EFFECT OFVITAMIN D3 IN PATIENTS WITH RESISTANT ASTHMA AMONG CHILDHOOD AND ELDERLY ASTHMATICS

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ABSTRACT

Background: Bronchial asthma is a chronic inflammatory disorder that is related with hyperresponsiveness of the airways and leads to repeated episodes of wheezing, dyspnea, chest tightness, and cough, which is often reversible, either spontaneously or after treatment Severe, steroid-resistant asthma is clinically and economically important, patients with this disease experience more frequent exacerbations of asthma, and are more likely to be hospitalized, and have a poorer quality of life. The association between vitamin D deficiency and asthma and allergies has recently increased significantly. Epidemiologic data in most of the reported studies suggest that low serum vitamin D (defined as circulating levels of 25(OH)D of ,30 ng/mL) in children with asthma is associated with more symptoms, exacerbations, reduced lung function, increased medication usage, and severe disease.

The aim of the current study is to evaluate the effect of vitamin D3 in patients with resistant asthma among childhood and elderly asthmatics.

Methods: This study includes 60 Resistant asthmatic subjects including 30 patients with serum 1.25 OH Vitamin D3 deficiency, who will be followed up after VITAMIN D3 supplementation therapy for three months and will be compared with 30 resistant asthmatic subjects with normal serum 1.25 OH Vitamin D3.

Results: during the study period 1000 IU Vitamin D3 were supplemented to childhood asthmatics and 2000 IU Vitamin D3 were supplemented to elderly

resistant asthmatics and Vitamin D3 was measured at the start and the end of the study.
Conclusions: improvement in the pulmonary functions (FEV1, FVC, FEF) especially with those of vitamin D3 deficiency after vitamin D supplementation for 12 weeks.
Recommendation: The study recommend that Measurement of vitamin D must be a routine step in resistant asthma among childhood and elderly resistant asthmatics, Vitamin D supplementation during childhood and adolescence, in adequate doses could be among the national nutritional priorities.
Keywords: Resistant Asthma, Vitamin D3

INTRODUCTION

According to the Global Initiative for Asthma, bronchial asthma is a chronic inflammatory disorder that is related with hyperresponsiveness of the airways and leads to repeated episodes of wheezing, dyspnea, chest tightness, and cough, particularly at night or early in the morning. These episodes are usually associated with extensive but variable bronchial obstruction, which is often reversible, either spontaneously or after treatment (GINA, 2012).

In the majority of patients control of asthma as defined by guidelines can be achieved with long-term maintenance medications (Brehm *et al*., 2009). However, a substantial proportion of patients do not achieve optimal asthma control despite even high dose treatment. In particular inadequately controlled patients with severe persistent asthma are at high risk of severe exacerbations and asthma-related mortality. These patients represent the greatest unmet medical need among the asthmatic population today (Freishtat *et al*., 2010).

Although most patients with chronic asthma have significant improvement in their airway function with corticosteroid therapy, a subset of asthmatics are insensitive to corticosteroid (Martin *et al*., 2007).

Clinical studies have revealed suboptimal response to ICS in about 50% of asthmatics (Szefler *et al*., 2010). Failure to detect corticosteroid insensitivity early in the course of illness may affect the treatment strategy and outcome. It should be noted that the term steroid resistant (SR) asthma refer to a relative insensitivity to corticosteroid (Corticosteroid dependent asthma) rather than absolute resistance (Corticosteroid resistant asthma) which is very rare and found in less than 1:1000 asthmatics, about 95% patients respond well to β2 agonist and corticosteroids with or without add on therapies like montelukast and long acting theophyllines. However, 5-10% of patients do not respond well to this treatment. These cases are labelled as difficult / therapy resistant asthma (Chung *et al*., 1999).

Corticosteroid resistant asthma is defined as less than 15% improvement in baseline FEV1 after 14 days course of oral prednisolone (40 mg/day) in patients who demonstrate more than 15% improvement in FEV1 following the inhaled β2 agonist, Salbutamol. Furthermore, the patients who show FEV1 improvement of 30% or more are considered corticosteroid sensitive (Chung, *et al*., 2006).

As bronchial asthma is still the most common chronic disease of childhood (Mannino *et al*., 2002).And one of the leading causes of morbidity in children worldwide (Kunisaki *et al*., 2012).

The number of studies concerning the association between vitamin D deficiency and asthma and allergies increased significantly. Epidemiologic

data in most of the reported studies suggest that low serum vitamin D (defined as circulating levels of 25(OH)D of ,30 ng/mL) in children with asthma is associated with more symptoms, exacerbations, reduced lung function, increased medication usage, and severe disease (Bousquet *et al*., 2000).

Asthmatic airway walls present an accumulation of activated eosinophils lymphocytes, mast cells, macrophages, dendritic cells, and myofibroblasts, which, combined, determine bronchial structural changes and disease progression and severity (van Oosterhout *et al*., 2005).

Medical therapy involves two different classes of medication – inhaled corticosteroids used as daily controller and beta-adrenergic agonists used for broncho dilation (Dejaco *et al*., 2006).

Asthma has become one of the most prevalent diseases worldwide causing a major public health concern. While there is evidence that the condition of asthma is multifactorial in etiology, changing environmental factors may underlie the rising prevalence of asthma, such as atmospheric pollution, dietary changes, allergens, improvements in health and hygiene, and lifestyle changes (GINA, 2012).

Among nutritional hypotheses, vitamin D status is of particular interest regarding the controversial beneficial effects in non-skeletal disorders, such as cardiovascular disease, cancer, schizophrenia, multiple sclerosis, and asthma. (Litonjua *et al*., 2007, Wang, *et al*., 2008, Toner, *et al*., 2010, Rosen *et al*., 2013, Ross *et al*., 2011).

Several studies have suggested that vitamin D deficiency and insufficiency are extremely common, even in people with abundant sun exposure (Brehn *et al*., 2009, Binkley, *et al*., 2007).

The vitamin D receptor is present in the bronchial smooth muscle (Bosse *et al*., 2007) and low vitamin D levels may lead to bronchial smooth muscle proliferation, cytokine release and airway remodeling (Damera *et al*., 2009, Banerjee *et al*., 2008, Song *et al*., 2007).

In addition, vitamin D has been shown to play a role in immune-modulation by interacting with T lymphocytes, dendritic cells, mast cells, monocytes and macrophages (Sandhu *et al*., 2010).

Therefore, it is not surprising that vitamin D deficiency has been associated with airway hyperresponsiveness, lower pulmonary function, and worse asthma control (Black *et al*., 2005).

The aim of the current study is to evaluate the effect of vitamin D3 in patients with resistant asthma among childhood and elderly asthmatics.

MATERIALS AND METHODS

This study is observational cohort study conducted at New Cairo Police Hospital, in Chest Department from January 2016 till January 2017 including 60 Resistant Asthmatic subjects including 30 patients with serum 1.25 OH Vitamin D3 deficiency, who will be followed up after VITAMIN D3 supplementation therapy for one month and will be compared with 30 Resistant Asthmatic subjects with normal serum 1.25 OH Vitamin D3.

Subjects will be grouped into: Group I: 30 Resistant Asthmatic subjects with 1.25 OH Vitamin D3deficiency. Group II: 30 Resistant Asthmatic subjects with normal 1.25 OH Vitamin D3.

All study subjects were recruited on voluntary basis and a written informed consent was obtained from the patients or from the patient's parent or legal guardian when the patient under the age of 18 years.

The following steps may help in the diagnosis of steroid resistant or insensitive asthma (Hartl *et al*., 2005).

1. Patient should have a prebronchodilator morning FEV1 < 70% of predicted with a 15% improvement following a rapidly acting bronchodilator treatment. This value of FEV1 is recorded as baseline.
2. These patients should be given oral steroid (prednisolone 40 mg/day) for at least two weeks.
3. These patients fail to show increase in prebronchodilator morning FEV1 by 15% over baseline value even after 2 weeks of oral steroid.

Patients with incorrect diagnosis, non-adherence with therapy and patients with a radiological diagnosis of pneumonia, impaired consciousness on admission or smoking history >10 packs/year were excluded from the study.

The steroid resistant asthma should be differentiated from "Brittle asthma", where patient experience recurrent episode of severe airways narrowing that appear rapidly over minute to hours, occurring anytime of the day with no obvious trigger. These patients have either normal lung function between episodes which cannot be prevented by steroid or a persistent

background of wide variability in airways obstruction. Such episodes may respond to either subcutaneous adrenaline or terbutaline (Gregg *et al*., 2005).

The following parameters will be performed to patients and control groups: Full history and physical examination. Complete blood count, Erythrocyte sedimentation rate, reticulocytic count. Aspartate transaminase, Alanine transferase, Total bilirubin, Direct bilirubin, Total protein, Serum albumin, Serum creatinine, Blood urea nitrogen, Serum Uric acid. (1,25 OH VITAMIN D3) Spirometry (FEV1, FVC, FEC1/FVC).

RESULTS

This study highlights the response to vitamin D3 supplementation as vitamin D deficiency was associated with a decrease in spirometric measures in the Childhood and Elderly resistant asthmatics as shown in the following tables:

Table (1): Demographic comparative analysis between "Cases" and Control:

Variable	Cases vitamin D3 deficiency (0-30 ng/mL) Mean ± SD	Control vitamin D3sufficiency (>30 ng/mL) Mean ± SD	T test(1)	P Value	Significance
Childhood					
Age	13.54±3.61	15.15±2.19	0.62	0.542	Non-Significant
BMI	21.22±1.72	23.21±1.78	0.57	0.573	Non-Significant
baseline vit.D (ng/mL)	11.23± 6.2	43.53±1.23	3.76	0.0004	Significant
Elderly					
Age	49.12±9.17	50.35±8.95	1.24	0.224	Non-Significant
BMI	26.20±2.25	26.40±2.95	0.22	0.828	Non-Significant
baseline vit. D (ng/mL)	8.76± 4.1	33.64±1.18	7.48	0.0006	Significant

Table 1 shows the study subjects' characteristics at baseline, there was no significant association as regarding age, BMI between "Cases" and "Control «, but there was significant difference as regarding baseline vitamin D (ng/mL) level.

Table (2): Comparative statistical analysis of spirometric measures in "Cases" and "Control "Before oral supplementation with 1000 IU vitamin D3 for children and 2000 IU vitamin D3 for elderly of D3:

Variable	Cases Mean ± SD	Control Mean ± SD	T test(1)	P Value	Significance
Childhood					
Actual FVC	2.76±0.49	2.84±0.20	0.597	0.556	Non-Significant
%Pred FVC	75.19±13.46	81.51±13.21	1.207	0.239	Non-Significant
Actual FEV1	1.52±0.15	1.68±0.15	2.628	0.015	Significant
%Pred FEV1	52.81±7.38	60.77±5.76	3.067	0.005	Significant
Actual FEF	0.78±0.18	0.88±0.09	1.876	0.077	Non-Significant
%Pred FEF	25.49±1.84	26.88±2.27	1.715	0.099	Non-Significant
Elderly					
Actual FVC	2.57±0.18	2.67±0.28	1.266	0.216	Non-Significant
%Pred FVC	72.51±14.89	77.94±9.83	1.257	0.219	Non-Significant
Actual FEV1	1.50±0.20	1.67±0.15	2.766	0.009	Significant
%Pred FEV1	52.01±8.14	58.72±7.29	2.535	0.016	Significant
Actual FEF	0.77±0.18	0.85±0.13	1.552	0.131	Non-Significant
%Pred FEF	25.51±2.54	26.57±0.80	1.664	0.119	Non-Significant

Table 2 shows significant association between "Cases" and "Control "Before oral supplementation with 1000 IU vitamin of D3 in Childhood and 2000 IU Elderly Resistant Asthmatics as regarding the mean "Actual FEV1% and Predictive FEV1" while there was non significant association as regarding the other spirometric measures.

Table(3): Comparative statistical analysis of spirometric measures in "Cases" and "Control" after oral supplementation with 1000 IU vitamin D3 for children and 2000 IU vitamin D3 for elderly from day 1 to day 90:

Variable	Cases Mean ± SD	Control Mean ± SD	T test(1)	P Value	Significance
Childhood					
Actual FVC	3.08±0.33	2.89±0.18	1.737	0.099	Non-Significant
%Pred FVC	82.01±10.78	81.53±12.24	0.107	0.916	Non-Significant
Actual FEV1	1.72±0.18	1.69±0.13	0.609	0.548	Non-Significant
%Pred FEV1	60.51±8.41	60.79±5.17	0.099	0.922	Non-Significant
Actual FEF	1.42±0.25	1.51±0.23	0.954	0.350	Non-Significant
%Pred FEF	43.28±7.38	44.09±5.87	0.307	0.761	Non-Significant
Elderly					
Actual FVC	2.98±0.36	2.82±0.16	1.714	0.100	Non-Significant
%Pred FVC	83.10±8.70	77.95±8.37	1.760	0.088	Non-Significant
Actual FEV1	1.82±0.11	1.75±0.16	1.601	0.120	Non-Significant
%Pred FEV1	59.70±7.61	58.72±6.99	0.338	0.701	Non-Significant
Actual FEF	1.34±0.26	1.36±0.38	0.139	0.90	Non-Significant
%Pred FEF	43.93±9.84	43.58±6.70	0.120	0.906	Non-Significant

Table 3 shows no significant association in spirometric measures between "Cases" and "Control" after oral supplementation with 1000 IU vitamin D3 for children and 2000 IU vitamin D3 for elderly from day 1 to day 90.

Table(4): Comparative spirometric analysis in "Control" before and after oral supplementation with 1000 IU vitamin D3 for children and 2000 IU vitamin D3 for elderly from day 1 to day 90:

Variable	Cases Mean ± SD	Control Mean ± SD	T test(1)	P Value	Significance
Childhood					
Actual FVC	2.84±0.20	2.89±0.18	1.539	0.150	Non-Significant
%Pred FVC	81.51±13.21	81.53±12.24	0.020	0.984	Non-Significant
Actual FEV1	1.68±0.15	1.69±0.13	0.160	0.876	Non-Significant
%Pred FEV1	60.77±5.76	60.79±5.17	0.010	0.993	Non-Significant
Actual FEF	0.88±0.09	1.51±0.23	9.732	0.000	Significant
%Pred FEF	26.88±2.27	44.09±5.87	11.348	0.000	Significant
Elderly					
Actual FVC	2.67±0.28	2.82±0.16	2.008	0.062	Non-Significant
%Pred FVC	77.94±9.83	77.95±8.37	0.001	0.999	Non-Significant
Actual FEV1	1.67±0.15	1.75±0.16	1.838	0.085	Non-Significant
%Pred FEV1	58.72±7.29	58.72±6.99	0.004	0.997	Non-Significant
Actual FEF	0.85±0.13	1.36±0.38	7.836	0.000	Significant
%Pred FEF	26.57±0.80	43.58±6.70	11.075	0.000	Significant

Table 4 shows significant association in "Control" before and after oral supplementation with 1000 IU vitamin D3 for children and 2000 IU vitamin D3 for elderly from day 1 to day 90 in Childhood and Elderly Resistant Asthmatics as regarding the mean "Actual and Predictive FEF " while there was non-significant association as regarding the other spirometric measures.

Table(5): Comparative spirometric analysis in "Cases" before and after oral supplementation with 1000 IU vitamin D3 for children and 2000 IU vitamin D3 for elderly from day 1 to day 90:

Variable	Cases Mean ± SD	Control Mean ± SD	T test(1)	P Value	Significance
Childhood					
Actual FVC	2.76±0.49	3.08±0.33	2.882	0.014	Significant
%Pred FVC	75.19±13.46	82.01±10.78	5.576	0.0001	Significant
Actual FEV1	1.52±0.15	1.72±0.18	3.908	0.0021	Significant
%Pred FEV1	52.81±7.38	60.51±8.41	7.534	0.000007	Significant
Actual FEF	0.78±0.18	1.42±0.25	23.481	0.000	Significant
%Pred FEF	25.49±1.84	43.28±7.38	10.985	0.000	Significant
Elderly					
Actual FVC	2.57±0.18	2.98±0.36	4.769	0.0002	Significant
%Pred FVC	72.51±14.89	83.10±8.70	4.786	0.0002	Significant
Actual FEV1	1.50±0.20	1.82±0.11	6.297	0.00001	Significant
%Pred FEV1	52.01±8.14	59.70±7.61	6.211	0.00001	Significant
Actual FEF	0.77±0.18	1.34±0.26	8.566	0.0000002	Significant
%Pred FEF	25.51±2.54	43.93±9.84	8.144	0.0000004	Significant

Table (5) shows that there is significant association in"Cases" before and after oral supplementation with 1000 IU vitamin D3 for children and 2000 IU vitamin D3 for elderly from day 1 to day 90 as regarding all spirometric measures "Actual and Predictive FEV1, FVC,FEF".

Table(6): Comparative spirometric analysis (change) in "Cases" and "Control " before and after oral supplementation with 1000 IU vitamin D3 for children and 2000 IU vitamin D3 for elderly from day 1 to day 90:

Variable	Cases Mean ± SD	Control Mean ± SD	T test(1)	P Value	Significance
Childhood					
FVC% change	6.82±4.41	0.02±4.06	4.088	0.0004	Significant
FEV1% change	7.71±3.69	0.02±5.79	4.041	0.0005	Significant
FEF% change	17.79±5.84	17.20±5.47	0.266	0.793	Non-Significant
Elderly					
FVC% change	10.59±9.12	0.00±3.54	4.462	0.00009	Significant
FEV1% change	7.69±5.11	0.00±3.54	5.104	0.00001	Significant
FEF% change	18.42±9.32	17.02±6.33	0.512	0.612	Non-Significant

Table 6 shows that there is significant association in the (change) in "Cases" and "Control" before and after oral supplementation with 1000 IU vitamin D3 for children and 2000 IU vitamin D3 for elderly from day 1 to day 90 in FEV1% change and FVC% change and there was non-significant association as regarding FEF% change.

DISCUSSION

In the present study we investigated the role of vitamin D in a group of children and elderly subjects with asthma. Similar to our study, a systematic review and meta-analysis incorporated evidence from 435 child and 658 adults participating in nine double-blind, randomised, placebo-controlled trials of vitamin D supplementation, of these, one trial involving 22 children and two trials involving 658 adults contributed to the analysis of the rate of exacerbations requiring systemic corticosteroids. Administration of vitamin D resulted in a clinically and statistically significant reduction in the rate of

asthma exacerbations requiring treatment with systemic corticosteroids (Martineau *et al*., 2016).

CONCLUSION

This study highlights the response to vitamin D3 supplementation as vitamin D deficiency was associated with a decrease in spirometric measures in the Childhood and Elderly resistant asthmatics. However, there is still need to evaluate this effect of vitamin D3 in patients with resistant asthma among childhood and elderly asthmatics through further studies.

RECOMMENDATIONS

Measurement of vitamin D must be a routine step in resistant asthma among childhood and elderly asthmatics. Vitamin D supplementation during childhood and adolescence, in adequate doses could be among the national nutritional priorities.

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دراسة تأثير فيتامين د٣ فى مرضى حساسية الصدر المقاومين للعلاج فى الأطفال والمسنين

[٥]

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المستخلص

يمثل الربو واحدا من أكثر الأمراض المزمنة شيوعا ويشكل مشكلة صحية عامة رئيسية في جميع أنحاء العالم. يمكن السيطرة على الربو في الغالبية العظمى من المرضى الا ان هناك نسبة كبيرة من المرضى لا يحققون السيطرة المثلى للربو على الرغم من العلاج بالجرعات العالية من الكورتيزون.

معظم مرضى الربو المزمن لديهم تحسن كبير في وظيفة مجرى الهواء مع العلاج بالكورتيزون، إلا أن هناك مجموعة من مرضى الربو غير حساسة للكورتيزون. وقد كشفت الدراسات السريرية استجابة دون المستوى الأمثل ل الكورتيزون المستنشق في حوالي ٥٠٪ من مرضى الربو.

يعد الفشل في الكشف عن حساسية الكورتيزون في وقت مبكر من المرض قد تؤثر على استراتيجية العلاج والنتيجة. وتجدر الإشارة إلى أن مصطلح (الربو المقاوم للكورتيزون) يشير إلى الحساسية النسبية للكورتيزون وهو أمر نادر جدا ووجد في أقل من ١: ١٠٠٠ من مرضى الربو.

يواجه المرضى الذين لا يسيطرون بشكل كاف مع الربو المستمر الشديد خطرا كبيرا من التفاقم الشديد والوفيات المرتبطة بالربو. هؤلاء المرضى يمثلون اهتماما طبيا بين مرضى الربو اليوم.

لفيتامين (د٣) أهمية خاصة لحالات الربو المقاومة للكورتيزون ويعد من اهم الفرضيات التغذوية فيما يتعلق بالآثار المفيدة المثيرة للجدل في الاضطرابات غير الهيكلية، مثل أمراض القلب والأوعية الدموية والسرطان والفصام والتصلب المتعدد والربو.

وقد أشارت العديد من الدراسات الى أن نقص فيتامين (د٣) وعدم كفايته شائعة للغاية وانخفاض مستويات فيتامين (د٣) قد يؤدي إلى نمو العضلات الملساء فى الشعب الهوائية، وإطلاق السيتوكين وإعادة تشكيل مجرى الهواء مما يؤدى الى عدم او صعوبة السيطرة على الربو.

وتبين الدراسة أن نقص فيتامين (د٣) قد ارتبط بانخفاض وظائف التنفس، وصعوبة السيطرة على الربو في الاطفال والمسنين.