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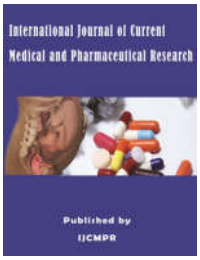

THE RELATIONSHIP OF THE SERUM VITAMIN D LEVELS WITH ASTHMATIC SEVERITY RESPONSES IN ASTHMATIC CHILDREN

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ABSTRACT

Rationale: Vitamin D has been found to have anti-inflammatory and immune-modulating effects.
Objective: the purpose of this study was to determine the relationship between the serum Vitamin D levels and clinical asthmatic types
Material and Methods: We studied 74 asthmatic children, aged from 5 to 15, who were admitted to the Children´s Hospital (Santisima Trinidad) of Córdoba, Argentina. The group was divided into severe asthma (n: 51), moderate asthma (n: 5), mild asthma (n: 18), in agreement with GINA and compared with healthy children (n: 21), sex and age matched, control group. We measured serum vitamin D levels.
Results: The patients in severe asthma presented normal level in 24, insufficient: 21, and deficient: 6 cases; in moderate asthma: normal 2, insufficient 1 and deficient 2, in mild asthma: normal 9, insufficient 8, deficient 1 and in controls all presented normal level (p= 0.0169). The IgE levels were in severe asthma 508±58.41 kU/L, in moderate asthma 329±78.91kU/L, in mild 172.9± 33.4 kU/L, in control: 37.86±5.44 kU/L, p<0.0001. The blood eosinophil levels were in severe asthma: 425.8±49.9 x mm3, in moderate asthma: 414± 75.77 x mm3, in mild asthma: 228± 31.59 x mm3, in control group: 160±15.7 x mm3 (p=0.0016).
Conclusions: There was not a correlation between serum vitamin D levels and asthma control statuses in our asthmatic children groups. More studies are required to determine the role of vitamin D in asthma.

INTRODUCTION

Asthma is a chronic inflammatory disorder that causes hyper responsiveness, leading to recurrent episodes of wheezing, breathlessness and coughing that are associated with variable airflow obstruction. Historically, asthma has been described as having an underlying Th2 mediated inflammatory profile. However, there is increasing evidence for heterogeneity of asthma phenotypes and endotypes, with a significant proportion of asthmatic patients demonstrating a low or no Th2/Th9 phenotypes that appear less sensitive to control by glucocorticoids (1 - 4).

Inhaled corticosteroids (ICS) are glucocorticoid (GC) preparations widely employed as the principal controller therapy for patients with persistent asthma (4-5). Although studies suggest that the majority of patients with asthma are successfully treated with ICS-containing regimens (5-6), there is variability in response to ICS, with a substantial proportion of patients not achieving optimal asthma control despite even high-dose ICS treatment (4-7). In addition to impairing response to treatment, as measured by improved asthma control, steroid resistance has been associated with alterations in the long-term prognosis of asthma, as indicated by accelerated deterioration in lung function (7). Given this situation, alternative treatment strategies need to be considered for patients who continue to experience suboptimal asthma control after initiation of ICS. Furthermore understanding the mechanisms that underlie the lack of universal response to ICS in asthma is critical for improving strategies for optimizing asthma treatment (6-7). A number of potential explanations exist for the variable clinical response to ICS, and insensitivity to the anti-inflammatory effects of GCs must be considered as

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one of them in patients who do not respond optimally. The mechanisms of GC insensitivity are complex, reflecting the multiple steps involved in GC action (8).

Some published data suggest that vitamin D interacts with GC signaling pathways in ways that are clinically relevant, although little experimental work has been published in this area (9 – 12). In 2006, Xystrakis *et al* (12) reported that supplementation with the active pharmacological form of vitamin D_3 enhanced dexamethasone (DEX)-induced expression of IL-10 by T regulatory cells. Furthermore, they demonstrated that allergen-induced T helper type 2 cell cytokine production was inhibited by allergen –induced IL-10–secreting T regulatory cells in an IL-10–dependent manner. And in subjects with steroid-resistant asthma, pre-incubation of T cells with both IL-10 and vitamin D_3 overcame defects in DEX-induced $CD4^+$ T cell IL-10 production, perhaps by a mechanism in which vitamin D_3 reversed ligand-induced down-regulation of the GC receptor. Complementing these experimental data, a recent population study suggested an association between lower vitamin D levels and increased ICS requirements in children, with a reduced need for anti-inflammatory controller therapy as vitamin D levels increased (12).

One hypothesis for the increasing prevalence of asthma involves Vitamin D. Some have argued that different factors associated with westernization have led to lower Vitamin D levels, which in turn have resulted in higher rates of asthma. However, others have argued that Vitamin D has more of a deleterious effect on allergic pathogenesis(9 – 12). Although multiple studies have examined maternal Vitamin D and subsequent wheezing in offspring's, (13) there are limited data on Vitamin D levels in children with asthma, as well as asthma features associated with Vitamin D levels. A study of children from Costa Rica showed a significant inverse association between Vitamin D levels and use of anti-inflammatory medication (ICS o leukotriene inhibitors) in the previous year, total IgE serum levels, and eosinophil counts (13 – 14).These important findings require confirmation. To our knowledge, the prevalence of Vitamin D insufficiency/deficiency is unknown for children with asthma living in southern latitude, Córdoba Argentina. In this area the UV – B light irradiation have very high level in summer, and high levels in spring and autumn, as well as medium level in winter (15 – 17). In addition, more information is needed regarding the specific clinical and therapeutic variables associated with lower Vitamin D levels in patients with childhood asthma. To assess the association between vitamin D levels, asthma phenotype, and steroid response in children, the first purpose of this work was to investigate the hypothesis that reduced serum vitamin D concentration would be associated with worsening of a number of relevant asthma clinical manifestations from a group of patients living in southern latitudes. Secondly to further define what variables, including corticosteroid use and markers of allergy, such as IgE serum levels and skin allergen sensitivity and blood eosinophil levels are associated with vitamin D, normal / insufficiency / deficiency in childhood asthma.

METHODS

Subjects

Children with asthma referred to Children Hospital of Córdoba, Argentina were identified through focused searches of laboratory data using codes for 25 – hydroxyl vitamin D assay. Data were collected between March 1, 2012 and July 31, 2013. The study is prospective and the patient information was obtained by using the clinical history record of the Children Cordoba Hospital. Patients between the ages of 5 to 15 who had 25-hydroxy vitamin D serum levels drawn were included if they had a physician diagnosis of asthma. Patients were excluded if there was documentation that they were taking Vitamin D supplements or if they had chronic pulmonary conditions, (bronchiectasis or cystic fibrosis).

The investigation was approved and controlled by the Research and Ethic Committee of the Childhood and Adulthood of the Sanitary Polo of Córdoba, Argentina; Resolution N° 308– 11. The parents of patients younger than seven signed the consent to include the kids in this study. And both parents and children older than seven signed the agreement together with the control group.

Data collection

The group was divided into: severe asthmatic responses (n: 51); moderate asthmatic patients 5 cases, and mild asthmatic responses (n: 18) in agreement with GINA (1, 18) and compared with healthy children (n: 20), sex and age matched (Controls).

We measured Serum 25 hydroxy Vitamin D levels by Roche electrochemiluminescence, following the laboratory instructions; values were reported in nanograms per milliliter. Vitamin D levels were separated in: normal level ≥ 30 ng/ml, insufficient from ≤ 29.90ng/ml to ≥20 ng/ml and deficit ≤ 19.9 ng/ml following Xystrakis *et al*(12).

Skin prick testing was performed according to publications aspreviously described (19 –20) by using histamine and saline controls. Positive reactions were recorded for wheal sizes greater than or equal to 3 mm diameter larger than those elicited by negative saline control. Seasonal and annual aeroallergens tested were common of the Córdoba region, such as: Dermatophagoides pt, Alternaria alternata, Cladosporium, Penicillium, Aspergillus, Mucor, Rhizophus, Celtis tala, Grasses, Ragweed, Amaranthus, and Pool of tree, Cat and Dog, purchased in Allergopharma Laboratories, Buenos Aires Argentina.

In addition we determined the total serum IgE levels by ELISA test following Bio Merieux France indications and another previous publication (20). Reflex titer assay were done to quantify IgE levels of greater than 5000 kU/L. Blood Eosinophil level in all patientswas performed by hemocytomether technique

Latitude of the patient´s home address was determined based on data from the Argentine Census of 2010. The latitude is 31 ° 21"south, the longitude is 64 ° 18 "west and altitude is 410 m of sea level. The levels of UVB light were studied previously by different groups of Córdoba Argentina, from 1998 to 2013 (15 – 17). The UVB levels irradiance in this Córdoba area were from medium level UVB in winter (4 to 5 Units) to high level UVB in summer (10 to 11 UVB U) and medium levels in spring and autumn (6 to 9 UVB U)(15 – 17).

Demographic and clinical manifestation and treatment with and without inhalant corticosteroid (IC) responses were determined by correlation coefficient and X^2tests approximation when they were categorical.

For the laboratory analysis of Vitamin D and IgE were expressed as Means ± SD. The Kruskal –Wallis and Dunn´s

multiple comparison tests were used to compare samples that did not fit Gaussian distribution. All reported p values were based on 2 side tests.The statistics analysis were performed by Graph Pad Prism 5 software, CA, US. We considered statically significant p<0.05.

RESULTS

Subjects characteristics

We studied 74 asthmatic children, aged 5 to 15 years old. Racial data were available for 71 to 74 cases. Sixty-two (87,32 %) were white, Asian were 2 cases(2.81%) and mixed race 7 cases(9,87 %). The others characteristics such as age, sex, BMI, serum IgE, skin prick test to aeroallergens, eosinophil levels and season are present in table 1.

Table 1 Patients´ Characteristics

Characteristics	Sample Size	Data
Age (y)	74	8.08 ± 2.49 (5 - 15)
Separated in:		
a)5 to 9.9 y	55	6,9 ±1,6
b)10 to 10 y	19	11±1,07
Sex		
a)5 to 9.9 y	54	Male (28) (51.8 %)
b)10 to 15 y	19	Male (5) (26.31 %)
Race	71	White 62 (87.32 %) Asian 2 (2.81 %) Mix 7 (9.87 %)
No determined	3	
BMI		
20 to 24.99	74	71 (95.95 %)
≥ 25 to 29.99		2 (2.70 %)
≥ 30		1 (1.35 %)
IgE kU/L	74	Severe (n:51) 508± 361.7 Moderate /Mild (n:23) 182± 151,1 Controls (n:20) 38,5 ± 28,57
Log 10 IgE	51	Severe 2.705
	23	Mild/Moderate 2.26
	20	Controls 1.585
N° of positive aeroallergen by Skin Prick test	47	41 (+)
Non Done	27	
Eosinophil count (cells/mm3)	74	Severe (n:51)= 425± 356 Mild to Moderate (n:23) =216±188 Controls (n:20) = 160±72
Season	Summer	54 (72.97 %)
	Autumn	8 (10.81 %)
	Winter	6 (6.77 %)
	Spring	7 (9.45 %)

The asthmatic patients were divided in severe (n: 51), moderate (n:5) and mild (n:18), figure 1. The sex of the mild/moderate asthmatic group (n:23) was male in 56 % of cases in patients from 5 to 9.9 ,and from 10 to 15 it was predominant female, 87, 5 %. In the severe asthmatic group from 5 to 9.9 (n: 39) the female was predominant in 56 % of the cases, and in the sub group from 10 to 15 (n: 12)in 8 out of 12 was female (66%). Table 2

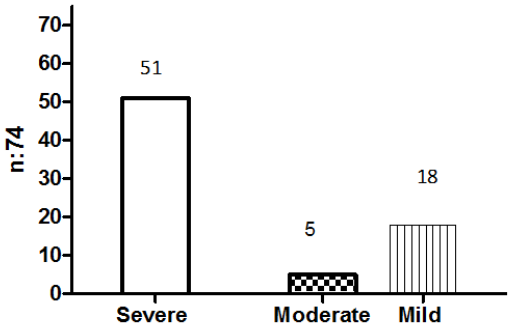

Figure 1 Asthmatic patients separated by type of severity

Table 2 Sex distribution of asthmatic patients, separated by Age and Severity. (p=0.0003)

Severity of Asthma	Age : 5 to 9.9 years		Age : 10 to 15 years	
	Male	Female	Male	Female
Mild/ Moderate (n:23)	7	11	1	4
Severe (n:51)	17	22	4	8

The date of the 25-hydroxyvitamin D level was obtained and recorded to assess seasonal variations in frequency of specimen collection: in the severe asthmatic group was performed in 31 cases in summer, in 8 cases in spring, in 7 cases in autumn, and in 5 cases in winter. The mild to moderate asthmatic group was obtained in 22 out of 23 cases in summer and the remaining case was performed in winter. Latitude and season of year, summer vs winter, were not significantly associated with Vit D level. Figure 2

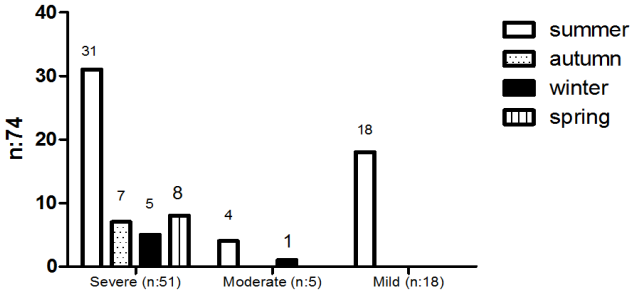

Figure 2 The different seasons to perform the collection of serum samples of vitamin D

ANOVA 2 ways, p <0.029

Among all the asthmatic studied, the median serum 25 – hydroxyl vitamin D level in severe asthmatic within ICS treatment (n:29) was 30.18.±8.55 ng/ml, without ICS (n:22) was 27.62 ± 7.507 ng/ml, inmoderate asthmatic group was 24.84 ± 10.11 ng /ml, and in mild asthmatic patients within ICS(n:15) was 34.44 ± 8.76 ng/ml and without ICS was 27.68± 11.93 ng/ml, and in control group was 38.45± 4.55 ng/ml,p=0.0003. Figure 3

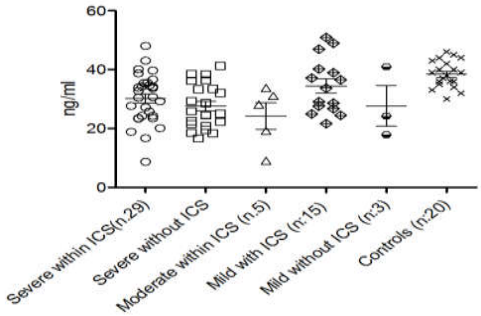

Fig 3 Serum Vitamin D level in Asthmatic patients within and without ICS vs Control group.)

Kruskal – Wallis p=0.0003

The eosinophil level was in severe group 425.8±356 per mm3, in moderate to mild asthmatic groups was 215±187 per mm3 and control group was 159 ± 71.92 per mm3, p=0.0022.Whereas the eosinophil counts demonstrated correlation with the severe asthmatic group vs mild to moderate asthmatic groups. Figure 4

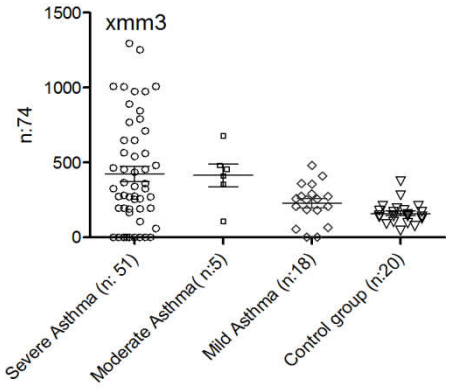

Figure 4 Blood Eosinophil level in Severe, Moderate and Mild Asthmatic patients vs control group.

(p=0.0016)

The IgE levels was in severe asthmatic groups 508±361 kU/L, (ranged between 1218 and 15 kU/L), in moderate to mild asthmatic group was 182.5±151.1 kU/L,(ranged 538 to 13 kU/l), and in controls 38±25.6 kU/L; p<0.0001.Among markers for atopy the IgE level was significantly higher in severe asthmatic group with compared with moderate to mild asthmatic patients and control group Figure 5

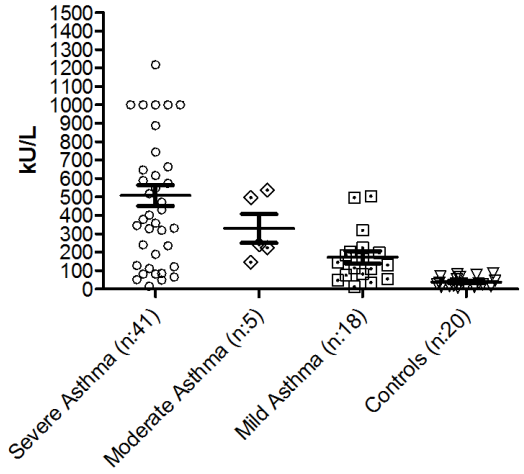

Figure 5 IgE serum levels in Severe, Moderate, Mild Asthmatic patients vs control group.

Kruskal – Wallis p <0.0001

The overweight was presented in 2 out of 74 cases in one case with Vitamin D insufficient level and the other case with normal level and in one case out of 74 cases presented obesity and deficient vitamin D level. The 71 out of 74 cases presented normal weight and different vitamin D levels. Table 1

The atopic background was similar in severe asthmatic group 40 out of 51 cases and the mild to moderate asthmatic group in 18 out of 23 cases, not significantly, and in control group 2 out of 20.Figure 6

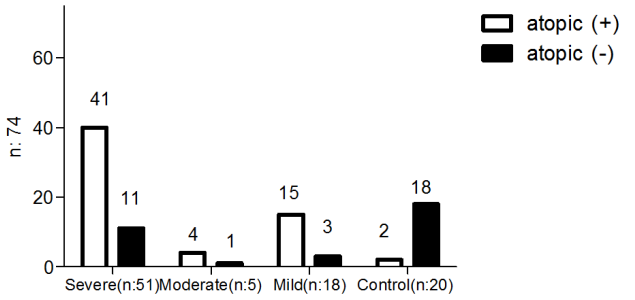

Fig 6 Atopic conditions in different asthmatic groups vs control group

p<0.0001

Positive environmental skin prick test responses showed significant positivity to Der pt. Table 3. Separate univariate analyses were performed on individual aeroallergens. Sensitivity Der pt was the most common skin test finding in 55 % cases and was not associated with low vitamin D levels. Mold allergens and alternaria species in particular showed a trend toward lower Vitamin D levels but was not significant. Among the different therapeutic modalities assessed (Table 4) (Figure 7), the use of inhaled and oral steroids, plus the use of long - acting β agonists did not show significant association with lower vitamin D. In asthmatic severe group the use of ICS was performed in 29 of 51 cases, and in 22 cases did not receive this type of treatment, the Vitamin Dserum levels were similar in these two groups as well as in moderate and mild asthmatic patients.

Table 3 Allergic Sensitivity demonstrated by Skin prick Test in asthmatic patients

Group	Der pt	Alternaria	Aspergillus	Der pt + Alternaria	Der pt Amaranthus	Grasses	Prick (-)	Not done
Severe	5	1	1	1	0	0	19	24
Mild Moderate	13	4	1	1	1	1	2	0

p<0.0001

The use of ICS was similar in moderate asthmatic group 5 of 5 cases and mild asthmatic group in 15 of 18 patients.

Table 4 Univariate analysis of Serum Vitamin D levels and medication use

Medication used sample size	Vit D level expressed as Median ± SD and range in ng/ml	p value Kruskal – Wallis among asthmatic groups	Spearman Rank Correlation
Within ICS (n: 47)			
Mild Asthma (n:15) Oral corticosteroids Short β2 agonist to demand	31.53 ± 9.9963 (17 - 50) Not used < 2 days a week		
Moderate Asthma (n:5) Oral corticosteroid in 1 to 2 series per year LABA associated with ICS	24 ± 9.95 (9.04 -28.1)		
Severe Asthma (n:28) Oral corticosteroid in 5 or more series per year IV corticosteroid (n:28) LABA associated with ICS in all cases	29.88 ± 8.209 (16.64 - 43)	0.0338	NS
Without ICS Mild Asthma (n:3) Oral corticosteroids Short β2 agonist at demand	38.33 ± 6.807 (33-46) Not used		

Severe Asthma (n:23)	
Oral corticosteroid (n:23) in 5 or more series per year	30.15 ± 10.1 (8.67 – 48.7)
IV corticosteroid (n:23)	done
LABA associated with ICS	Not done

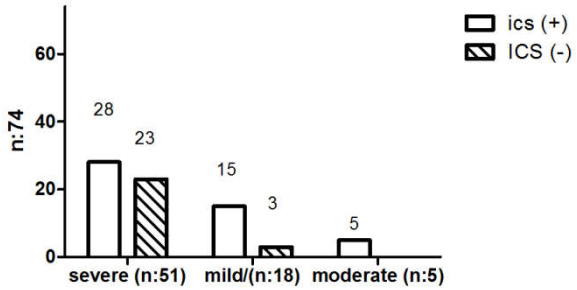

Figure 7 Correlation between the use of the ICS in asthmatic groups separated by Severity

p=0.0021

In the three categories of asthmatic patients the more frequent association with serum vitamin D levels were normal and insufficient, 65 out of 74 cases, the deficit of vitamin D level was present in 9 out of 74 cases , p=0.0169, Table 5.

Table 5 Association between Asthma Severity and different categories of Vitamin D levels

Groups of Asthmatic patients separated by severity (n: 74)	Normal level ≥ 30 ng/ml	Insufficient level 29.9 to 20 ng/ml	Deficit level ≤ 19.9 ng/ml
Severe within ICS (n:29)	19	9	1
Severe without ICS (n:22)	5	12	5
Moderate within ICS (n:5)	2	1	2
Mild within ICS (n:15)	6	8	1
Mild without ICS (n:3)	3	0	0
Total	35	30	9

X2 ; p = 0.0169

DISCUSSION

Our study classified the level of asthma control based on the GINA guideline (18, 21-22). The percentages of reliever use, hospitalization, Emergency Department visits, systemic corticosteroids use were significantly higher in the severe uncontrolled group than moderate and mild asthmatic groups. This confirms that our patients were properly classified.

In this study we did not find any association of serum levels of 25 (OH) D with prevalence and incidence with diagnosed severity of asthma and atopy by different doctors,(clinical pediatricians, allergists and therapists). In our population of pediatric patients with asthma, the prevalence of normal VitD levels (≥30 ng/mL) was 45 % of severe asthmatic patients, the prevalence of VitD insufficiency level (<30 ng/mL) was 43.13%, and 11.78 % of patients being VitD deficient (<20 ng/mL). The moderate asthmatic patients presented in 60 % normal level and 20 % insufficiency level and 20 % deficient. The mild asthmatic patients presented 61 % normal levels, in 22 % insufficient level and deficient level in 17 %. These normal percentages were higher in severe asthmatic group than in study in equatorial populations of Costa Rica, in which 28 % had Vit D insufficiency (13).The moderate and mild asthmatic group had insufficiency in 20% and 22 % in both groups respectively. The deficient Vit D level was 20 % in moderate group and 17 % in mild asthmatic pediatric patients.

A possible explanation for lack of association between serum levels of 25 (OH) D and asthma or atopy in our study could be that participants who were primarily from latitudes above 30 ° S with good exposure to sun light and UV irradiation (15 – 17) in agreement with Hughes *et al* (23) and different to Peru and Iran studies (24- 25).

Other possible mechanisms of potential association between vitamin D and development of asthma is that adequate vitamin D levels during the pregnancy and early childhood prevent respiratory infections, promote lung development and decrease the risk of asthma. It has also been suggested that vitamin D status affects in the development of immune tolerance and the epithelial barrier function in early childhood and thus relates to development of atopy. These proposed mechanisms work in the early life, and therefore, vitamin D status in childhood wheezing would not be incidentalat the age of 5 or more (26–27).This finding is according with Camargo *et al*, who found a significant inverse association between cord blood levels of vitamin D and the risk of respiratory infections and childhood wheezing(28). They point out that childhood wheezing is a non-specific finding that might have been confused with incident asthma in previous studies showing associations between vitamin D status and asthma (28 -29).

Vitamin D may influence tissue modeling and repair the lungs throughout life and thus low levels of vitamin D may have a negative impact on lung function. In addition, an association between inadequate vitamin D levels and impaired lung function could be partially explained by the severity of childhood asthmatic patients with an increased risk of respiratory infections or a negative influence on muscle function (30). However, an association in a cross sectional study does not establish a causal relationship. Even though we have adjusted for potential confounding by passive smoking status, dietary habits and physical activity, we cannot rule out that association is due to residual or unmeasured confounding. We have previously shown that high serum levels of vitamin D [25(HO) D] may be considered a marker of an overall healthy lifestyle. (10 – 11, 21, 27,29- 33).

The clinical relevance of potential relation between serum 25(HO) D and lung function can be questioned. Thus association that may be of limited clinical relevance might have turned out statistically significant in our analyses due probably to the moderate number of participants. It would have been preferable to have more than one measurement of serum 25(HO) Don each participant to obtain more precise assessments of vitamin D status. Another weakness of this study is the not participation rates at 5 to 10 years follow up. At those who participate at follow-up are probably influenced by some selection bias. However, as participation in follow-up seemed to be independent of serum 25 (HO) D, selections bias may not be a significant problem.

Our study presented normal index mass body in 71 out of 74 cases with predominance of normal or insufficient of 25(HO) D levels; in the three residual cases with alteration of normal index mass body one case presented obesity and deficit of 25(HO) D and the other 2 cases with overweight presented in one case insufficient level and the other case normal level. These features are different from Thailand study with 36 % of cases with obesity in uncontrolled, partial controlled asthma or

controlled asthma (14) and in agreement with Lang (34). The measurement of airway inflammation in the obese asthmatic patient is an area to need of further study. Currently there is little evidence that obesity leads to greater allergic airway inflammation in children, this feature is in accordance with our findings (34).

We also could not find the correlation between serum 25(HO) D levels and total serum IgE level, eosinophil counts, or positivity of skin prick test to common aero – allergens in Córdoba region. In these aspects our findings are similar to Sherenian *et al*, (35) and different to Ho Yip *et al* (31). Moreover, inpatients have significantly higher IgE levels than out patients during all seasons. In our study, total serum IgE level was significantly elevated in children during asthma exacerbations requiring hospitalization than in those seen in our outpatient clinics. The study is also consistent with findings that total serum IgE levels increase with age and vary with sex. This study is in agreement with previous study publications (35 – 38).

Other aspects are the treatment of asthma and prevention of exacerbation with IC. In the mild persistent and moderate asthmatic groups received a correct use of inhaled corticosteroids but the 25(HO) D levels were wide dispersed and similar to severe asthmatic group. This last group was divided in two sub groups, one of them within IC (n:28) and the second group without IC (n:23) and the two sub groups presented severe asthmatic responses with admission to hospitalization in the 51 cases from one to eight times per year in each different patient. The two sub groups presented similar 25(HO)D serum levels but the non ICS asthmatic sub group did not present significative tendency to insufficient levels. Probably the sub group without IC did not fulfill the GINA recommendation but served as comparison with other therapeutic methods. Furthermore, many confounding factors can affect vitamin D and asthma severity may depend on genotype and phenotype of asthmatic patients, specially in enhanced production of IL 17 A in patients with severe asthma probably it is inhibited by 25 HO vitamin D in a glucocorticoid independent fashion (39). Other probably explanation is the association of vitamin D receptor polymorphisms with asthma risk (40 – 41).

Concluding remarks: there was not a significant correlation between serum vitamin D levels and asthma control statuses in Córdoba (Argentina) asthmatic children. More studies are required to determine the role of vitamin D in asthma and the promising role of vitamin D supplements in such patients.

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