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Predictive role of IL-17A/IL-10 ratio in persistent asthmatic patients on vitamin D supplement

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ABSTRACT

Asthma is an airway inflammatory disorder. Vitamin (Vit) D is a potent immuno-modulator. It suppresses Interleukin (IL)-17 and induces IL-10. This study aims to investigate the role of IL-17A and IL-10 in predicting asthma control in case of Vit D supplementation. Seventy-nine patients enrolled in this study (42 patients received Vit D supplement and 37 patients did not receive the supplement). The enrolled patients were assessed at the beginning of this study and after 3 months. At the end of the study, there was a significant improvement in pulmonary function parameters in the Vit D supplemented group when compared to both the baseline values and the non-supplemented group. There was a significant decrease in serum IL-17A levels and a significant increase in serum IL-10 levels in comparison with the baseline values ($p < 0.0001$). The highest correlation of FEV1% improvement percentage was associated with the baseline IL-17A/IL-10 ratio ($r = 0.65$; $p < 0.0001$). The IL-17A/IL-10 ratio at a cutoff ≥ 2.66 had a sensitivity of 72.2% and a specificity of 83.3%. The IL-17A/IL-10 ratio had an adjusted odds ratio = 4.66 ($p = 0.04$). Vit D supplementation reduces the serum IL-17A levels and elevates the serum IL-10 levels in persistent asthmatic patients. So, Vitamin D can be used as an adjunct therapy side by side with the conventional asthma therapy. The IL-17A/IL-10 ratio seems to be a possible predictive biomarker for asthma improvement in patients depending on Vit D supplementation.

1. Introduction

Asthma is defined as an airway chronic inflammatory disorder. Asthma symptoms are depicted as attacks of shortness of breath, chest tightness, wheezing and coughing. Asthma symptoms tend to happen during the night or in the early morning (King and Moores, 2008). Diverse cells are implicated in asthma, as inflammatory cell products may assume a role in asthma pathogenesis and airway hyperresponsiveness (Luo et al., 2015).

Vitamin D (Vit D) is an important factor in skeletal and non-skeletal health. Vit D is a potent modulator of the immune response as it regulates cell proliferation and differentiation (Chambers and Hawrylowicz, 2011). So, Vit D reduces the risk of chronic diseases as well as infectious, allergic, and autoimmune diseases and malignancies (Krishnan et al., 2017).

Various ways by which Vit D may affect asthma pathogenesis pathways were suggested. As the failure of immune tolerance is the main allergic asthma characteristic, Vit D has immune regulation effects. Also Vit D regulates alarmin cytokines which have roles in nonallergic asthma (Urry et al., 2012). The cytokine profile is affected by Vit D due to the inhibition of IL-2 and Interferon gamma (IFN-γ) production, and the stimulation of IL4, IL5, IL10, and IL13 (Lang and Aspinall, 2017). Vit D can decrease the frequency of exacerbations by intensifying the antimicrobial pathways and improving response to steroids in steroid resistance patients (Pfeffer and Hawrylowicz, 2018).

The Vit D supplementation associated with lymphocyte polarization shifts toward T-helper 2 cells (Goncalves-Mendes et al., 2019). Vitamin D hinders the development of asthma or its exacerbation through either the inhibition of Interleukin (IL)-17 or the augmentation of IL-10 productions (Chambers et al., 2015). IL-17A is secreted from the T helper-17 cells and has a pro-inflammatory action. Vit D actions performed via the vitamin D receptor signal pathway, ending with the repression of IL-17 transcription (Joshi et al., 2011). IL-10 is secreted by regulatory T cells, dendritic cells and macrophages. It has a suppressive action on the activated innate immune response (Schülke, 2018). Vit D induces IL-10expression in different immune system cells (Medrano et al., 2018).

Abbreviations: ELISA, enzyme-linked immunosorbent assay; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; GINA, Global Initiative for Asthma; IL, interleukin; Vit, vitamin

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The cytokines imbalance is portrayed as an etiology of numerous diseases as alzheimer's disease, obsessive-Compulsive Disorder (Esawy et al., 2018), Rheumatic diseases (Tan et al., 2017), and hepatic diseases (Paquissi, 2016).

Vit D deficiency has a high prevalence. Its deficiency has been explained by many factors such as geographical sites, population skin color, sun exposure and Vit D insufficient diet (Tabrizi et al., 2018). As signs and symptoms of Vit D deficiency are nonspecific, the deficiency is detected in almost half of the healthy population (Hughes et al., 2011). Vitamin D deficiency has been demonstrated in association with numerous pathologic conditions of various ages (Boucher, 2012). Hence Vit D supplementation is associated with a decrease in the risk and severity of asthma. Additionally, it is related to better asthma control (Sharma et al., 2017). So, this study aims to investigate the role of IL-17A and IL-10 in predicting asthma control in case of Vit D supplement.

2. Patients and methods

2.1. Study design

A double blinded randomized controlled interventional study was conducted at Chest Department and Clinical Pathology Department, Zagazig University Hospitals. The duration of the study extended from February 2018 to March 2019. The proposition of this study was assessed and affirmed by the institutional ethics committee. All participants read the study information sheet and signed the partake consent.

2.2. Patient enrollment

A total of 172 asthmatic Egyptian patients, referred to Zagazig University Outpatient Chest Clinic, were screened for the enrolment into this study. Thirty-nine patients were excluded as they have a normal blood level of Vit D and 30 patients were precluded as they had the exclusion criteria. This study started with 103 patients, and follow-up information of 24 patients was missing. At last, 79 patients completed the study visits and were divided into two groups: 42 patients with supplement dose of Vit D, and 37 patients without any type of Vit D supplement (Fig. 1).

Vit D supplement was performed by a single-dose therapy regimen: a single dose of 300,000 IU of cholecalciferol (Memphis for pharmaceuticals and chemical industries, Egypt). Subjects, either placebo (saline) or Vit D, were received a single intramuscular dose. The enrolled patients were followed up for 3 months and the laboratory tests were reevaluated at the end of a three month period following the baseline evaluation.

2.3. Instructions

Patients continue to use their medications as usual according to the stepwise approach in which doses and selection of drugs were adjusted in line with the asthma severity. The used drugs were inhaled corticosteroids (fluticasone, budesonide, and ciclesonide), leukotriene antagonist (montelukast), long-acting beta agonists (salmeterol and formoterol), and theophylline.

All subjects were informed to refrain from taking any Vit D supplements and foods rich in Vit D during the evaluation period. Also direct sunlight exposure for 10 h per week or more was prohibited. Instructions were revised during the follow-ups visits.

2.4. Exclusion criteria

Patients beneath 19 years or with morbid obesity were excluded. Patients on medications as systemic steroids or immunosuppressants, as well as patients who have a history of intake of Vit D or calcium in the past one month were excluded. Comorbidity with gastrointestinal, thyroid, parathyroid, renal or liver diseases was an exclusion criterion. Hospitalization during the past 4 weeks was likewise an exclusion standard.

2.5. Study tools

Patients were diagnosed in accordance with their clinical manifestations following the current Global Initiative for Asthma ***(GINA)*** criteria and affirmed by spirometry ***(Spirotube, PC Spirometer, THOR laboratories, Budapest, Hungary)***. Pre and post-bronchodilator spirometry was done to measure the forced expiratory volume in the first second (FEV1) besides the forced vital capacity (FVC). The test included 2 puffs of inhaled salbutamol (each of 200 μg). The percentage of

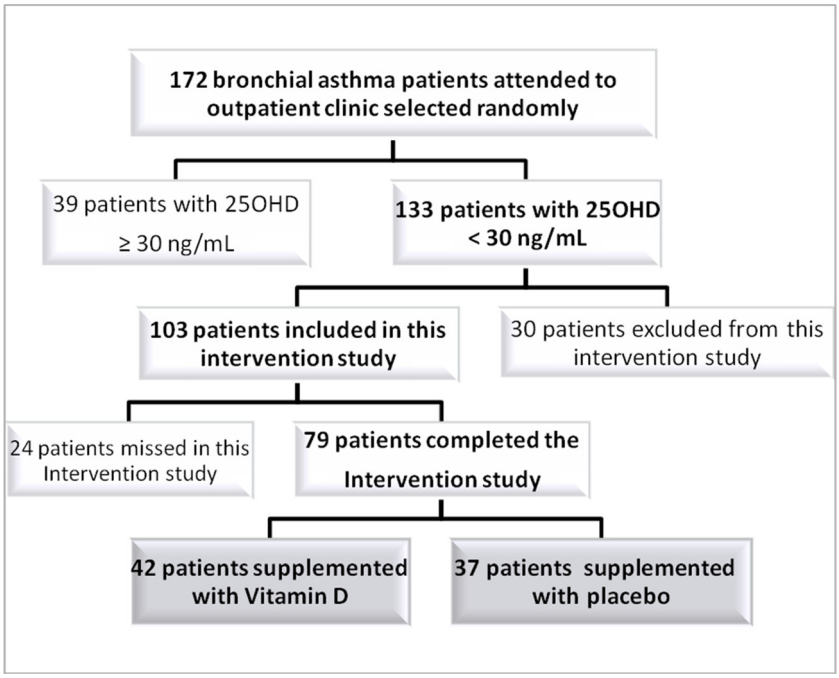

Fig. 1. Flow chart of design and conduct of this intervention study.

Table 1
Demographic, clinical and laboratory characteristics of the studied groups.

Parameter	Placebo group Baseline	Placebo group After 3 m	Vit D supplement group Baseline	Vit D supplement group After 3m	p [1]	p[2]	p[3]	p[4]
Number of subjects	37	37	42	42				
Age (years)	35.50 ± 7.00		34.00 ± 7.40		0.36			
Sex : Male/ Female	25/12 (67.57/32.43)		26/16 (61.90/38.10)		0.60			
Smoking status								
• Non smoker	35 (94.59)		39 (92.89)		0.75			
• Current	0 (0)		0 (0)					
• Ex	2 (5.41)		3 (7.14)					
BMI	26.68 ± 2.82		25.15 ± 5.75		0.15			
Duration of disease (years)	5.90 ± 2.50		5.03 ± 1.90		0.09			
Persistent asthma severity								
• Mild	10 (27.03)		11 (26.19)		0.81			
• Moderate	10 (27.03)		9 (21.43)					
• Severe	17 (45.95)		22 (52.38)					
Co-morbidity								
• Hypertension	10 (27.03)		9 (21.43)		0.56			
• Diabetes	5 (13.51)		7 (16.67)		0.70			
• Cardiac	3 (8.11)		4 (9.52)		0.83			
Serum Vit D, ng/mL	18.16 ± 2.89	17.97 ± 3.21	17.56 ± 2.74	25.00 ± 2.87	0.35	< 0.0001*	0.31	< 0.0001*
FEV1 % predicted	67.54 ± 9.93	68.03 ± 9.90	68.38 ± 12.00	78.18 ± 11.35	0.74	< 0.0001*	0.03*	< 0.0001*
FEV1/FVC %	64.41 ± 7.90	63.06 ± 6.99	63.21 ± 10.95	68.01 ± 12.49	0.59	< 0.0001*	0.09	< 0.0001*
Serum IL17A, pg/mL	17.41 ± 4.63	17.63 ± 5.05	18.48 ± 5.48	8.15 ± 2.34	0.35	< 0.0001*	0.39	< 0.0001*
Serum IL10, pg/mL	6.64 ± 2.16	6.28 ± 2.07	6.39 ± 1.71	9.06 ± 2.44	0.58	< 0.0001*	0.52	< 0.0001*
IL17A/IL10 ratio	2.94 ± 1.42	3.09 ± 1.35	3.16 ± 1.49	0.96 ± 0.37	0.50	< 0.0001*	0.56	< 0.0001*

Vit D: Vitamin D, BMI: Body mass index; FEV1: Forced expiratory volume in 1 s; FVC: forced vital capacity.
Data are presented as No. (%) or mean ± SD.
The duration of disease was considered from physician diagnosed asthma.
The re-measurement performed after 3 months from the baseline one.
p1: The comparison between Vit D supplement group and placebo group at the baseline (Student *t*-test for quantitative variables; chi-squared ($\chi 2$) test for categorical ones).
p2: The comparison between Vit D supplement group and placebo group at the end of study (Student *t*-test).
p3: The comparison between placebo group before and after the supplement (PairedT-test).
p4: The comparison between Vit D supplement group before and after the placebo (PairedT-test).
* Significant.

Table 2
Laboratory results changes throughout the study.

Parameter	Placebo group	Vit D supplement group	p
Serum Vit D			
• Difference (ng/mL)	−0.19 ± 1.86	7.45 ± 3.97	< 0.0001*
• Difference %	−0.70 ± 11.77	47.62 ± 38.33	< 0.0001*
Serum IL17A			
• Difference (pg/mL)	0.22 ± 1.57	−10.33 ± 5.71	< 0.0001*
• Difference %	1.20 ± 10.64	−52.66 ± 18.37	< 0.0001*
Serum IL10			
• Difference (pg/mL)	−0.35 ± 3.32	2.67 ± 2.73	< 0.0001*
• Difference %	8.63 ± 61.06	55.22 ± 74.08	0.003*
IL17A/IL10 ratio			
• Difference	0.15 ± 1.56	−2.20 ± 1.64	< 0.0001*
• Difference %	19.27 ± 55.30	−62.80 ± 22.06	< 0.0001*

Vit D: Vitamin D, IL: interleukin.
The difference = result after 3 months - baseline results.
The difference % = (result after 3 months - baseline results)/ baseline results x 100.
* Significant (Student *t*-test).

improvement in FEV1% was calculated using this equation [(After supplement FEV1% - baseline FEV1%) / baseline FEV1% x100]. The reversibility is considered when the FEV1 increment by (≥12%) approaches the pre-bronchodilator value.

2.6. Sampling and biochemical analysis

In BD Vacutainer® Plus Plastic Serum Tubes, whole blood sample was obtained. After 30 min of blood collection, the tubes were centrifugated at 1200 × g for 10 min. Serum 25-hydroxyvitamin D reflects both cutaneous and dietary sources (Bordelon et al., 2009). In this way, Elecsys® Vitamin D total II kit on Cobas 8000 Modular Analyzer series/ e602 **(Roche Diagnostics, Mannheim, Germany)** was used to quantify serum 25-hydroxyvitamin D levels. Serum Vit D impairment is diagnosed when the concentration of serum 25-hydroxyvitamin D is below 30 ng/mL (Holick, 2008).

Enzyme-linked immunosorbent assay (ELISA) is a reliable method for cytokines level measurement. Serum IL-17A was measured using human IL-17A platinum ELISA kit **(eBioscience, San Diego, CA, USA)** [Catalog number: BMS2017]. Serum IL-10 levels were measured by Human IL-10 ELISA Kit **(Shanghai Sunred Biological Technology Co., Ltd., China)** [Catalog number: 201-12-0103]. The ELISA steps were carried out following the procedures of the manufacturer. The same sampling and analysis protocols were repeated after 3 months.

2.7. Statistical analysis

The Shapiro-Wilk test was utilized to check the distribution. Student *t*-test, Paired *t*-test, Mann Whitney U-test and chi-squared ($\chi 2$) test were used to evaluate the significance. Correlation study was performed using Pearson's test. Receiver operating characteristic (ROC) curve determines the best cutoff. The area under the ROC curve (AUC) surveys the performance. The adjusted Odds Ratio (OR) was dictated by multiple logistic regression analysis. Statistical analysis was done using SPSS program (SPSS Inc., USA). At a p-value lower than 0.05, the

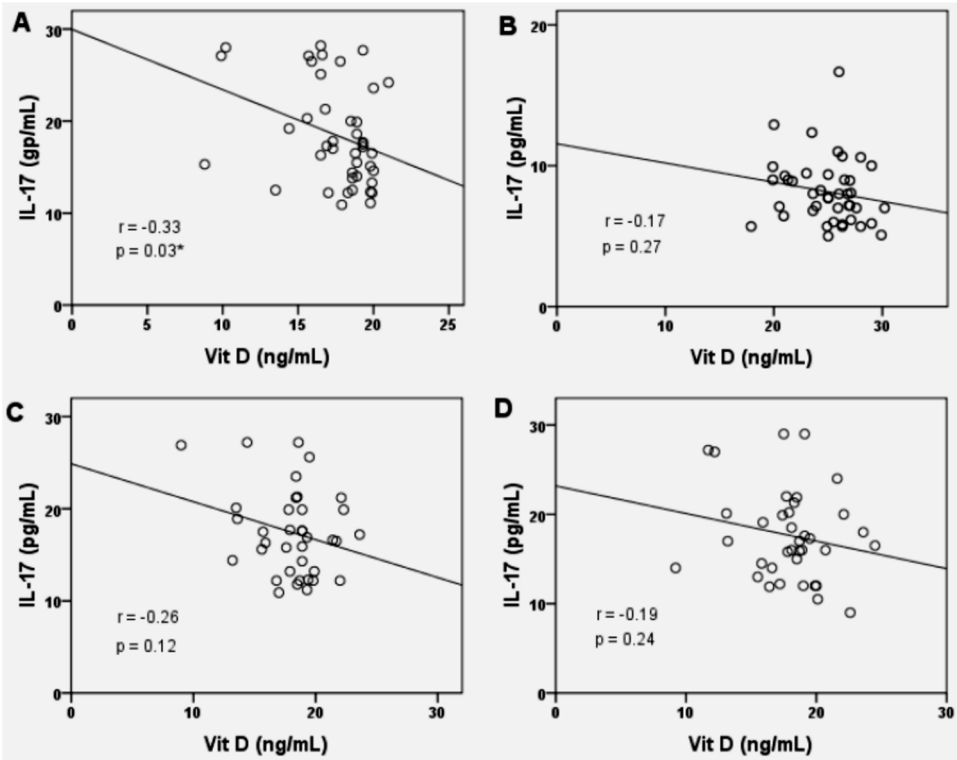

Fig. 2. The correlations between Vit D and IL-17. A: Baseline Vit D supplemented group, B: After Vit D supplement, C: Baseline placebo group, and D: After placebo use. *Vit D: Vitamin D; IL: interleukin; *: significant. (Pearson's test)*.

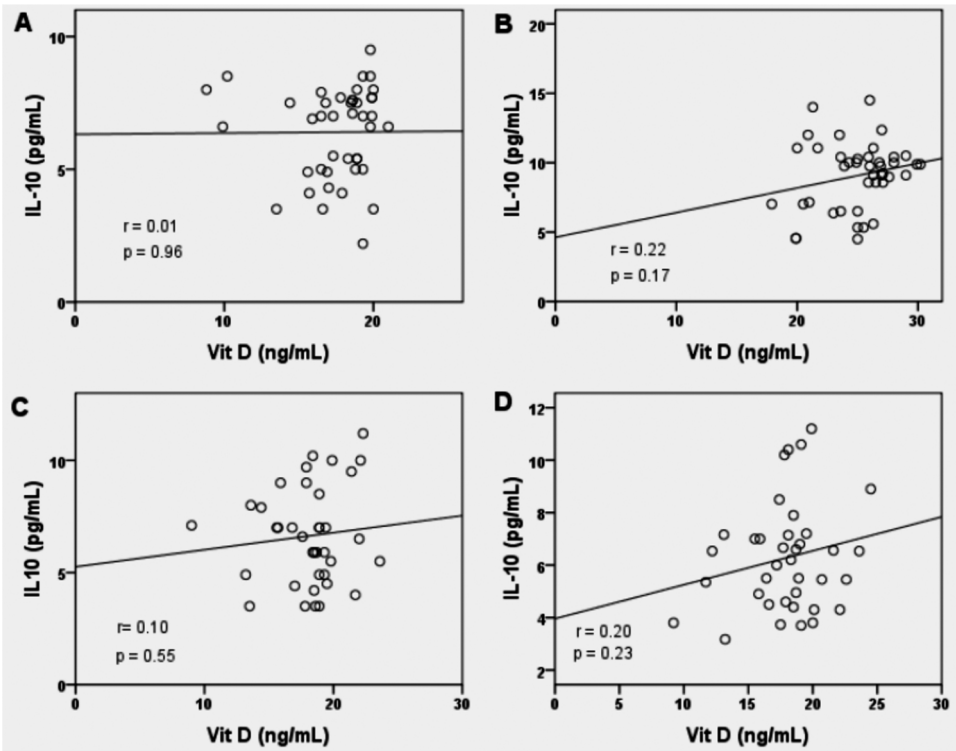

Fig. 3. The correlations between Vit D and IL-10. A: Baseline Vit D supplemented group, B: After Vit D supplement, C: Baseline placebo group, and D: After placebo use. *Vit D: Vitamin D; IL: interleukin. (Pearson's test)*.

Table 3
Correlation of FEV1 improvement percent with laboratory markers in Vit D supplemented group.

Parameter	Percent of FEV1 % improvement			
	Vit D supplement group		Placebo group	
	r	p	r	p
Baseline				
• Serum Vit D	0.03	0.84	0.01	0.94
• Serum IL-17A	0.41	0.006*	0.06	0.71
• Serum IL-10	−0.42	0.005*	0.09	0.57
• IL17/IL-10 ratio	0.65	< 0.0001*	−0.03	0.84
After Vit D supplement				
• Serum Vit D	0.03	0.87	0.06	0.75
• Serum IL-17A	−0.33	0.038*	0.03	0.84
• Serum IL-10	0.32	0.034*	−0.03	0.85
• IL-17/IL-10 ratio	−0.51	0.001*	0.02	0.92

Vit D: Vitamin D, IL: interleukin; FEV1: Forced expiratory volume in.1 s.
* Significant (Pearson's test).

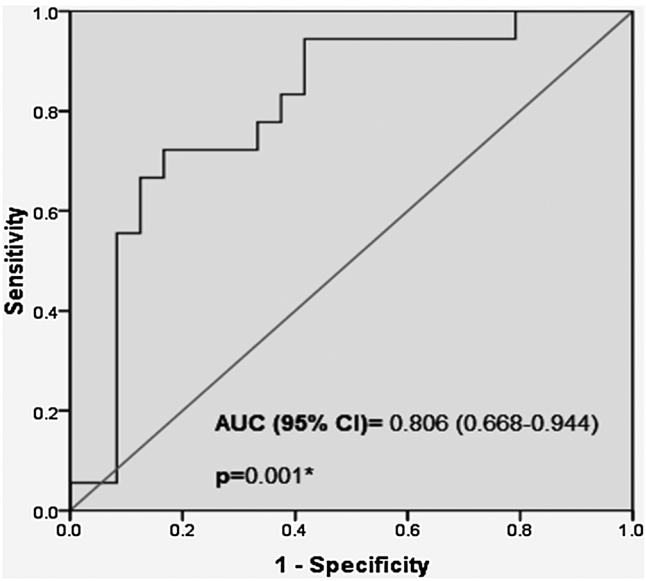

Fig. 4. ROC curve for baseline IL17/IL10 ratio as predictor of FEV1% improvement. *AUC: Area under the curve; CI: Confidence interval; *: significant.*

significance is proved.

3. Results

Demographic, baseline clinical and baseline laboratory characteristics of study subjects are shown in Table 1. There were no significant differences between Vit D supplemented group and placebo group at the baseline conditions. Regarding the ex-smokers, the median and range of total pack per year were 42 (33–51) and 44 (39–55) for placebo and Vit D supplemented groups respectively (Mann Whitney U-test, p = 0.56).

There was a significant improvement in lung functions in Vit D supplemented group when compared to placebo group ($p < 0.0001$). At the end of this study, lung functions in placebo group had a significant improvement of FEV1 percentage (p = 0.03) and a trend for change in FEV1/FVC percentage (p = 0.09) when compared to the baseline values.

The assessed cytokines levels throughout the study are shown in Table 2. After vitamin D supplementation, there was a significant decrease in serum IL-17A levels in contrast with the baseline values *($p < 0.0001$)* and a significant increase in serum IL-10 levels compared to the baseline values *($p < 0.0001$)*.

The correlation between the Vit D and the cytokines levels are illustrated in Figs. 2 and 3. Another correlation study was performed setting the relation between the percentage of improvement in FEV1% and the laboratory markers in order to detect the best predictive marker. The correlation coefficients were presented in Table 3. The highest correlation was associated with the baseline IL-17A/IL-10 ratio (r = 0.65; $p < 0.0001$).

The ROC curve was created to investigate the potential utility of the baseline IL-17A/IL-10 ratio as a predictive biomarker of FEV1 reversibility response in asthmatic Vit D supplemented patients (Fig. 4). The IL-17A/IL-10 ratio at a cutoff ≥ 2.66 had a sensitivity of 72.2% and a specificity of 83.3%. The probability of predicting no improvement (negative predictive value) was 76.92% while the positive predictive value was 81.25%.

The multivariate analysis upholds the results of the ROC curve analysis. Multiple logistic regression analysis of FEV1 reversibility in Vit D supplemented group revealed a significant improvement in the higher IL-17A/IL-10 ratio (adjusted OR = 4.66, 95% CI = 1.07–20.33, p = 0.04). This OR was adjusted to age, sex, disease severity, disease duration, baseline serum Vit D level and baseline (FEV1%).

4. Discussion

Asthma pathogenesis has not completely delineated yet. Despite the therapeutic science progression, the pervasiveness of asthma is still high (Loftus and Wise, 2015). Inquires about asthma mechanisms help in discovering diagnostic methods, treatment modalities, and prevention tools (Tamašauskienė et al., 2015).

Studies on Vit D in asthma found that its deficiency can cause inflammation and its supplementation assuages an impact (Yawn et al., 2015; Kerley et al., 2015; Ali and Nanji, 2017). As Vit D acts on different cells in both innate and adaptive immunity pathways, added to the airway structural cells (Berraies et al., 2014; Barragan et al., 2015; Hall et al., 2016). Vit D modulates many cytokines effects (IL-17A down-regulation and IL10 up-regulation) through the reduction of the T helper-17 cells and the enhancement of T regulatory cells (Pfeffer et al., 2014). Along these lines, this study was planned to evaluate IL-17A and IL-10 roles in asthmatic patients control with Vit D supplementation. This study used the intramuscular route bolus dose which was effective in the treatment of Vitamin D deficiency. Similar results were obtained as the intramuscular injection caused a rapid and sustained increase of the Vit D level in relation to the baseline (Wylon et al., 2017).

In this study, Vit D deficiency (< 30 ng/mL) was a common finding among asthmatic patients as 133 out of 172 patients showed a low serum Vit D level (77.3%). In this regards, Maalmi et al. (2012) revealed that 84.6% of asthmatic patients had low Vit D levels. Vit D levels were low in asthmatic patients of all age groups in different countries (as Iran and Tunisia) (Alyasin et al., 2011; Maalmi et al., 2012). In contrast, Menon et al. (2012) and Gergen et al. (2013) found no correlation between serum Vit D level and asthma.

This study showed that serum IL-17A levels seem to be elevated in Vit D deficient asthmatic patients, but IL-10 levels tend to be diminished. According to Kupaev and Nurdina (2018) who reported that deficiency of Vit D disturbed the balance between IL-17 and IL-10 levels in Russian asthma patients, the current study found a significant negative correlation between baseline Vit D and IL-17. However, the study found no significant correlation between Vit D and IL-10. Similar findings were found by Kupaev and Nurdina (2018) especially in uncontrolled asthma.

After 3 months of single dose of Vit D, the serum Vit D level was increased to 47% in comparison with the baseline levels. Both Solidoro et al. (2017) and Sluyter et al. (2017) had changes in percentages (approximately 140%) after injected loading dose and maintenance oral doses for a period of 1 year.

In this study, there was a significant improvement in pulmonary

function parameters in the Vit D supplemented group when compared to their baseline values and when compared to non-supplemented group. Regarding the significant change in the lung function, the difference in magnitude between the 2 groups is impressive. Tachimoto et al. (2016) and Solidoro et al. (2017) reported that Vit D supplementation improved the values of pulmonary function tests. The same was revealed by Sluyter et al. (2017) especially in asthmatic smoker patients of New Zealand. Wang et al. (2019) stated that Vit D supplementation not only improved the lung functions but also reduced the asthma exacerbation rate. On the contrary, Kerley et al. (2015) found that Vit D treatment could not improve FEV1. Luo et al. (2015) and Sharma et al. (2017) reported no benefit of Vit D supplementation for the lung function, and Jolliffe et al. (2018) also found no association between Vit D levels and asthma control. This discrepancy in Vit D supplementation response may be due to variable human practices and distinctive climate conditions. Also, Vit D supplementation was not adjusting the serum level in all patients (Kerley et al., 2015). A meta-analysis performed in 2017 encountered a reduction of asthma exacerbation rate after Vit D supplementation and the participants' data such as age, sex, ethnicity and body weight might not affect the reduction rate (Joliffe et al., 2017). As the respiratory infections are the common cause of asthma exacerbations, Martineau et al. (2017) performed a meta-analysis to assess the role of Vit D supplementation in the acute respiratory tract infection risk. They confirmed the ability of Vit D supplementation to prevent acute respiratory tract infections.

After vitamin D supplementation, in the current study, there was a significant decrease in serum IL-17A levels when compared to the baseline values and a significant increase in serum IL-10 levels in comparison with the baseline values. These findings are supported by the results of in-vitro cytokines production in cells culture from asthmatic patients after treatment with Vit D. T regulatory cells elaborated the anti-inflammatory cytokines (IL-10) (Maalmi et al., 2012). In asthmatic patients of United Kingdom, Vit D supplement restored the immunological roles of IL-10, especially steroid-resistant cases (Xystrakis et al., 2006; Nanzer et al., 2014). Vit D treatment reduced the differentiation and expansion of T Helper-17 cells and inhibited its cytokine production (Nanzer et al., 2013; Hamzaoui et al., 2014). In contrast, Reid et al. (2016) reported no effect of Vit D treatment on serum cytokines (IL-17 and IL-10) levels.

In the correlation analysis, the improvement of FEV1 was not associated with Vit D levels, either at the start or at the end of the study although the serum Vit D level increased significantly. Elnadya et al. (2013) found that serum Vit D had a positive correlation with the levels of asthma controls and Havan et al. (2017) found the lack of asthma control in patients with Vit D deficiency. However, the present study data suggested that the improvement percentage of FEV1 was directly associated with the baseline IL-17A and negatively associated with the baseline IL10. The FEV1 improvement showed the reversed association pattern with the cytokines levels after Vit D treatment. The pre and post-Vit D supplementation cytokine ratio (IL-17A/IL-10) was calculated and both had higher associations with the percentage of improvement. This suggested that the improvement was dependent on the degree of cytokines levels adjustment not on the serum Vit D levels. FEV1 reversibility in Vit D supplemented group showed a significant improvement with the higher baseline IL-17A/IL-10 ratio. So, the IL-17A/IL-10 ratio was found to be a possible predictive biomarker of FEV1 reversibility response in asthmatic Vit D supplemented patients.

This study had some limitations. First, the small sample size which limits the ability to stratify patients according to the degree of deficiency. Second, cytokines were evaluated the peripheral blood, the target tissue cytokines expression changes in these patients were not evaluated. Third, the controversy in the appropriate Vit D supplementation strategy (oral or intramuscular route, daily or intermittent dose, fixed or titrated dose): this study evaluates only the intramuscular fixed intermittent strategy. Lastly, the dose of Vit D supplement was not adjusted to the body mass index for each patient.

As Vit D will not cure asthma patients, it may alleviate the asthma symptoms in Vit D deficient patients through its immuno-modulatory consequences on the cytokines. Further studies are recommended on a larger sample size to establish these findings and to evaluate the IL17A/IL10 ratio roles in the forecast of exacerbations, steroid response and treatment resistance.

5. Conclusion

Vit D supplement reduces the serum IL-17A levels and elevates the serum IL-10 levels in persistent asthmatic patients. So, Vitamin D can be used as an adjunct therapy with conventional asthma therapy. The IL-17A/IL-10 ratio seems to be a possible predictive biomarker for asthma improvement in patients who depend on Vit D supplementation.

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Declaration of Competing Interest

None.

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