise renal hydroxylation for its activation.

It has a half-life intermediate between natural vitamin D (cholecalciferol described above) and those prepared by hydroxylation at position 1 to be discussed later; which lasts approximately 15 to 30 days.

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In our country and to the date, there is only one company that markets this formulation: Hidroferol®, with three preparations forms (drops: 1 drop being equivalent to 240UI; in ampoules of 0,266mg, equivalent to 16.000UI; and shock-blisters with 3mgr, equivalent to 180.000UI).

- There are two derivatives of vitamin D hydroxylation at position 1, and which are 1,25-OH-D3 (or calcitriol) and D3 1alpha-OH (or alfacalcidiol); which ones have a shorter mean half-life.

Calcitriol is available in Spain in generic formulations (Teva®, Kern®) in ampoules of 1 and 2 mcg/ml and in capsules (Rocaltrol®) at doses of 0.25 and 0.5 mcg.
This is the active form of vitamin D, and does not require subsequent liver or kidney transformations.
It is effective in microgram dose, and speed of action is the main advantage, but also its main drawback, being only 3 hours, which can cause major variations in serum calcium.

Alfacalcidiol (1-OH-D3) is available in our country under the name of Etalpha®, in ampoules 1mcg/0.5ml and 2mcg/1ml, and capsules of 0.25, 0.5 and 1 mcg.
It needs to hepatic transformation for activation but can be used in cases of renal insufficiency.
Its power is less than calcitriol, requiring double dose for similar efficacy, but has a longer half-life (1 to 5 days).

Equivalences between different presentations of vitamin D are as follows:

1ng / ml = 2.5 nmol / l
1 drop of calcifediol (Hidroferol®) = 240 IU = 4 mcg
1mcg calcifediol (Hidroferol ®) = 60 IU
1 IU vit D3 = 3 IU vitamin D2

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The presentation of vitamin D that will be used in this study is calciferol (Hidroferol®) at a dose of 0,266mg/weekly (16.000UI/week), of which there are studies supporting its effectiveness compared to cholecalciferol, inducing an more rapid increase and sustained serum levels of 25-OH-D3 (22).

There are very few published trials using this preparation and therefore there is little evidence on the optimal recommended dose of calcifediol to be used.

3.2.2. Guidelines supplementation with vitamin D.

Considering vitamin D deficiency as serum levels of 25-OH-D3 <30ng/ml, several protocols can be found in the literature, highlighting the guidelines of the US Endocrine Society (14), whose recommendations in adults are as follows:

- Dose of 50,000 IU/week of vitamin D2 or D3 for 8 weeks to reach the target level of 25-OH-D3, followed by 1,500-2,000 IU/day for maintenance.
- In patients with obesity, malabsorption syndromes or treated with drugs that may affect the metabolism of vitamin D: 6.000-10.000UI dose/day to achieve the target values, followed by 3.000-6.000UI/day for maintenance.
- The maximum tolerable maintenance dose should not be taken without medical supervision is 4.000UI/day.

For its part, the International Osteoporosis Foundation (15) recommends consuming 800-1000 IU/day of vitamin D2 or D3, but believes that may be required up to 2,000 IU/day in patients at risk, such as obesity, osteoporotic, low sun exposure (as institutionalized), malabsorption problems ...

3.2.3. Safety of vitamin D.

They are not known accurately doses of vitamin D from which toxic effects may occur.

Both IOM and the American Society of Endocrinology consider 4.000UI dose/day, which should not be exceeded without medical supervision.
As for serum 25-OH-D3, the Endocrine Society believes that it should exceed the levels of 150ng/ml so that there could be risk of hypercalcemia.

There have been numerous studies that have shown the safety of various preparations of vitamin D at much higher doses than those commonly used, such as some studies conducted by Hathcock et al (23), where they used 10.000UI/day, without finding hypercalcemia or other manifestations of toxicity. Nor hypervitaminosis occurred in another study using single dose of 500.000UI (24).

The symptoms described in acute intoxication vitamin D are generally due to hypercalcemia and include confusion, polyuria, polydipsia, anorexia, vomiting and muscle weakness. Chronic intoxication can cause nephrocalcinosis, demineralization and bone pain (23).

Although vitamin D toxicity is rare, it is still much unknown about it, since most of the available information comes from sporadic cases (25-27).

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4. Vitamin D and asthma.

4.1. Experimental studies.

There are several mechanisms by which vitamin D might influence asthma, according to results of several experimental studies, and we could summarize in the following sections:

- Influence of vitamin D on innate immunity.

Certain infectious agents and allergens can stimulate the receptors of antigen presenting cells, which in turn increase the expression of CYP27B1 enzyme in macrophages, monocytes and epithelial cells (28, 29). That improve the active form of vitamin D, 1,25-OH-D3, that binds VDR and genomic VDRE, modulating various proinflammatory cytokines and increasing the production of antimicrobial peptides, as cathelicidin and beta-defensin2 (30-32).

- Influence of vitamin D on adaptive immunity.

The type of T cell response is directly influenced by the antigen presenting cells, which are themselves modulated by vitamin D. In addition, vitamin D has direct effects on T cells: inhibits Th1 cytokines associated to the phenotype of T cells in vitro and animal studies (33); while the effects on Th2 cells are more complex, but particularly important because Th2 cytokines lead to IgE synthesis, essential in allergic asthma pathogenesis. Vitamin D may either inhibit or promote Th2 response in different animal models and in vitro human T cells (34).
Hypponen et al (35) demonstrated that plasma levels of 25-OH-D3 did not have a linear relationship with serum IgE levels, so that IgE levels were elevated only with very low or very high levels of 25-OH-D3.

In vitro, it has been observed that calcitriol reduces IgE production in peripheral human B cells and increases the synthesis of IL-10 by these cells (36, 37). Besides producing B cells also synthesize IL-10 IgG4, isotype associated with beneficial results after desensitization with certain allergen immunotherapy (38).

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Some cytokines such as IL-17 play a central role in epithelial defense against bacterial and fungal infections. However, excessive levels of this cytokine has been implicated in severe asthma, associated with neutrophilic present in many patients with severe asthma (39-42).

That IL-17 has been shown to promote bronchial hyperresponsiveness and remodeling, resistance to steroids and synthesis of proinflammatory cytokines (41, 43, 44). Meanwhile, vitamin D has been shown to reduce IL-17 responses in both mice and humans with severe asthma (39, 45).

- Effects on regulatory T cells.

Regulatory T cells (Tregs) are essential for the prevention and control of excessive and inappropriate immune responses, including allergy-related processes and asthma (46). In asthmatic patients has observed decreased levels of these cells Tregs (47, 48) and also observed lower levels of IL-10 compared to healthy subjects (49, 50). In vitro vitamin D showed improving several actions of Tregs (51), including promoting those that synthesize IL-10 and depending of existing levels of vitamin D (52).

- Effects on response to corticosteroids.

It has been described that the CD4+ T cells in peripheral blood of corticosteroid-resistant asthmatic patients were not able to increase the secretion of IL-10 in vitro when they received dexamethasone, as opposite that in corticosteroid-sensible asthmatic patients or in healthy subjects (50). In addition, supplementation with vitamin D, either by addition of 1,25-OH-D3 to the culture or by oral supplementation for 7 days of asthmatic patient's refractory to steroids, allowed to restore the induction of IL-10 by dexamethasone (50).

Interestingly it has been found that dexamethasone may increase production of IL-17 from mononuclear peripheral blood cells and CD4+ T cells in vitro, showing a positive association between the dose of inhaled corticosteroid and synthesis of IL-17. These data suggest that corticosteroids could contribute to disease progression in severe asthma for increased response mediated IL-17 (53); while vitamin D has been shown to strongly inhibit the production of IL-17 induced by corticosteroids in vitro (39).

- Effects on airway remodeling.

Remodeling of the airway in asthma causes reduction in lung function irreversibly and is poorly controlled with current therapies (54). Some studies have found that vitamin D is associated with reduced smooth muscle mass airway (ASM) (55, 56).

It has been found an inverse relationship between ASM and serum levels of 25-OH-D3 in pediatric patients with asthma (57); and so the addition of vitamin D to cultures of human ASM has been found to reduce the proliferation of such muscle cells (58).

4.2. Vitamin D and asthma: Descriptive studies.

In addition to experimental studies described above, there are observational studies, that found a relationship between plasma levels of 25-OH-D3 with different aspects of asthma, in both children and adults; and only some of them will be exposed here.

Bener et al (59) in 2012, conducted a large study of 966 asthmatic children and their healthy controls, finding that vitamin D deficiency was higher in the group of asthmatic children (AOR = 4.82, 2.41-8.63).

Six studies investigated the association between plasma levels of 25-OH-D_3 and asthma exacerbations, defined by need of hospitalization or use of systemic corticosteroids (oral or parenteral) (57, 60-64).

In all of them, except in the study by Gergen et al (63), found that low 25-OH-D3 plasma levels were associated with an increased risk of asthma exacerbations.

In adults, Devereux et al (65), conducted a case-control study in the UK in 2010, selecting 160 adults between 18 and 50 years old and found no significant association between serum vitamin D levels and the prevalence of asthma (AOR = 0.98 [0.91 to 1 06]).

In the same year, Sutherland et al (66) carried out a cross sectional study in 54 asthmatic patients over 18 years, non-smoking; measuring the relationship

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between plasma levels of vitamin D and the values obtained in pulmonary function tests, and found a significant association between higher serum 25-OH-D3 and better results in pulmonary function tests, measured as FEV1 and the methacholine test.

In another cross-sectional study conducted in 2013 by Korn et al (67), serum vitamin D in 280 asthmatics adult patients from Germany were determined, and stratified depending on the degree of control (in three subgroups: well controlled, partially controlled and uncontrolled) and asthma severity (four subgroups: intermittent, mild persistent, moderate persistent and severe), using the GINA criteria (68). The results obtained were as follows: plasma levels of vitamin D were lower in the greater severity of asthma and in the poorer disease control. The odds ratio of patients with severe or uncontrolled asthma to present inadequate levels (<30 ng / ml) of plasma vitamin D was 1.9 (95% CI: 1.2 to 3.2) and 2.1 (1.3-3.5) respectively.

In 2014 Confino-Cohen et al (69), selected 21237 asthmatic adults 22-50 years, from Israel, and measured their plasma levels of 25-OH-D3 and so the number of asthma exacerbations who had submitted during the previous year (defining exacerbation as prescription oral corticosteroids, prescription > 5 short-term beta agonists, or more than 4 visits to a doctor for asthma-related symptoms). Levels of 25-OH-D3 were also measured in non-asthmatic patients, finding a similar prevalence in both groups. However, found an inverse linear association between the ratio of asthmatic exacerbations and plasma levels of 25-OH-D3 ($p < 0.0001$).

4.3. Vitamin D and asthma: Clinical Trials.

Among the main clinical trials Vitamin D in asthmatic children till the date, three of them investigated the influence of vitamin D on asthma exacerbations (70-72) and another clinical trial (73) studied their relationship to the degree of asthma control determined by the ACT questionnaire (74).

In the latter RCT, conducted in 2012, by Lewis et al (73), they selected 30 children with persistent asthma, aged between 6 and 17 years. They were then randomized in the intervention group (IG), which was administered 1000 IU/day of vitamin D orally, and in the control group (CG), receiving placebo. They measured at baseline, at 6 and 12 months later, the serum levels of 25-OH-D3 and the ACT questionnaire (74). As a result, it was noted that all patients except one, had plasma initial values of 25-OH-D3 below 15 ng/ml and they increased throughout the study in both groups, but without any of them getting higher values to 30ng/ml, and also presenting significant variations in these levels depending on the season (summer or winter).

For the score on the ACT questionnaire in both groups, no significant differences were found. As conclusion the authors believed that they probably should have used higher doses of vitamin D, in order to achieve serum levels of 25-OH-D3 > 30ng/ml, and so they may had observed most significant results.

We can find 3 RCTs that investigated the association between vitamin D supplementation and asthma exacerbations in children (70-72).

In the first one in chronological order, in 2010, by Urashima et al (70), they selected 167 asthmatic children between 6-15 years of age, being randomized into the IG, which received oral supplements 1200UI/day of vitamin D, and the CG receiving placebo. Follow-up lasted 16 weeks, during the winter months, and for which the incidence of influenza A (determined in nasopharyngeal aspirate) and the number of asthma exacerbations (defined as wheezing improved with short-acting beta2 agonists) were measured. The results obtained were as follows: The incidence of influenza A in the group supplemented with vitamin D was 10.8%, compared with 18.6% of affected children in the placebo group (RR = 0.58; CI 95% 0.17 to 0.79; p = 0.006). As conclusion, the authors suggested that supplementation with vitamin D preparations for the winter season, could reduce the incidence of influenza A and the number of asthma attacks in children, but consider that studies should be conducted with a larger sample size.

The second RCT, in 2011, by Majak et al (71), selected 48 children with newly diagnosed asthma in children aged 5-18 years. They were randomized into two groups: IG (which was prescribed 500UI/day of vitamin D orally) and CG (with placebo). Both groups received 800mcg/day budesonide inhalation. The follow

up period was 6 months, measuring at the beginning and at the end of the study, the plasma levels of 25-OH-D3 and the incidence of asthma attacks (defined by the need for use of short-acting beta2-agonists).
As a result, it was found that the average levels of 25-OH-D3 at baseline were greater than 30 ng/ml in both groups (35,1ng/ml in the placebo group and 36,1ng/ml in GI), with a subsequent decrease in the levels on the first group at the end of the study (31,9ng/ml) and a slight increase in the group supplemented with vitamin D (37,6ng/ml) after 6 months of treatment. They presented 4 asthma attacks in IG (17%) and 11 in CG (46%) (p = 0.029).
The conclusion of their authors was that supplementation of vitamin D may reduce the risk of asthma exacerbations, but recommended further studies.

The last of these RCT in children, was published in 2014 (72) in which was selected 100 asthmatic children (according to the criteria of the GINA 2011), aged between 3 and 14 years. They were randomized between IG (which received 60.000UI/month oral vitamin D) and CG (placebo also monthly). The follow-up period was 6 months, making monthly reviews and found that the number of asthma attacks during the study was significantly lower in the vitamin D group compared with the placebo group.

In adults and till the date, we find four main RCTs that studied the influence of supplementation with vitamin D in adult patients with asthma.

The first one was the VIDA study (Vitamin D Add-on Corticosteroid Therapy Enhances Responsiveness in Asthma) (75), published in 2014. It was a multicenter double-blind study, in which 408 patients with symptomatic asthma (median score on the ACT of 20points and a slight spirometric alteration) and vitamin D deficiency were included (25-OH-D3 plasma <30ng / ml).
For this study, the researchers created a period of "bleach", in which the previous asthma treatment of patients was suspended, and all of them were changed to inhalated ciclesonide (320mcg/day) and levalbuterol for 4 weeks, and added oral prednisone 40mg/day of in the last week of that month of “bleach”.
The patients were assigned randomly into two groups: the IG that received vitamin D (once 100,000 IU initial, followed by 4000 IU/day orally) and the CG,

who took placebo in a similar way. Following this randomization, the only treatment that was maintained for asthma control was inhaled ciclesonide 320mcg/day for 12 weeks; after which patients were retested and those with good control were reduced the dose to half (ciclesonide 160mcg/day), which was kept for another 8 weeks; and again were reevaluated and those with good control were reduced their dose of ICS to half (ciclesonide 80mcg/day) for another 8 weeks. The total length of patient follow-up was 28 weeks.
The main objective in this VIDA study, was the rate of treatment failure and number of asthma exacerbations among patients who took vitamin D supplementation or placebo, without finding differences between them. The researchers only found significant differences in the total dose of ICS at the end of the study, which was a 25% smaller in the IG with respect to the CG; although in absolute terms, the total difference in the accumulated dose between the groups was small (15mcg/day).

In the same year, S.Arshi et al (76), carried out another RCT, in which selected 108 patients, 10-50 years old, with mild-moderate persistent asthma as criteria GINA 2012. All patients were treated with ICS (budesonide) with / without formoterol depending on the degree of control, and then were divided 2 groups: IG, who received vitamin D (a single dose of 100,000 IU IM, followed by 50,000 IU/week orally) and CG, who were not added any treatment apart from ICS (+/- beta2). It was therefore an open unblinded study.
All of them were measured FEV1 and plasma levels of 25-OH-D3, prior to randomization and at weeks 8 and 24 of the study.
As a result, they found an improvement in FEV1 similar in both groups at week 8, while in week 24 the improvement in FEV1 was significantly higher in the vitamin D group compared to the placebo group.
In the conclusion, the authors described that vitamin D supplementation could help to improve response to the ICS in the control of asthma at long term, specifying that at least 24 weeks of supplementation with these preparations should be used before to observe their immune effects.

In 2015, JC de Groot et al (77), selected 44 non atopic asthmatics patients, whose induced sputum were eosinophilic (> 3%) and / or neutrophilic (> 53%),

and all of them had serum 25-OH-D3 were less than 40ng/ml. These patients were randomized into two groups: the IG, receiving vitamin D (a single dose of 400.000UI) and CG, which received one dose of placebo: They all continued their regular medication for asthma. At baseline and after 9 weeks, the analysis of induced sputum, pulmonary function tests and questionnaires AQLQ (Asthma Quality of Life Questionnaire was conducted(78)) And ACQ (Asthma Control Questionnaire (79)) were determined. As a result, it was observed that treatment with vitamin D did not significantly affect the total percentage of neutrophils or eosinophils between IG and CG. Although, in the group of patients with higher levels of sputum eosinophils (> 26%), it was observed that this percentage was reduced following treatment with vitamin D (from 41% to 11.8%) compared with the placebo group, whose percentage increased (from 51% to 63%, p = 0.034). Also the group of vitamin D showed slightly better score in the ACQ questionnaire (0.8 in IG and 1.1 in CG; p = 0.08).

In conclusion, the authors suggested that vitamin D could be an adjunctive therapy to the ICS effective in the subgroup of patients with severe asthmatic eosinophilic inflammation of the airway.

In the last RCT, carried out by Martineau et al (80), in 2015 and in the UK, 250 asthmatic patients were selected, aged between 16 and 80 years. They were randomized into two groups: the IG, which received vitamin D (120.000UI 2 times/month orally for 3 months, followed by a dose of 120,000 IU vo every 2 months until one year), and CG who took placebo in a similar pattern. The main objective of this study was to investigate whether there were differences between the two groups in the time to first severe exacerbation (defined as requiring treatment with oral corticosteroids, hospitalization, consultation in the emergency department, or decreased PEF>25%) (81).

The results were as follows:

-The prevalence of vitamin D deficiency (<30 ng / ml) in asthmatic patients was 83%.

-No significant differences between IG and CG was observed in time to first exacerbation; and there were no differences in the overall rate of exacerbations or respiratory infections throughout follow-up.

-The only significant difference between the two groups, was the improvement in quality of life as measured by SGRQ (questionnaire Sant George (82)) In the IG respect to CG.

The researchers concluded that supplementation with bolus of vitamin D did not influence the time to first severe asthma attack or first respiratory infection in the upper airway in a population of adult asthmatic patients with a high prevalence of vitamin deficit D.

5. Objectives of the ACVID study.

- Primary: Evaluate the efficacy of vitamin D supplementation in asthmatic patients with vitamin D deficiency in the degree of asthma control.

- Secondary: Evaluate the efficacy of vitamin D supplementation in those patients in improving the quality of life, reducing the number of exacerbations, decreasing the dose of inhaled corticosteroids, the number of oral corticosteroid cycles, the number of emergency visits, and the number of unscheduled consultations with the primary care physician and hospitalizations for asthma.

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6. Design and study protocol.

6.1. Design.

It will be a prospective, randomized and triple-blind study, to be carry out in Morales Meseguer Hospital of Murcia, Spain; which gives health coverage to an estimated population of 240,000 inhabitants.

Sample size calculation, randomization and analysis of the results will be performed by a computer program and by a professional statistician, independent and outside of the studio.

Researchers and patients throughout the study will be unaware which group of patients belong to IG, who will receive vitamin D supplementation, and who to CG, who will receive placebo.

6.2. Equipment and funding.

The research team consists of two specialists in Endocrinology, one specialist in Pneumology and one expert in statistical analysis and data processing.

Blisters vitamin D and placebo will be provided by the pharmaceutical company FAES FARMA, essential for blinding them, but without receiving from it or any other industry any funding or donations. Therefore, the research team for this study declares no conflict of interest.

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6.3. Randomization and recruitment.

Patients will be selected from lists of income hospital and in the emergency department during the years 2013 and 2014, with the main or secondary diagnosis of asthma.

After this search, all patients will be contacted by telephone and invited to participate in the study, sending them a flyer for a blood extraction, to identify those with vitamin D deficiency, and being cited those who accept in a first visit in consultations of Endocrinology in Morales Meseguer Hospital of Murcia, Spain.

In that first recruiting visit the inclusion and exclusion criteria will be assessed, and patients will be asked for signing the informed consent (Annex I).

For randomization, random numbers will be generated by computer and by an external researcher to the study.
Each patient will be assigned to each group by a system of opaque numbered envelopes, that will be held by the principal researcher.

In the recruiting visit, if considered the inclusion of patients in the study, the main researcher will open consecutively an envelope with the group of each patient, identified as "A" or "B" to maintain blinding, without knowing which of them would correspond to CG or IG.

Patients assigned to one group or another, will be given the ampoules named as “A” or “B”, ignoring if they contain vitamin D or placebo, while continuing with their usual medical assistance and habitual treatments for asthma.

ThI study was approved by the Ethics Committee for Clinical Research Morales Meseguer Hospital dated 29 April 2015 (Annex II).

6.4. Inclusion and exclusion criteria.

Patients must be over 18 years, with a medical diagnosis of bronchial asthma, and have vitamin D deficiency (25-OH-D3 < 30 ng/ml).

Exclusion criteria:

-Tobacco use > 10 pack-years.

- Be already taking vitamin D supplementation.

- Renal-disease (serum creatinine> 2 mg / dl)

- Hypercalcemia (protein corrected serum calcium> 10.5mg / dl).

- Repeated kidney stones (> 2 episodes).

- Diseases affecting ability of intestine to absorb vitamin D (as Crohn's disease or great intestinal resections).

-Pregnancy or breastfeeding.

- Severe psychosocial problems (dementia, alcoholism or other drug abuse psychiatric disorders such as major active depression or schizophrenia).

6.5. Study variables.

Data to be collected can be grouped into several subtypes: socio-demographic, clinical, laboratory and respiratory function; as summarize below:

6.5.1. Socio-demographic data.

- Age.
- Sex.
- Educational level: completed basic, medium or university studies.

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6.5.2. clinical variables.

- Body mass index (BMI): calculated using the following formula:

$$BMI = \frac{\text{Weight (kg)}}{\text{Size (m)}^2}$$

- Immunization history: Influenza and pneumococcal vaccination of patients.

- Smoking: smoking history accumulated, expressed in pack-years, in order to exclude possible diagnostic confusion with COPD; and so there will be excluded all patients whose consumption is equal to or greater than 10 pack-years. This index is calculated by the following formula:

$$\text{Packyears index} = \frac{\text{Nº cigarettes smoked per day} \times \text{Nº smoking years}}{\text{twenty}}$$

- Degree of dyspnea: measured by the scale Medical Research Council (MRC) (Fletcher, BMJ, 1959) (83, 84) reviewed by Schilling in 1955 and recommended for use in obstructive diseases (85). This instrument has the advantage of simplicity and reflect breathlessness caused by activities of daily life, and helps in predicting quality of life and survival (86-88). We will use this scale to measure baseline dyspnea of patients, and check if there are differences between the two groups.

- Clinical factors related to asthma:
    - Years of development asthma.
    - Extrinsic or intrinsic asthma.

- Classification of asthma severity, according to the criteria defined by GINA, in four groups: Intermittent, mild persistent, moderate persistent or severe persistent.

Severity of asthma will be determined only at the initial visit to check the possible difference between the two groups, but without being repetead at the end of the study, since there will be not changes in the specific treatment for asthma over the 6-month study.

GINA Classification of Asthma Severity

	Symptoms/Day	Symptoms/Night	PEF or FEV1	PEF variability
STEP 1 **Intermittent**	< 1 time a week Asymptomatic and normal PEF between attacks	</= 2 times a month	>/= 80%	< 20%
STEP 2 **Mild Persistent**	> 1 time a week but < 1 time a day Attacks may affect activity	> 2 times a month	>/= 80%	20-30%
STEP 3 **Moderate Persistent**	Daily Attacks affect activity	> 1 time a week	60%-80%	> 30%
STEP 4 **Severe Persistent**	Continuous Limited physical activity	Frequent	</= 60%	> 30%

- The degree of asthma control, assessed by questionnaire ACT score (Asthma Control Test) (Annex III).

It is a simple self-administered questionnaire by the patient, to quantify the degree of asthma control.

Developed in 2004 by Nathan et al (74), it has been validated in different populations (89) and different measurement criteria. It has also been validated the Spanish version (90).

It consists of 5 questions that assess: the limitations on physical activity, the degree of dyspnea, nocturnal symptoms, use of rescue medication and the

perception of patients with respect to the control of their disease; all these aspects for the four weeks preceding the survey. These questions are graded with a score ranging from 1 (worst) to 5 (best), and the resulting score is the sum of responses, that may range from 5 (poor control) and 25 (excellent control). Cutoff scores have been studied, in order to establish a relationship with the degree of control with the GINA and other criteria (such as Exhaled Nitric Oxide Fraction -FENO- or spirometry), concluding that a score equal or greater than 20 is consistent with very well controlled asthma, a score between 19-16 with partially controlled asthma, and ratings at or below 15 with poorly controlled asthma (91).

Similarly has been established minimally significant difference, defined as the smallest difference in that test score representing a clinically significant change in patients, and whose value is equal to or greater than 3 points (92).

In our study, we will collect the score on the ACT in both groups at the beginning and at the end of the study. In the first case, to determine the possible differences between the two study groups at the beginning of the trial. Then we will compare the final score between the groups, to assess whether the vitamin D supplementation could have caused significant differences between them; and we will analyze the variation of the final score with respect to the initial in each of the groups.

As a last aspect in this point, we will value the necessary number of patients to treat (NNT) required to achieve a clinically meaningful improvement (3 points) (92) in ACT score (74) using the formula proposed by Suissa (93) in 2012. This parameter, the NNT, has been described as a simple and valid tool to assess the impact of an intervention (94).

- Quality of life, which will be measured with the questionnaire Mini-AQLQ (Annex IV).

This is the short version of the validated questionnaire AQLQ (Asthma Quality of Life Questionnaire) (95), whose shorter version has also been validated (96) and so its adaptation in Spanish (97).

It is a self-administered questionnaire that includes 15 questions with a score from 1 (always) to 7 (ever), through which four asthma-related aspects are evaluated:

- Respiratory symptoms (in items 1,4,6,8,10);
- possibility to perform activities (items 12, 13, 14, 15);
- environmental stimuli (items 2,7,11);
- emotions against these symptoms (items 3,5,9).

It has been studied in relation to the AQLQ and all versions (mini-AQLQ, AQLQ (S) and Acute AQLQ) the difference in score considered minimally important, defined as the smallest difference in the test score that patients perceive as beneficial (98, 99), and which has been set in 0.5 for minimal; a difference equal to or greater than 1 point would be considered moderate, and a difference equal to or greater than 1.5 points would be considered important.

- Specific treatment for asthma, both inhaled and systemic; specifying the number of cycles of oral corticosteroids in the 6 months prior to baseline and during the trial. In the case of ICS we will use a conversion of equivalent doses of different preparations, according to the criteria defined by the GINA, to be able to classified them in three groups: low, medium or high doses.

	LOW DOSES (µg/día)	MEDIUM DOSES (µg/día)	HIGH DOSES (µg/día)
Beclometasona dipropionato	200-500	501-1.000	1.001-2.000
Beclometasona extrafina	100-200	201-400	> 400
Budesónida	200-400	401-800	801-1.600
Ciclesonida	80-160	161-320	321-1.280
Fluticasona furoato	-	92	184
Fluticasona propionato	100-250	251-500	501-1.000
Mometasona furoato	100-200	201-400	401-800

- Number of asthma attacks

Crisis or asthma exacerbation is defined retrospectively as the need of increase the specific treatment for asthma for at least 3 days. For this, we will ask directly to the patients and consult the medical record.

-Number of unscheduled consultations with primary care physician for asthma-related causes.

Similarly, to obtain such data we will directly ask the patients and consult the medical record.

-Number of consultations in the emergency department for asthma-related causes.

We will ask patients and then check the information with the hospital computer program.

-Number of hospital admissions for asthma-related causes.

We will ask the patients and check this information with the medical record.

6.5.3. Laboratory data.

- Plasma levels of 25-OH-D3 (ng / ml).
- total serum protein (mg / dl), to calculate corrected calcium by proteins.
- Total serum calcium (mg / dl).
- Calcium corrected by proteins (CCP), calculated using the following formula, to detect possible cases of hypercalcemia:

CCP = Total measured calcium / [0,6 + (proteins/18.5)].

- Hemogram, with particular interest in the white series, in particular eosinophils (both absolute number and percentage).
- Immunoglobulin E (IgE).

6.5.4. Spirometry.

Spirometry is a diagnostic test of choice in both the diagnosis and monitoring of asthma patients.

In our study, we will collect the following data: Forced vital capacity (FVC), FEV1

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and index FEV1/FVC, indexed by height and age, and according to the reference values of the European Respiratory Society (ERS).

These data will be obtained to verify the similarity of the two study groups, giving value to randomization, and to test whether vitamin D supplementation would have any impact on the respiratory function tests.

Measurements will be made with the spirometer MIR® Spirobank type, version 1.6 with A23-04P.01282 number series.

6.5.5. Other data.

- Any data on possible side untoward effects throughout the study will be collected patients and so the dropout rate thereof.

- We will collect data on all-cause mortality that could occur from the time of recruitment and until the end of the study.

- Days to first hospitalization for asthma-related causes. Defined as the number of days until patients present the first hospital admission for asthma.

- Days until the first emergency care for asthma-related causes. Defined as the number of days until patients need to be attended for the first time in the emergency department for asthma-related causes.

6.6. Initial visit.

After contacting patients by telephone, they will be cited in consultation for recruitment, checking the criteria for inclusion and exclusion of each patient. Previously they should had received a steering wheel for analytical extraction, to include only those patients whose serum 25-OH-D3 levels < 30ng/ml.

All candidates to participate in the trial will be adequately informed about the purpose and development of the study, and asked for signing the informed consent (CI) (Annex I). Then we will open the opaque envelopes, assigning randomly and blindly patients to group "A" or "B", without knowing which would be the GC and which the intervention group, nor by patients or researchers.

After inclusion, we will collect the different baseline socio-demographic, clinical, analytical and spirometric data, and after that we will give to patients blisters "A" or "B", making them know how to take it: once a week orally.
The composition of ampoules containing vitamin D will be in a presentation of 266 mcg calcifediol (equivalent to vitamin D3 16.000U) while placebo blisters will contain the same amount (1.5ml in each ampoule) but only with an oily substance.

On this visit, the pulmonologist researcher will collect the clinical variables, the spirometry tests and questionnaires, to establish the degree of asthma control patients at that time; and if necessary will adjust treatment in both groups to ensure that patients take the proper specific treatment for asthma in both groups, equally, without knowing who belong to the CG or the IG.

Finally, we will provide to patients a new steering wheel for their next analytical extraction at the end of the study, and give a scheduled 6-month review date.

6.7. Monitoring.

During follow-up, a mobile phone will be activated and available, so patients could directly call the researchers if they had any questions.

Patients will be telephoned once a month, to remind proper medication adherence and ask them about the appearance of side effects.

6.8. Final visit.

The last visit will be 6 months after the initial visit, and patients should have already taken the “A" or "B" blisters. Then, we will collect the final data: clinical, analytical and spirometric, and so the possible side effects associated with the

blisters, the number of dropouts, mortality, the number of days until the first emergency care for asthma or until the first hospital admission for reasons related with asthma.

6.9. Data Collect

We will use a database SPSS® for Mac® environment, that will be created by the researchers.

The database will allow to collect the data during the initial and final visits, and later will be analyzed by an independent statistician, who also will not know the treatment received in groups “A” or “B”.

6.10. Statistical analysis.

The data analysis will be performed by intent-to-treat. To calculate the sample size, and accepting an alpha risk of 0.05 and a beta risk of 0.2 (80% power), 100 participants would be required in total, 50 in each group, to detect an absolute difference of 3 points in the ACT questionnaire, considering the mean of 19 and a standard deviation of +/- 5. A loss rate of 7% of patients will be estimated.

The baseline characteristics and results will be expressed as numbers (%) for qualitative variables and mean (SD) or median (interquartile range [IQR]) for quantitative variables, depending of their distribution. The 95% confidence intervals will be calculated for the outcome endpoints. The comparison between qualitative variables will be performed using Pearson's chi-squared test or Fisher's exact test (two-tailed). The comparison between quantitative and qualitative variables will be performed using the Student's t-test or the Mann-Whitney U test, depending on whether the qualitative variable is distributed normally or not. The comparison between quantitative variables will be performed with a test to compare the means for paired data. The final ACT score will be compared between groups by analysing the covariance (ANCOVA), with the

initial ACT score as a covariante. For the correlations between qualitative variables, Spearman's rho will be used, expressing it with the correlation coefficient and statistical significance. The statistical package SPSS® version 15.0 ® was used for the analysis.

6.11. Ethical and legal aspects.

The development of research is based on the *Declaration of the Helsinki World Medical Association* and the Code of Ethics of the Association of Medical Colleges of Spain. Patients and relatives will be informed about the nature of the study, voluntary participation in it, the proposed objectives and potential adverse effects that might occur in their realization. Each patient or family member will be provided with a sheet with the information, and will be asked for signing the Informed Consent (Annex I).

Treatment, communication and transfer of personal data of all participants subject will be adjusted to the provisions of Law 15/1999 of 13 December Protection of Personal Data (LOPD). According to the provisions of the above legislation, patients could exercise the rights of access, modification, opposition and cancellation of data, for which should be addressed to the study doctor in case of medical emergency or legal requirement.

Access to personal information will be restricted to the researcher / collaborators, health authorities (Spanish Agency for Medicines and Health Products), the Ethics Committee for Clinical Research and authorized by the sponsor personnel when necessary to check the data and procedures study, but always maintaining the confidentiality of the same in accordance with current legislation.

Similarly, patients who will be taken by the study test all security measures established by Royal Decree 1720/2007, of 21 December approving the Regulations implementing the Organic Law approving 15 reported / 1999 of

December 13, Protection of Personal data and is subject to all the provisions applicable to them under Law 41/2002, of 14 November, regulating basic patient autonomy and rights and obligations regarding information and clinical documentation.

This RCT was approved by the Ethics Committee for Clinical Research (CEIC) of Morales Meseguer Hospital in 29 April 2015 (Annex II).

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8. Annexes.

8.1. ANNEX I: INFORMED CONSENT.

INFORMED CONSENT, English version:

"Effectiveness calcifediol supplementation in asthma control in patients with vitamin D deficiency".

Researcher: Lourdes Salinero González.

Please read this information, and ask anything you do not understand.

We ask for your permission to include you in a study aimed to evaluate the efficacy of vitamin D supplementation in asthmatic patients with vitamin D deficiency, in relation to the degree of asthma control.

Vitamin D supplementation used (Hidroferol®) Is used in common for treating vitamin D deficiency states on habitual clinical practice.

The study methodology consists in taking a preparation in the form of drinkable ampoule, which may or not contain vitamin D supplement with a probability of 50%, and should be taken once a week until the end of the study. The follow-up period ends at 6 months after, and then you will be prescribed dose vitamin D supplement that needs to normalize the deficiency.

If you decide not to participate, we will recommend you taking this vitamin D supplement anyway, but your data and results of treatment will not be used for our study.

If you become pregnant during the 6 months of follow-up, you should inform the principal researcher to be removed from this study.

WILLFULNESS:

Participation in this study is completely voluntary. If at any time you decide not to continue, simply notify the specialist with whom you spoke.

Andújar-Espinosa R, *et al. Thorax* 2020;0:1–8. doi: 10.1136/thoraxjnl-2019-213936

DISADVANTAGES AND BENEFITS:

The benefits you can get are the possible improvement in the control of your respiratory disease due to interventions in the study, and whose knowledge is the ultimate goal of this study.

Drawbacks you could get would be the extractions of analytical variables, performing pulmonary function tests (spirometry), answer two specific questionnaires on asthma and will be called by phone one monthly to check adherence to treatment.

SIDE EFFECTS:

No side effects of this study are expected, since no different vitamin D supplements are used to those used today.

Medical care will be performed by a specialist in Endocrinology and another in Pneumology, and does not vary regarding recommended in these types of queries, so it can not be obtained negative health effects.

WITHDRAWAL OF STUDY:

The patient and his family may void the consent at any time, without incurring any negative consequences for later attention on this or any other hospital.

ALTERNATIVE TREATMENTS:

On the market other business presentations vitamin D, also effective in normalizing vitamin D deficiency.

In case of not wanting to participate, your data will not be taken into account for the results and conclusions of the study.

CONFIDENTIALITY (Clause is provided).

Treatment, communication and transfer of personal data of all participants

subject is governed by the provisions of Law 15/1999 of 13 December protection of personal data, Royal Decree 1720/2007 of 21 December, approving the Regulation implementing the Law 15/1999 and Law 41/2002, of 14 November, a basic regulatory Patient Autonomy and Rights and Obligations approved information and clinical documentation.

Only they are transmitted to third countries and other data collected for the study, which in any case contain information that can identify you directly, such as name, initials, address, etc. In the event that such transfer occurs, will be for the same purposes of the study described and ensuring the confidentiality and at least the level of protection equivalent to that provided by current legislation in our country.

Data collected for the study will be identified by a code and only your study doctor or collaborators of health workers can relate these data with you and your medical history. Therefore, your identity will not be disclosed to any person except exceptions, medical emergency or legal requirement. The data of the data is the principal investigator of the project.

You may contact at any time with the principal investigator of the study, to exercise their rights of access, rectification, cancellation and opposition (ARCO rights) regarding your personal data, according to the aforementioned law 15/1999.

Access to their personal information will be restricted to the study doctor, employees, health authorities (Spanish Agency for Medicines and Health Products), the Ethics Committee for Clinical and Research staff authorized by the promoter, when they need to check the data and procedures study, but always keeping them confidential according to the legislation referred to above. Access

to their medical records will be for study purposes only.

INFORMED CONSENT:

Mr./Ms…….....

or Mr./Ms.....as your representative

EXPOSE:

that Dra. Lourdes Salinero Gonzalez, a specialist in Endocrinology informed me the opportunity to participate in this study:

She has ensured that all medical care I receive will dictate the current recommendations of good medicine, so the treatment or testing are equal to those of any other patient with my illness that was not in this study.

She has explained that the objective is to evaluate the effectiveness of supplementation with calcifediol (vitamin D) in patients with vitamin D deficiency, in relation to the degree of control of asthma; and a totally confidential Data will be collected to analyze the results and to compare them with other studies.

MANIFEST:

I asked what I considered necessary to be fully informed about the advantage that participate in this study and has been answered to my satisfaction.

And so I give consent for them to use data from my clinical and analytical evolution, understanding that this consent may be revoked by me at any time.

Murcia, of 201

Firm:

INFORMED CONSENT, Spanish version:

"Eficacia de la suplementación con calcifediol en el control del asma en pacientes con déficit de vitamina D."

Investigador principal: Lourdes Salinero González.

Por favor, lea esta información, y pregunte todo aquello que no entienda.

Le pedimos su autorización para incluirle en un estudio que pretende evaluar la eficacia de la suplementación con vitamina D en pacientes asmáticos que presentan dicho déficit, respecto al grado de control del asma.

En ningún momento, se probará ningún tipo de preparado ni medicamentos nuevos; el suplemento de vitamina D utilizado (hidroferol®) se usa en la práctica clínica habitual para tratar los estados deficitarios de dicha vitamina.

La metodología del estudio consiste en la toma de un preparado en forma de ampolla bebible, que puede contener o no dicho suplemento vitamínico con una probabilidad del 50%, y que deberá tomar inicialmente una vez a la semana, y posteriormente con la periodicidad que se le indique.

Cuando finalice dicho periodo de seguimiento de 6 meses, e independientemente del tipo de preparado recibido, se le prescribirá la dosis de suplemento de vitamina D que precise, para normalizar dicho déficit.

Si usted decide no participar, de igual modo se le recomendará la toma de dichos suplementos vitamínicos, pero sus datos y los resultados de su tratamiento no serán utilizados para nuestro estudio.

Si se quedara embarazada durante los 6 meses de seguimiento, debería comunicarlo al investigador principal, para ser retirada de este estudio.

VOLUNTARIEDAD:

La participación en este estudio es totalmente voluntaria. Si en cualquier momento decide no continuar, sólo tiene que comunicarlo al especialista con el que habló.

BENEFICIOS E INCONVENIENTES:

→Los beneficios que puede obtener son la posible mejoría en el control de su enfermedad, debido a las intervenciones realizadas en el estudio, y cuyo conocimiento es el objetivo final de dicho estudio.

→Los inconvenientes que podría obtener sería la extracción de variables analíticas, la realización de pruebas de función pulmonar (espirometría y FeNO), responder 2 cuestionarios específicos sobre el asma, así como se le llamará por teléfono en una ocasión para comprobar la adherencia al tratamiento, revisión de resultados analíticos o cualquier otra incidencia que pudiera aparecer.

EFECTOS SECUNDARIOS:

No se espera ningún efecto secundario de este estudio, puesto que no se utilizan suplementos vitamínicos diferentes a los utilizados en la actualidad.

La atención médica será realizada por un especialista en Endocrinología y Nutrición, y otro en Neumología, y no varía respecto a la recomendada en este tipo de consultas, por lo que no puede obtenerse efectos negativos para su salud.

RETIRADA DEL ESTUDIO:

El enfermo y su familia pueden anular el consentimiento en cualquier momento, sin que suponga ninguna consecuencia negativa para su atención posterior en este u otro hospital.

TRATAMIENTOS ALTERNATIVOS:

Andújar-Espinosa R, *et al. Thorax* 2020;0:1–8. doi: 10.1136/thoraxjnl-2019-213936

Existen en el mercado otras presentaciones comerciales de vitamina D, igualmente eficaces a la hora de normalizar dicho déficit vitamínico.

En caso de no querer participar, sus datos no serán tenidos en cuenta para obtener los resultados y conclusiones del estudio.

CONFIDENCIALIDAD (se aporta claúsula).

El tratamiento, la comunicación y la cesión de los datos de carácter personal de todos los sujetos participantes se rige por lo dispuesto en la Ley Orgánica 15/1999, de 13 de diciembre de protección de datos de carácter personal, el Real Decreto 1720/2007, de 21 de diciembre, por el que se aprueba el Reglamento de desarrollo de la citada Ley Orgánica 15/1999, y la Ley 41/2002, de 14 de noviembre, básica reguladora de la Autonomía del Paciente y de Derechos y Obligaciones en materia de información y documentación clínica.

Sólo se transmitirán a terceros y a otros países los datos recogidos para el estudio, que en ningún caso contendrán información que le pueda identificar directamente, como nombre y apellidos, iniciales, dirección, etc. En el caso de que se produzca esta cesión, será para los mismos fines del estudio descrito y garantizando la confidencialidad y, como mínimo, con el nivel de protección equivalente al que contempla la legislación vigente en nuestro país.

Los datos recogidos para el estudio estarán identificados mediante un código y sólo su médico del estudio o colaboradores del personal sanitario podrán relacionar dichos datos con usted y con su historia clínica. Por lo tanto, su identidad no será revelada a persona alguna salvo excepciones, en caso de urgencia médica o requerimiento legal. El responsable del fichero de los datos es el investigador principal del proyecto.

Usted podrá ponerse en contacto en cualquier momento con el investigador principal del estudio, para ejercer sus derechos de acceso, rectificación, cancelación y oposición (derechos ARCO) respecto a sus datos personales, según la ley ya citada 15/1999.

El acceso a su información personal quedará restringido al médico del estudio, colaboradores, autoridades sanitarias (Agencia Española del Medicamento y Productos Sanitarios), al Comité Ético de Investigación Clínica y personal autorizado por el promotor, cuando lo precisen para comprobar los datos y procedimientos del estudio, pero siempre manteniendo la confidencialidad de los mismos de acuerdo a la legislación referida anteriormente. El acceso a su historia clínica será sólo para los fines del estudio.

CONSENTIMIENTO INFORMADO:

D./Dª.....

o D./Dª.....como su representante

EXPONGO:

Que la Dra. Lourdes Salinero González, médico especialista en Endocrinología y Nutrición, me ha informado de la posibilidad de participar en el estudio:

Me ha garantizado que toda la atención médica que reciba será la que dictan las recomendaciones actuales de la Buena Medicina, por lo que el tratamiento o las pruebas serán iguales a las de cualquier otro paciente con mi enfermedad que no estuviera en este estudio.

Me explican que el objetivo es evaluar la eficacia de la suplementación con calcifediol (vitamina D) en pacientes con dicho déficit vitamímico, respecto al grado de control del asma; y que de forma totalmente confidencial se recogerán

los datos para analizar los resultados obtenidos y poder compararlos con otros estudios.

MANIFIESTO:

Que he preguntado lo que he considerado necesario para estar perfectamente informado acerca de la ventaja que tiene participar en el presente estudio y se me ha contestado satisfactoriamente.

Y por ello **OTORGO MI CONSENTIMIENTO** para que puedan utilizar los datos de mi evolución clínica y analítica, entendiendo que este consentimiento puede ser revocado por mí en cualquier momento.

Murcia, a de de 201

Firma:

8.2. ANNEX II:

DOCUMENT OF ACCEPTANCE OF THE STUDY BY THE CEIC and address of H. MORALES MESEGUER.

Informe Dictamen Protocolo Favorable
Otros Estudios
C.P. - C.I. EST:18/15
29 de Abril de 2015

CEIC Hospital General Universitario José María Morales Meseguer

Dra. María Dolores Nájera Pérez
Presidenta del CEIC Hospital General Universitario José María Morales Meseguer

CERTIFICA

1º. Que el CEIC Hospital General Universitario José María Morales Meseguer en su reunión del día 29/04/2015, acta ORDINARIA ha evaluado la propuesta del promotor referida al estudio:

Título: Proyecto de Investigación: "Eficacia de la suplementación con calcifediol en el control del asma en pacientes con déficit de vitamina D".

Código Interno: EST:18/15
Promotor: Investigador Principal.
Versión Protocolo Evaluada: Marzo-2015
Versión Hoja Información al Paciente Evaluada: GENERAL / Marzo-2015
Fecha Entrada de Aclaraciones: 27/03/2015
Investigador Principal: **Dra. Lourdes Salinero González**, Endocrinología y Nutrición. H.G.U. "Morales Meseguer".

1º. Considera que:

- Se respetan los principios éticos básicos y es adecuado el procedimiento para obtener el consentimiento informado.

2º. Por lo que este CEIC emite un **DICTAMEN FAVORABLE**.

3º. Para la realización del Estudio, como prueba extra y fuera de la práctica clínica habitual, es necesaria la realización de 270 analíticas de Vitamina D a los participantes.

Lo que firmo en Murcia, a 29 de Abril de 2015

Dra. María Dolores Nájera Pérez
Presidenta del CEIC Hospital General Universitario José María Morales Meseguer

Hospital General Universitario J.M. Morales Meseguer
Marqués de los Vélez s/n Murcia 30008 Murcia España
Tel. 968 36 52 02 Fax. 968 36 09 49 Correo electrónico: ceic.hmm@carm.es

Página 1 de 1

Area VI Vega Media del Segura

Servicio Murciano de Salud

APROBACIÓN DE REALIZACIÓN DE ESTUDIO
POST AUTORIZACION DE TIPO OBSERVACIONAL

CEIC Hospital General Universitario Morales Meseguer

CONFORMIDAD DE LA DIRECCIÓN DEL CENTRO

D. Tomás Salvador Fernández Pérez, Director Gerente del Área VI, vista la autorización del Comité Ético de Investigación Clínica del Hospital Morales Meseguer,

CERTIFICA

Que conoce la propuesta realizada sobre el Estudio: **Proyecto de Investigación: "Eficacia de la suplementación con calcifediol en el control del asma en pacientes con déficit de vitamina D".**

Código Interno: ESTUDIO: 18/15

Y que será realizado por la Dra. Lourdes SALINERO GONZÁLEZ. Endocrinología y Nutrición del Hospital Morales Meseguer.

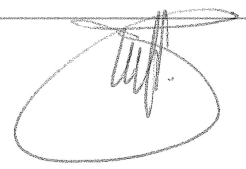
Que está de acuerdo con los aspectos económicos de este estudio.

Que acepta la realización de dicho estudio.

Fecha de aprobación por el CEIC del Área VI Hospital General Universitario "Morales Meseguer" el día 29 de Abril de 2015 para la realización del Estudio, como prueba extra y fuera de la práctica clínica habitual, es necesaria la realización de 270 analíticas de Vitamina D a los participantes.

Lo que firma en Murcia, a 25 de mayo de 2015.

Director Gerente del Área VI



Fdo.: D. Tomas Salvador Fernández Pérez

8.3. APPENDIX III: ACT (Asthma Control Test)

English Version:

asthma.com

Name: _____ Today's Date: _____

ASTHMA CONTROL TEST™

Know your score.

The Asthma Control Test™ provides a numerical score to help you and your healthcare provider determine if your asthma symptoms are well controlled.

Take this test if you are 12 years or older. Share the score with your healthcare provider.

Step 1: Write the number of each answer in the score box provided.

Step 2: Add up each score box for the total.

Step 3: Take the completed test to your healthcare provider to talk about your score.

IF YOUR SCORE IS 19 OR LESS, **Your asthma symptoms may not be as well controlled as they could be.**
No matter what the score, bring this test to your healthcare provider to talk about the results.
NOTE: If your score is 15 or less, your asthma may be very poorly controlled. Please contact your healthcare provider right away. There may be more you and your healthcare provider could do to help control your asthma symptoms.

					SCORE
1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?	All of the time **[1]**	Most of the time **[2]**	Some of the time **[3]**	A little of the time **[4]**	None of the time **[5]**	.....
2. During the past 4 weeks, how often have you had shortness of breath?	More than Once a day **[1]**	Once a day **[2]**	3 to 6 times a week **[3]**	Once or twice a week **[4]**	Not at all **[5]**	.....
3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?	4 or more nights a week **[1]**	2 to 3 nights a week **[2]**	Once a week **[3]**	Once or twice **[4]**	Not at all **[5]**	.....
4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?	3 or more times per day **[1]**	1 to 2 times per day **[2]**	2 or 3 times per week **[3]**	Once a week or less **[4]**	Not at all **[5]**	.....
5. How would you rate your asthma control during the past 4 weeks?	Not Controlled at All **[1]**	Poorly Controlled **[2]**	Somewhat Controlled **[3]**	Well Controlled **[4]**	Completely Controlled **[5]**	.....

TOTAL: .....

This material was developed by GSK.

ACT questionnaire: Spanish version:

Asthma Control Test™ (La Prueba de Control del Asma) es:

- Una prueba rápida que produce un resultado numérico para evaluar el control del asma.
- Reconocida por los Institutos Nacionales de la Salud (National Institutes of Health - NIH) en sus directrices sobre el asma de 2007.[1]
- Convalidada clínicamente por espirometría y evaluaciones de especialistas.[2]

Para pacientes de 12 años de edad en adelante:

1. Conteste cada pregunta y escriba el número de la respuesta en el cuadro que aparece a la derecha de la pregunta.
2. Sume sus respuestas y escriba el puntaje total en el cuadro del TOTAL que se muestra abajo.
3. Hable con su médico sobre sus resultados.

1. En las últimas **4 semanas**, ¿cuánto tiempo le ha impedido su **asma** hacer todo lo que quería en el trabajo, en la escuela o en la casa?

Siempre 1	La mayoría del tiempo 2	Algo del tiempo 3	Un poco del tiempo 4	Nunca 5

2. Durante las últimas **4 semanas**, ¿con qué frecuencia le ha faltado el aire?

Más de una vez al día 1	Una vez al día 2	De 3 a 6 veces por semana 3	Una o dos veces por semana 4	Nunca 5

3. Durante las últimas **4 semanas**, ¿con qué frecuencia sus síntomas del **asma** (respiración sibilante o un silbido en el pecho, tos, falta de aire, opresión en el pecho o dolor) lo/la despertaron durante la noche o más temprano de lo usual en la mañana?

4 o más noches por semana 1	De 2 a 3 noches por semana 2	Una vez por semana 3	Una o dos veces 4	Nunca 5

4. Durante las últimas **4 semanas**, ¿con qué frecuencia ha usado su inhalador de rescate o medicamento en nebulizador (como albuterol)?

3 o más veces al día 1	1 ó 2 veces al día 2	2 ó 3 veces por semana 3	Una vez por semana o menos 4	Nunca 5

5. ¿Cómo evaluaría el control de su **asma** durante las **últimas 4 semanas**?

No controlada en absoluto 1	Mal controlada 2	Algo controlada 3	Bien controlada 4	Completamente controlada 5

PUNTAJE

TOTAL

Si obtuvo 19 puntos o menos, es probable que su asma no esté bajo control. Hable con su médico sobre sus resultados. Las siguientes respuestas no deben sumarse al puntaje total. Converse con su médico acerca de estas respuestas.

En los últimos 12 meses, ¿cuántas veces ha acudido al servicio de emergencias debido al asma (que no hayan resultado en una hospitalización)? _____

En los últimos 12 meses, ¿cuántas veces ha estado hospitalizado debido al asma? _____

Referencias: 1. Departamento de Salud y Servicios Humanos de EE. UU., Institutos Nacionales de la Salud, Instituto Nacional del Corazón, los Pulmones y la Sangre. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma (EPR-3 2007).* Ítem de NIH No. 08-4051. http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Consultado el 10 de septiembre de 2007. **2.** Nathan RA y otros. *J Allergy Clin Immunol.* 2004;113:59-65.

ASTHMA ACTION AMERICA®

HM2701RO May 2010

8.4. ANNEX IV: mini-AQLQ (Asthma Quality of Life Questionnaire).

Spanish version:

CUESTIONARIO DE CALIDAD DE VIDA EN PACIENTES CON ASMA - VERSIÓN REDUCIDA (SPANISH VERSION) AUTO-ADMINISTRADO

ID PACIENTE:_____

FECHA:_____

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Le rogamos responda **a todas** las preguntas señalando con un círculo la respuesta que mejor describa cómo se ha encontrado **durante las dos últimas semanas, debido al asma.**

EN GENERAL, ¿CON QUÉ FRECUENCIA **DURANTE LAS 2 ÚLTIMAS SEMANAS**:

	Siempre	Casi siempre	Gran parte del tiempo	Parte del tiempo	Poco tiempo	Casi nunca	Nunca
1. NOTÓ QUE LE FALTABA EL AIRE debido al asma?	1	2	3	4	5	6	7
2. Sintió que le molestaba el POLVO, o tuvo que evitar un lugar debido al POLVO?	1	2	3	4	5	6	7
3. Se sintió FRUSTRADO O IRRITADO debido al asma?	1	2	3	4	5	6	7
4. Sintió molestias debido a la TOS?	1	2	3	4	5	6	7
5. TUVO MIEDO DE NO TENER A MANO SU MEDICACIÓN PARA EL ASMA?	1	2	3	4	5	6	7
6. Notó una sensación de AHOGO U OPRESIÓN EN EL PECHO?	1	2	3	4	5	6	7
7. Sintió que le molestaba el HUMO DEL TABACO, o tuvo que evitar un lugar debido al HUMO DEL TABACO?	1	2	3	4	5	6	7
8. Tuvo DIFICULTADES PARA DORMIR BIEN POR LA NOCHE debido al asma?	1	2	3	4	5	6	7

EN GENERAL, ¿CON QUÉ FRECUENCIA **DURANTE LAS 2 ÚLTIMAS SEMANAS**:

	Siempre	Casi siempre	Gran parte del tiempo	Parte del tiempo	Poco tiempo	Casi nunca	Nunca
9. Se sintió PREOCUPADO POR TENER ASMA?	1	2	3	4	5	6	7
10. Sintió SILBIDOS O PITOS en el pecho?	1	2	3	4	5	6	7
11. Sintió que le molestaba o tuvo que evitar salir de casa debido AL TIEMPO O A LA CONTAMINACIÓN ATMOSFÉRICA **?**	1	2	3	4	5	6	7

¿HASTA QUÉ PUNTO **EL ASMA LE HA LIMITADO** PARA HACER ESTAS ACTIVIDADES **DURANTE LAS 2 ÚLTIMAS SEMANAS?**

	Totalmente limitado	Extremada-mente limitado	Muy limitado	Moderada-mente limitado	Algo limitado	Poco limitado	Nada limitado
12. ESFUERZOS INTENSOS (como darse prisa, hacer ejercicio, subir escaleras corriendo, hacer deporte)	1	2	3	4	5	6	7
13. ESFUERZOS MODERADOS (como caminar, hacer las tareas del hogar, trabajar en el jardín o en el huerto, hacer la compra, subir escaleras sin correr)	1	2	3	4	5	6	7

¿HASTA QUÉ PUNTO **EL ASMA LE HA LIMITADO** PARA HACER ESTAS ACTIVIDADES **DURANTE LAS 2 ÚLTIMAS SEMANAS?**

	Totalmente limitado	Extremada-mente limitado	Muy limitado	Moderada-mente limitado	Algo limitado	Poco limitado	Nada limitado
14. ACTIVIDADES SOCIALES (como hablar, jugar con niños/animales domésticos, visitar a amigos/familiares)	1	2	3	4	5	6	7
15. ACTIVIDADES RELACIONADAS CON SU TRABAJO (tareas que tiene que hacer en su trabajo*)	1	2	3	4	5	6	7

** Si no está trabajando, responda a esta pregunta pensando en las tareas que tiene que hacer la mayoría de los días.*

CLAVE DE LAS DIMENSIONES:

Síntomas: 1, 4, 6, 8, 10
Limitación de actividades: 12, 13, 14, 15
Función emocional: 3, 5, 9
Estímulos ambientales: 2, 7, 11