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Evaluation the Effect of Supplements Containing Vitamin D and Trace Elements in Patients with Moderate to Severe Asthma

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Abstract

Background: Asthma is a common and major allergic disease in the world. We aimed to investigate the impact of supplements with vitamin D, folic acid, selenium, zinc, and copper in patients with moderate to severe asthma.

Method: In this clinical trial study 70 patients above six years old with moderate to severe asthma, were divided into two groups, randomly; one group received daily Asmavit syrup, 10 ml (Asmavit, Vitabiotics Ltd, London, UK), and the other group received daily 1000 IU vitamin D3 drops (Asmavit, Vitabiotics Ltd, London, UK) for two months along with ordinary treatment for asthma. Clinical and physical examinations, immunological and biochemical tests were carried out for each patient before and after the treatment.

Results: The mean age of patients was 39.9± 14.7 years old, and the mean disease duration was 8.8 ± 9.8 years. A significant increase in lung function, asthma control, and quality of life score tests was observed in both groups after the treatment ($P< 0.05$). There was no significant difference in cytokines expression levels before and after the treatment with vitamin D3 or Asmavit ($P> 0.05$). Serum levels of selenium and folic acid before treatment were correlated with disease severity, while post-treatment vitamin D levels significantly increased FEV1 ($P> 0.05$). Oxidative stress levels reduced in both groups, with greater reduction in the vitamin D group ($P< 0.05$).

Conclusion: Supplements, particularly vitamin D, when combined with standard asthma treatment, may effectively improve clinical symptoms and enhance the quality of life for asthmatic patients.

Keywords: Asthma, Vitamin D, Supplements, Oxidative stress.

Introduction

Asthma as a chronic inflammatory disorder caused by hyper-responsiveness of the bronchial airway has been proposed the serious medical problem in all countries (1). The increased prevalence of asthma is considered to be an important issue in public health (2). Recently, there has been a significant focus on the role of a healthy diet, incorporating vitamins, minerals, and antioxidants, and its potential impact on asthma control (1, 3-5). Previous studies on the asthma control concluded that vitamin D is effective in the treatment of asthma by multiple mechanisms in the control of inflammation and oxidative stress (6) which impact both the innate and acquired immune system (7, 8). Hypovitaminosis D is associated to poorer asthma control, increased asthma

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severity, and increased medication usage (7, 8). Additionally, this leads to a reduction in lung function and a diminished response to treatment with inhaled corticosteroids (7, 9). Vitamin D inhibits the function of T lymphocytes both directly and via effects on antigen presenting cells (APCs) and consequently inhibition of Th1-associated cytokine production. The effects of vitamin D on Th2 responses, which play a central role in the pathogenesis of asthma, are complex. Vitamin D can both inhibit and enhance Th2 cytokines such as interleukin (IL)-4, IL-5, and IL-13, while also inducing the production of Immunoglobulin E (IgE).(10). Increase of antioxidants agents under the consumption of antioxidant drugs increase in antioxidant enzymes activity that could be effective into better control of asthma (11). Increased levels of oxidative stress is associated with the production of oxygen free radicals and metabolites, protein structural and functional changes, and indicates the presence and intensity of inflammation (12). Many antioxidants' agents including glutathione reductase and glutathione peroxidase enzymes, catalase, and superoxide dismutase (SOD) are responsible for the removal of oxidants and oxygen free radicals. Furthermore, lower serum levels of zinc (Zn), copper (Cu) and selenium (Se), vitamin D, and folic acid in asthmatic patients compared than healthy people are reported (11, 13). Respected trace elements, Zn, Cu, Se and folic acid are also known as antioxidant enzymes cofactors which are effective in control of oxidative stress and the other immunological processes (13-15). The present study aimed to investigate the clinical assay along with immunological and laboratory assay on adding vitamin D and syrup containing vitamins and minerals including Zn, Cu and Se on treatment of patients with asthma.

Materials and Methods

Study Population

This clinical trial included 70 patients who were referred to Our Allergy and Clinical Immunology Department, Ghaem Hospital, Allergy and Inflammatory Diseases Research Centers of Mashhad University of Medical Sciences, Mashhad, Iran. All asthmatic patients over 6 years old that were diagnosed with moderate to severe asthma and were treated with standard therapy were included. All the patients were examined by two specialists of allergy and participants were underwent spirometry to check their lung function. They were fulfilled the criteria of persistent asthma based on the asthma guidelines. Asthma severity was evaluated on the basis of the Expert Panel Report 3 (EPR3) guidelines (16). Their asthma was confirmed according to EPR3 criteria for at least a six-month history of moderate to severe asthma and positive history of asthma symptoms including cough, shortness of breath, wheeze and chest tightness, which were confirmed by ratio of forced expiratory volume in the first second (FEV1) to forced vital capacity (FVC) less than 0.80 at least one time when FEV1 is less than 0.70 or increased FEV1 by more than 12% and 200 ml after inhaling a bronchodilator in spirometer. Pregnant patients and patients with unstable asthma were excluded from the study. This trial was registered on Iranian Registry of Clinical Trials (IRCT) under the registry number: IRCT20150716023235N16. A questionnaire was filed for all participated patients to collect and record both physical examination results and patients' history and demographic information including age, gender, place of residence (urban or rural area) and family history of allergy and asthma. The study was approved by the Ethics Committee of Mashhad University of Medical Sciences and all patients officially consented to participate in the study.

Sample size

Considering to any similar publication on the effect of multivitamins and minerals on asthmatics patients, the sample size was based on an unpublished author's pilot study with 95% success rate, 5% two-sided type I error in treatment, and the median outcome success of 60% based on FEV1 as the benchmark for

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measurement of pulmonary function (17) was 46 cases. Due to considering a loss to follow up of 25%, this number raised to 75 patients for both groups. Totally, 75 patients with asthma were enrolled. Then, 5 cases were excluded due to lack of eligible criteria or consent withdrawn (Fig. 1). Therefore, 70 patients with asthma were entered the study.

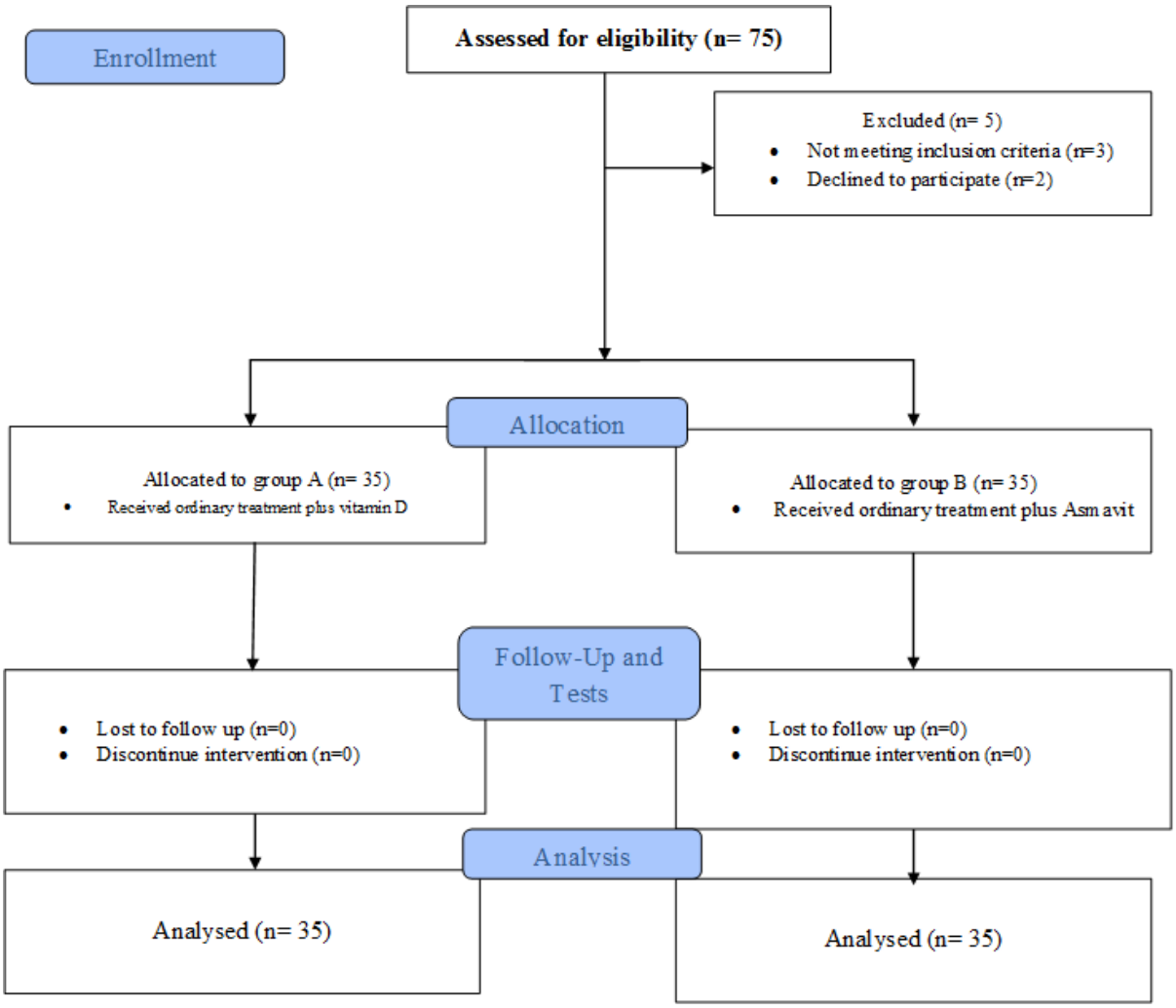

Fig. 1. Flowchart diagram of studied participants.

Study Protocol

Patients were divided into two groups by non-probability purposive sampling method. The patients who were referred in odd days were considered as group A and those who were referred in even days were considered as group B. The first group (group A) was treated by 1000 IU of vitamin D3 drops (Asmavit, Vitabiotics Ltd, London, UK) daily for two months, and the second group (group B) was treated by 10 ml of Asmavit syrup (Asmavit, Vitabiotics Ltd, London, UK) daily for two months. Supplements and trace elements in 10 ml Asmavit syrup are presented in the Table 1. During this period, prior administered medications for asthma control of patients were continued. For removing the confounding factors including nutrition, genetics and drug absorption among participants, clinical status and immunological criteria of each patient were compared before and after related treatment. Due to cost constraints, the control group (without supplements) was waived. Clinical studies, immunological and biochemical tests were carried out for each patient before and after supplemental treatments.

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Table 1. Supplements and trace elements in 10 ml of Asmavit syrup.

Contents	Amount
Vitamin A (Palmitate) B.P.	1500 I.U.
Vitamin D3 B.P.	200 I.U.
Vitamin E Acetate B.P.	10 mg
Vitamin B1 (Thiamine Hydrochloride) B.P.	3 mg
Vitamin B6 (Pyridoxin Hydrochloride) B.P.	1.5 mg
Vitamin B2 (Riboflavin) B.P.	1 mg
Folic Acid B.P.	200 mcg
Vitamin B 12 B.P.	2.5 mg
Vitamin C B.P.	40 mg
Nicotinamide B.P.	10 mg
L-Lysine Hydrochloride U.S.P.	25 mg
Citrus Bioflavonoids	10 mg
D-Panthenol B.P.	5 mg
Elemental Zinc (as Zinc Gluconate U.S.P)	5 mg
Elemental Iron (as Ferrous Sulphate Heptahydrate)	5 mg
Elemental Magnesium (as Magnesium Hydroxide)	50 mg
Elemental Manganese (as Manganese Gluconate)	05 mg.
Elemental Selenium (as Sodium Selenate)	25 mcg

*B.P.: British Pharmacopoeia Reference Standard, U.S.P.: The United States Pharmacopeia, I.U.: International Unit.

Clinical Assay

Sensitivity to allergens among studied asthmatic patients was confirmed through Skin Prick Test(SPT) using common allergen extracts including both aeroallergens and food allergens (GREER, USA) following international guidelines (18). Spirometry tests for evaluation the lung function carried out following American Thoracic Society and European Respiratory Society guidelines to assess asthma severity by measuring FEV1 and FEV1/FVC for each patient (19). Patients in both groups were classified based on the mean of FEV1 (%) before treatment, in which patients with FEV1 (%) ≤ 60% were considered severe asthma and patients with FEV1 (%)> 60% were considered moderate asthma. Also, patients were classified based on the rate of increase in FEV1 (%) in response to treatment (ΔFEV1 (%) ≤ 10% and ΔFEV1 (%)> 10%).

Furthermore asthma symptoms control was evaluated using an Asthma Control Test (ACT) questionnaire (20) containing five questions with five scores in which a total score of over 20 indicates good control of disease, a score between 16 to 19 indicates inappropriate control and scores below 15 are signs of poor control of asthma. Also assessment of quality of life in asthmatic patients was performed using Juniper quality of life questionnaire (QLQ)(21) which consists of 23 questions with seven scores and mean scores were calculated for each patient.

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Laboratory Assays

Assessment of immunological factors and some laboratory factors including trace elements, oxidative stress, and enzyme activity were carried out using 10 ml of peripheral blood samples obtained from all studied patients' brachial veins. The serum was then separated and stored in -80 ° C freezer in Ghaem Hospital Laboratory, Allergy ward, Mashhad, Iran for further immunological and biochemical tests. We measured serum level of IL-4, IL-10, IFNγ and transforming growth factor-beta (TGFβ) in plasma by ELISA. So freshly isolated heparinized peripheral blood samples were immediately centrifuged for 10 min at 500 g, and the plasma was separated. The concentration of respected cytokines in plasma was measured using bioactive diagnostic GmbH, Homburg, Germany according to manufacturer's instructions.

Furthermore, analysis of serum total IgE and vitamin D level were performed using ELISA method (respectively PishtazTeb kits, Iran and Euroimmune kit, Germany). Serum Folic acid level was assayed through Electrochemiluminescence (ECL device, Germany). Serum Zinc, Copper, and Selenium levels assay was performed through atomic absorption Spectroscopy (Perkin Elmer device, USA). Oxidative stress level was assayed by measuring Pro Oxidant-Antioxidant Balance (PAB) an activity of superoxide dismutase using Uric Acid as antioxidant and H_2O_2 as oxidant. Furthermore, nitrate production of serum samples were measured by chemiluminescence detection according to the manufacturer instructions of the (NOA 280; Sievers, Boulder, CO) after reduction in vanadium chloride in hydrochloric acid (Sigma, St. Louis, MO) at 95 °C before and after treatment.

Statistical Analysis

Statistical analysis was done using SPSS version 16 (SPSS Inc., Chicago, Illinois, USA). Quantitative and qualitative data were reported regarding mean and standard deviation and number and percentage in tables and charts, respectively. For comparison between quantitative demographic variables, Chi-Square test was used. Kolmogorov-Smirnov normality data test was used to determine whether data distribution is normal to choose the appropriate test to analyze the data. Accordingly, parametric tests were used to analyze normally distributed data (p-value greater than 0.05) and non-parametric tests were used to analyze abnormally distributed data (p-value smaller than 0.05), P values smaller than 0.05 (P< 0.05) was considered statistically significant.

Results

Demographic characters

The mean age of studied patients was 39.9 ± 14.7 years among 6 to 73 years old. There were 39 (55.72%) male patients and 31 (44.28%) female patients. The mean duration of disease was 9.8 ± 8.8 years for all patients. Of the patients studied, 50 (71.42%) patients were mentioned a history of allergic diseases. Most patients were living in urban areas (61 patients, 87.14%) and 9 (12.86%) patients in the rural area. There were no significant differences in distribution of patients in the two groups of vitamin D and Asmavit regarding the studied demographic data (P> 0.05) (Table 2).

Table 2. Demographic characteristics of study participants.

Variables	**Vitamin D group N=35**	**Asmavit group N=35**
Gender		
Male	19 (54.28)	20 (57.15)
Female	16 (54.72)	15 (42.85)
Age mean (year)	39.1 ± 16.6	40.5 ± 13.2
***Duration* (year)**	9.1 ± 10.1	10.4±7.6
Family history		
Allergic Disease	20 (57.14)	30 (85.71)
Asthma	25 (71.42)	25 (71.42)
Living Area		
Urban	30 (85.71)	31 (88.58)
Rural	5 (14.29)	4 (11.42)

*Numbers in the parenthesis showed percentage of related variable.

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Clinical findings

Clinical pulmonary tests including measuring of FEV1 and FEV1 to FVC and the other clinical findings including ACT and QLQ showed there was not any significant differences in the results of lung function test, asthma control and quality of life among patients of both groups before treatment and both groups were similar regarding FEV1 and FEV1/ FVC in the beginning of the study (P> 0.05) (Table 3). However, an increase was observed in lung function of both groups after treatment with supplements was statistically significant (P< 0.05). Analysis of disease severity by FEV1 classification showed that patients of the two treatment groups were not significantly different in severity of disease before and after the treatment (P> 0.05), (Table 4). However, a reverse statistically significant relationship was found between duration of the disease and asthma severity (FEV1%), as longer duration of the disease seems to be correlated with lower FEV1% (P=0.001). However, correlation of disease duration and ACT findings had not any significant (P=0.2). There was no statistically significant relationship between gender and ACT (P=0.5) and FEV1 (P=0.7).

Table 3. The results of studied clinical data between two studied groups before and after the treatment.

Variable	Vitamin D group			Asmavit group		
	Before Tx	After Tx	P Value*	Before Tx	After Tx	P Value*
FEV1 (lit)	2.04 ±0.56	2.27 ± 0.69	0.007	2.18 ± 0.8	2.6 ± 0.75	0.001
FEV1 (%)	71.5 ± 16.4	78.5 ± 17.3	0.02	73.3 ± 20.7	83.8 ± 18.4	0.001
FEV1/FVC	69.9 ± 12.3	76.8 ± 9.56	0.001	74.2 ± 11.1	79.8 ± 11.7	0.001
ACT	15.3 ± 1.3	22.8 ± 1.7	0.001	14.8 ± 3.02	23 ± 2.1	0.001
QLQ	4.2 ± 0.5	5.4 ± 0.45	0.001	4.1 ± 0.65	5.6 ± 0.57	0.001

Forced Expiratory Volume in first second (FEV1), Forced Vital Capacity (FVC), Asthma Control Test (ACT), Quality of Life Questionnaire (QLQ), Tx: treatment with supplements*: P values by Independent T Test.

Table 4. Distribution of FEV1 changes during study.

Variable		vitamin D	Asmavit	P-value
FEV1 (%)	FEV1(%) ≤ 60%	8 (29.6%)	13 (38.2%)	0.48
	FEV1(%) > 60%	19 (70.4%)	21 (61.8%)	
Δ FEV1 (%)	Δ FEV1(%) ≤ 10%	12 (50%)	8 (33.3%)	0.24
	Δ FEV1(%) > 10%	12 (50%)	16 (66.8%)	

Δ FEV1 (%): Changes in FEV1 (%) after treatment by supplements. P value calculated based on Fisher Exact Test

Laboratory's Findings

Measurements of studied cytokines before and after the treatment in each group were shown there was an increase in levels of IL-4, IFNγ and TGFβ and a decrease in IL-10 level in vitamin D group (Fig. 2). Only IFNγ levels increased in Asmavit group, and the other cytokines had a decrease in their amounts. In comparison between two treatment groups, there were not any differences in cytokine levels before and after treatment except that IL-10 was greater in Asmavit group and TGFβ in Vitamin D group which were statistically significant. Cytokine levels before and after treatment did not significantly correlate with mean increase in FEV1(%) and ACT scores except for TGFβ which had a significant inverse correlation with FEV1 (%) (P=0.03).

Serum total IgE levels increased into both groups after the treatment; however, the rate of increase was more in vitamin D group which was statistically significant (P= 0.001, Table

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5). A statistically significant increase was also observed in vitamin D levels in both groups after the treatment with a higher rate of increase in vitamin D group (P= 0.001), (Table 5). Oxidative stress indicated by PAB level was decreased in both groups after the treatment, with a significantly greater reduction in the vitamin D group (P= 0.05), (Table 5). The level of PAB before and after the treatments into both studied groups were not statistically correlated with changes of FEV1 during the treatment (P> 0.05). Superoxide dismutase and nitric oxide increased after the treatment and these changes in respected enzymes into both groups were not statistically significant during the study period (P> 0.05, Table 5). The level of nitrate has a significant reverse correlation with PAB changes after the treatment (P= 0.04).

The averages serum levels of vitamin D, folic acid, and trace elements in patients in correlation with FEV1% and ACT results before the treatment and the rate of change after the treatment were analyzed (Table 6). There was a statistically significant correlation between serum zinc level and ACT results (P= 0.05) and a similar correlation between selenium level and FEV1 (P=0.03). Serum folic acid level was significantly correlated with both ACT (P=0.05) and FEV1 (P=0.02) before the treatment. Lower levels of serum Se and vitamin D were found to be correlated with more changes in clinical parameters after the treatment (P< 0.05).

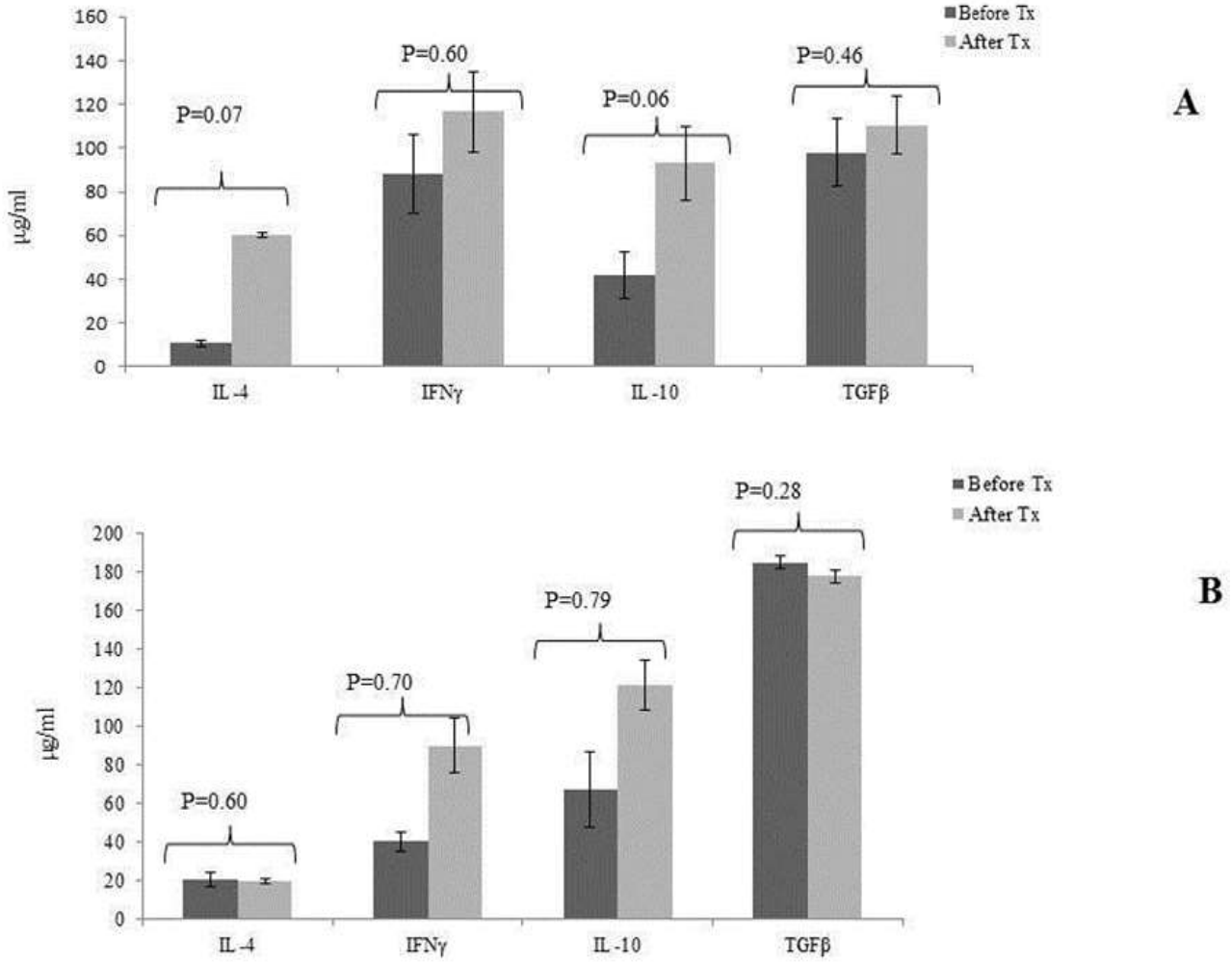

Fig. 2. A; Vitamin D group, B; Asmavit group, Tx: Treatment with supplements, IL-4: Interleukin 4, IFNγ: Interferon gamma, TGFβ: Transforming growth factor beta, IL-10: Interleukin 10, *: P values calculated by Wilcoxon Test.

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Table 5. Comparison of total IgE serum levels, vitamin D serum levels, PAB variation, oxidant, and antioxidant enzymes activity before and after treatment in vitamin D and Asmavit groups.

Variable (ng/mL)	Vitamin D group			Asmavit group		
	Before Tx	After Tx	P Value	Before Tx	After Tx	*P Value
IgE	362.7 ± 294.1	542.6 ± 424	0.001	225.4 ± 204.3	249.1 ± 213.2	0.6
vitamin D	14.8 ± 11.9	44.9 ± 29.4	0.001	13.2 ± 11.2	22.6 ± 12.8	0.006
PAB	151.7 ± 50	118.7 ± 36.1	0.001	135.2 ± 54.5	123.5 ± 44.2	0.1
SOD	0.16 ± 0.06	0.18 ± 0.05	0.2	0.18 ± 0.06	0.19 ± 0.1	0.3
Nitrate	565.3 ± 190.2	468.8 ± 266.5	0.6	359.9 ± 141	267.4 ± 185.5	0.1

Tx: Treatment with supplements, SOD: Superoxide dismutase, PAB; Pro oxidant Antioxidant Balance, *: P values calculated by Paired Sample t Test.

Table 6. Correlation of Serum Trace Elements and Vitamin levels with clinical parameters before treatment and changes in clinical parameters after treatment.

Variable (ng/mL)	Serum level before Tx	Mean of FEV1 before Tx	Mean of ACT before Tx	ΔFEV1(%) after Tx	ΔACT after Tx
		69.8 ± 18.5	14.8 ± 2.4	9.7 ± 12.2	7.8 ± 3.2
		P Value*	P Value*	P Value*	P Value*
Zinc	82.7 ± 18.8	0.3	0.05	0.14	0.25
Selenium	84.9 ± 11.8	0.03	0.67	-0.01	-0.05
Copper	1076 ± 248.4	0.55	0.7	0.7	0.85
Vitamin D	13.9 ± 11.6	0.5	0.11	-0.002	-0.003
Folic Acid	12.2 ± 4.4	0.02	0.05	0.24	0.12

Tx: Treatment with supplements, Δ FEV1 (%): Changes in Forced Expiratory Volume in first second (FEV1%) after treatment, ΔACT Changes in Asthma Control Test after treatment, *: P values calculated by Pearson correlation Test.

Discussion

In present study, we found that among seventy studied patients with moderate to severe asthma, who were treated under standard asthma drugs along with vitamin D and or Asmavit, there was a significant difference in terms of severity of asthma in lung function tests and ACT results. Our results were similar to previous studies done by Bar Yoseph et al. and Liu et al. (22, 23). Besides, we found that the mean duration of disease had a statistically significant correlation with asthma severity. Similar to Arshi et al., we found that the quality of life of patients who treated under Asmavit group was significantly higher than the other group (24). Total IgE serum levels were increased after the treatment in both groups, however, only significant difference in total Ig Ewere related to vitamin D group. This result is slightly different from the previous study (23). There was an increase in expression of IFN gamma which was consistent with the study of Lange et al. (25) and a decrease in IL-10 in both groups. However, IL-4 and TGFβ showed an increase in their expression in vitamin D group and reduction in Asmavit group. These results, especially in the case of IL-10 were not in accordance to previous study (11). One of the possible reasons for inconsistent changes in the expression of cytokines and total IgE serum levels could be due to their seasonal changes, as our studied participants were referred from late autumn to early summer. It is also suggested that vitamin D effects on the expression of Th2 cytokines, lymphocytes in particular, are influenced by dose and duration of use (26). There was no statistically significant correlation between expression of cytokines before treatment and a mean increase in FEV1 percent and ACT scores after the treatment, except for a reverse correlation between TGFβ and FEV1 percent. Relationship between the expressions of these cytokines after the treatment with clinical parameters in each group could not be studied

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and interpreted separately due to the lack of statistical information.

We found that serum zinc and asthma control test scores and selenium with FEV1 percent had statistically significant relationships before the study. These results were consistent with the results of the study done by Matsui et al. (14). Also, Ariaee et al concluded that low levels of trace elements, specifically Zn and Se in asthmatic patients, may have a role in the pathogenesis of allergic asthma. They recommended that replacement of these elements may be an effective treatment for asthmatic patients (13). Vitamin D levels before the treatment were associated with increasing of FEV1% and asthma control test results. Besides, similar to previous research (27), we found that Se and vitamin D serum levels had an inversely significant correlation with the clinical variables. This point might be suggesting that the lower pre-treatment serum levels of these two substances were correlated by higher increasing rate of clinical characteristics and better clinical outcomes of patients treated with these supplements.

In the present study, the levels of oxidative stress significantly decreased into both studied groups after the treatment. Although, this reduction was greater in vitamin D group compared to Asmavit group. This point was is in consistent with the effects of vitamin D in reduction of antioxidants level which was found in Karley et al. review in asthmatic patients (28). There was no significant association between the oxidative stress levels and clinical parameters before and after the treatment in both treatment groups. Moreover, significant differences were found in oxidative stress reduction in regards with the severity of disease and the increase in FEV1 percent after treatment. Thus, it is suggested that patients benefit more from treatment with supplements as it seems that higher amount of these elements could result in more reduction in oxidative stress. The level of oxidative stress was higher in patients with more severe disease (FEV1$\leq$ 60%) compared to others and so these changes after the treatment in this group of patients reported. Also, the reduction in level of oxidative stress in patients with more increase in FEV1 (ΔFEV1> 10%) was greater than the other patients. Superoxide dismutase enzyme activity was increased in both groups after treatment and no significant difference was observed in comparison between the two groups.

Treatment and control of allergic asthma show the better outcomes when prescribed supplements containing vitamins and trace minerals in combination with the standard drugs for treatment of asthma. Using such elements could be improved and enhanced the quality of life in most patients. Vitamin D supplements can be effectively helpful in asthma control through their antioxidant effect and impact on the immunological processes which result in reducing the level of oxidative stress in patients by controlling the related inflammatory processes.

One of the limitations of this study was the lack of control group just by receiving the ordinary treatments, which attempts were made to address the limitation with further explanation and follow up by the researchers. The late referral of patients and the lack of time for following the study participants were also the other study limitations. In addition, blinding was not done in this study.

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Conflict of Interest

The authors have no conflicts of interest.

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