Correlation between Endogenous Vitamin D Status and Body Mass Index in Asthmatic Patients Receiving Adjuvant Vitamin D₃ Supplement

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Keywords: Asthma, Asthma control test, Vitamin D status, Body mass index.

Abstract

Background: Most studies showed that the incidence of asthma is frequently associated with increased body mass index (BMI), vitamin D deficiency has been proposed as a risk factor that could explain a significant proportion of increased pattern of asthma prevalence. This study was aimed to track a correlation between body mass index and vitamin D status effect on asthma control in asthmatic patients.

Patients and Methods: This is a prospective randomized -controlled open-label interventional study to evaluate effect of vitamin D_3 on asthma control and it's correlation with body mass index in asthmatic patients who are allocated into two main groups: **Group 1**: Include 20 patients who have diagnosed with asthma are assigned to receive conventional therapy for asthma according to disease stage and

severity for three months period. **Group 2**: Include 24 patients who have diagnosed with asthma are assigned to receive conventional therapy for asthma according to disease stage and severity plus 2000 I.U vitamin D₃ fast dissolve mini tablet (Natrol, USA) for three months period. Serum 25-OH vitamin D level, Body mass index (BMI), asthma control test (ACT) scoring system was measured both initially and after three months treatment.

Results: A highly significant improvement in asthma control found in patients after 3 months treatment with vitamin D_3 supplement compared to pre treatment level (P<0.01), and was found significantly that among the 10 (42%) obese patients in group 2 with vitamin D deficiency, 6(25%) patients gained vitamin D insufficiency and 2(8%) patients gained vitamin D sufficiency after supplementation with vitamin D_3 (P<0.01). After treatment body mass index inversely correlated with vitamin D level in patients receive conventional therapy, meanwhile in patients with vitamin D_3 supplement the change in the body mass index after vitamin D_3 treatment was parallel to the improvement in endogenous vitamin D level. Also the reduction in the body mass index after vitamin D_3 treatment produce a positive correlation with asthma control test, though no significant (P>0.05). No direct correlation was found between endogenous vitamin D level and asthma control test in both study groups.

Conclusion: After vitamin D_3 supplement in the current study, the change in the body mass index produce improvement in endogenous vitamin D status parallel to the change in the body mass index and markedly improvement in asthma control. Also the reduction in the body mass index after vitamin D_3 treatment was positively correlated with asthma control.

العلاقة بين فيتامين د ومؤشر كتلة الجسم في مرضى الربو المعالجين بمكملات فيتامين د3 رشا سعدي عباس

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فرع الصيدلة السريرية/ كلية الصيدلة/ الجامعة المستنصرية/ بغداد-العراق الكلمات المفتاحية: الربو, اختبار السيطرة على الربو, فيتامين د, مؤشر كتلة الجسم.

الخلاصة

المقدمة: معظم الدراسات تبين أن حدوث الربو ملا لزيادة مؤشر كتلة الجسم في كثير من الأحيان، وقد تبين ان نقص فيتامين (د) يمكن ان يمثل عاملا" خطرا "مرتبطا" بزيادة حدوث الربو. هدفت هذه الدراسة إلى تتبع العلاقة بين مؤشر كتلة الجسم وتأثير فيتامين د على التحكم بالربو لدى مرضى الربو المزمن.

المرضى والطرق: هذه الدراسة التداخلية المفتوحة العشوائية لتقييم تأثير فيتامين (1) على السيطرة على الربو وعلاقته مع مؤشر كتلة الجسم عند المرضى المصابين بالربو الذين تم تقسيمهم الى مجموعتين: المجموعة (1) وتشمل (1) وتش

النتائج: وجد تحسن معنوي في السيطرة على الربو لدى المرضى بعد 8 أشهر من العلاج مع إضافة فيتامين د 8 مقارنة بمستوى ما قبل العلاج (0.01) > P)، ووجدت بشكل كبير أن من بين (0.01) > P)، من المرضى الذين يعانون من السمنة المفرطة في المجموعة الثانية مع نقص فيتامين (0.01) < P0.00) من المرضى قصور في فيتامين (0.01) < P0.00) من المرضى اكتسبوا فيتامين (0.01) < P0.00) وبعد العلاج كان مؤشر كتلة الجسم يرتبط عكسيا مع مستوى فيتامين (0.01) < P0.00) في المرضى الذين يتلقون العلاج التقليدي، وفي الوقت نفسه في المرضى الذين يتلقون فيتامين (0.01) < P0.00 كان التغيير في مؤشر كتلة الجسم بعد الفيتامين موازيا للتحسن في مستوى فيتامين (0.01) < P0.00 الدخاص مؤشر على الربو، على الربو، على الربو، على الربو، على الربو، على الربو، على الربو في كلتا المجموعتين الدراسيتين.

الاستنتاج: في الدراسة الحالية و بعد العلاج بمكملات فيتامين د3 ، هناك تحسن في وضع فيتامين د موازية للتغير في مؤشر كتلة الجسم بلاضافة الى تحسن ملحو□ في السيطرة على الربو. كما كان الانخفاض في مؤشر كتلة الجسم بعد العلاج فيتامين د3 مرتبطا بشكل إيجابي مع السيطرة على الربو.

1. INTRODUCTION

Asthma is a chronic inflammatory airway disease. The morbidity of this disease remains high worldwide [1]. Asthma and obesity have a massive impact on public health. Many studies show that obesity is a risk factor for asthma, with the risk increasing between 1.1-fold and 3-fold [2].

The incidence of asthma and increased body mass index (BMI) are frequently related as most of these studies show. More than 20 epidemiological studies of adults and children have confirmed an association between obesity and asthma along with the association between fatness and asthma which was found to be stronger in women [3, 4]. This influence of obesity occurs most often with asthma and airway hyper reactivity, and the relationship is independent of diet, physical activity, or allergic condition [5, 6].

The importance of vitamin D in health and disease has been documented beyond its known role in calcium metabolism and bone health [7]. In addition, reduced vitamin D levels in pediatric and adult patients with mild-to-moderate asthma may result in impaired lung function, increased airway hyper reactivity, and reduced corticosteroid response [8]. On the other hand, many studies shows that obese individuals, as a group, have low plasma concentrations of 25-hydroxyvitamin D (25(OH)D) [9-11].

While many nutritional factors could account for the etiology of asthma, vitamin D deficiency has been proposed as a risk factor that could explain a significant proportion of increased pattern of asthma prevalence [12]. Vitamin D deficiency is becoming an important public health problem in many countries with abundant sun exposure [13, 14].

This study was aimed to track a correlation between body mass index and vitamin D status effect on asthma control in asthmatic patients treated with conventional therapy alone or along with vitamin D₃ supplementation.

2. PATIENTS AND METHODS

Study design

This is a prospective randomized -controlled open-label interventional study to evaluate effect of vitamin D_3 on asthma control and it's correlation with body mass index in Iraqi asthmatic patients.

Patients

Group 1: Include 20 asthmatic patients assigned to receive conventional therapy for asthma according to disease stage and severity for three months period.

Group 2: Include 24 asthmatic patients assigned to receive conventional therapy for asthma according to disease stage and severity plus 2000 I.U vitamin D₃ fast dissolve mini tablet (Natrol, USA) for three months period.

Serum 25-OH vitamin D level measurement

It was determined using commercial enzyme-linked immunosorbent assay (ELISA) kit (Euroimmun, Germany), measured at baseline and after three months treatment in both study groups.

Measurement of body mass index (BMI)

Body mass index (BMI) was calculated according to the formula BMI = weight (kg)/height (m2) for all individuals [15].

The person weight status is categorized according to the level of their BMI with level (<18.5 kg/ m2) is "underweight", between (18.5-24.9 kg/ m2) is "healthy weight", level between (25-29.9 kg/ m2) is "overweight", and a level (\geq 30 kg/ m2) considered to be "obese" [15].

Assessment the control of asthma using asthma control test (ACT)

All patients were assessed for their control of asthma by using asthma control test (ACT) scoring system both initially and after three months treatment. ACT scoring is a self administered 5 item questionnaire developed for assessing asthma control level. The asthma control test (ACT) contains five items: the effect of asthma on daily

activities, daytime and nocturnal symptoms, use of rescue inhaler medications and self assessment of asthma control, and dealing with asthma control during the previous 4weeks; each item is scored between 1 and 5, with the total-score ranging from 5 to 25. An ACT score of (≥20) indicates that asthma is "controlled", whereas a score between (16-19) shows partially controlled asthma and a score of (<16) indicate "uncontrolled" asthma [16].

Statistical analysis

The Statistical Analysis System SPSS 20 (2011) was used. Data presented as (mean \pm SD). Chi-square test was utilized to detect significant differences among demographic variables, while paired *t*-test was used to compare between pre- and post-treatment results, two sample *t*- test used to compare pre or post treatment between group 1 and 2. Pearson correlation coefficient (r) is used to detect the correlation among studied parameter.

NS: No significant differences (P>0.05), (*) Significant difference (P<0.05), (**) Highly Significant difference (P<0.01).

3. RESULTS

Patients demographic and disease characteristics

Table (1) demonstrates the patient demographic and disease characteristic for 44 asthmatic patients including 33 female (75%) and 11 male gender (25%) with age range 14-71 year with no significant statistical difference among study groups was found in respect to genders, age, body mass index (BMI), family history, residence, duration of the disease (P>0.05).

Table (1) Patients demographic and disease characteristics

	Study groups				
Variable	Group 1	Group 2	<i>P</i> -value		
Age (year)	40.75±17.31	41.4±13.6	0.890^{NS}		
BMI(kg/m²)	33.20±8.54	29.25±7.44	0.114^{NS}		
Gender	n (%)	n (%)			
Female	13(65.0)	20(83.3)	0.299^{NS}		
Male	7(35.0)	4(16.7)			
Total	20(100)	24(100)			
Family history	n (%)	n (%)			
Positive	13(65.0)	14(58.3)	0.651^{NS}		
Negative	7(35.0)	10(41.7)			
Residence	n (%)	n (%)			
Urban	17(85.0)	19(79.2)	0.617^{NS}		
Rural	3(15.0)	5(20.8)			
Duration of the disease (year)	n (%)	n (%)			
≤20	16(80.0)	15(62.5)			

21-40	3(15.0)	6(25.0)	0.072^{NS}
41-60	1(5.0)	3(12.5)	
≥ 61	None	None	

Data presented as mean \pm SD, number of patients (n) and percentage (%).

NS: No significant differences (*P*>0.05)

Two-sample *t*-test are used for statistical analysis of (age, BMI, duration of the disease)

Chi-square test are used for statistical analysis of (gender, family history, and residence)

Assessment of asthma control test (ACT) both at baseline and after three months treatment in both study groups.

The 5 validated asthma control questionnaires in asthma control test revealed that there was a significant improvement in asthma control in group 2 patients after 3 months treatment with vitamin D_3 supplement mainly in the controlled (score \geq 20) highly significant increase (P<0.01), and uncontrolled (score<16) significant decrease (P<0.05) when compared to pre-treatment score. Meanwhile group 1 patients did not show any differences in all categories of asthma control test when compared to pre-treatment score (P>0.05), table (2).

Table (2) Assessment of asthma control test (ACT) both at baseline and after three months treatment in both study groups.

	Controlled (≥20)		Partially contro	olled (16-19)	Uncontrolled(<16)	
ACT	G1	G2	G1	G2	G1	G2
Pre-treatment	3(15%)	1(4%)	3(15%)	3(13%)	14(70%)	20(83%)
Post-treatment	8(40%)	12(50%)	5(25%)	3(13%)	7(35%)	9(37%)
P-value	0.0927^{NS}	0.0007**	0.4408^{NS}	1 ^{NS}	0.0882^{NS}	0.033*

Data presented as number (percentage), ACT: asthma control test, G1: group1, G2: group2 NS: No significant differences (P>0.05), (*) Significant difference (P<0.05), (**) Highly Significant difference (P<0.01).

Relationship between body mass index (BMI) and vitamin D status in asthmatic patients treated with conventional therapy and with vitamin D_3 supplement.

Table (3) showed that at baseline most of obese (BMI \geq 30 kg/m²) and overweight (BMI 25-29.9 kg/m²) asthmatic patients had vitamin D deficiency (<20ng/ml) which is considered in (60%) and (15%) of group 1, along with (42%) and (33%) of group 2 respectively. No vitamin D sufficiency was presented in both study groups at baseline.

At baseline prior to conventional treatment (group 1), it was found that among the 12(60%) obese patients with vitamin D deficiency, only 1 (5%) patients presented with significant vitamin D insufficiency (P<0.05). Meanwhile, it was found significantly that among the 10 (42%) obese patients in group 2 with vitamin D

deficiency at baseline, 6(25%) patients presented with vitamin D insufficiency and 2(8%) patients presented with vitamin D sufficiency after supplementation with vitamin D₃ (P<0.01). On the other hand no significant effect was noticed among underweight, normal weight and overweight patients (P>0.05).

Table (3) Relationship between body mass index (BMI) and vitamin D level in asthmatic patients treated with conventional therapy and with vitamin D_3 supplement after three months.

	Vitamin D level (ng/ml)						
$BMI(kg/m^2)$	Deficiency		Insufficiency		Sufficiency		
	(<20 ng/ml)		(20-29 ng/ml)		(≥30 ng/ml)		<i>P</i> -value
Group 1	pre	post	pre	post	pre	post	
Underweight(<18.5)							
Normal weight	3 (15%)	2(10%)					0.629 ^{NS}
(18.5-24.9)	9.70±6.6	8.17±3.1					
Over weight	3 (15%)	2(10%)	2(10%)	4(20%)			0.923 ^{NS}
(25-29.9)	10.29±5.1	8.43±1.0	23.78±3.3	23.77±2.6			0.796^{NS}
Obese (≥30)	12(60%)	11(55%)		1(5%)			0.010^{*}
	5.87±3.9	9.27±3.8		21.40±0.0			
Group 2	pre	post	pre	post	pre	post	<i>P</i> -value
Underweight(<18.5)	1(4%)			1(4%)			
	5.16 ± 0.0			22.20±0.0			
Normal weight	4(17%)	2(8%)		1(4%)		1(4%)	0.636^{NS}
(18.5-24.9)	7.32 ± 7.1	16.8±2.7		25.69±0.0		30.00±0.0	
Over weight	8(33%)	2(8%)	1(4%)	2(8%)		3(13%)	0.192^{NS}
(25-29.9)	4.69 ± 2.7	15.2±3.4	20.9±0.0	25.03±5.1		36.46±3.83	
Obese (≥30)	10(42%)	4(18%)		6(25%)		2(8%)	0.004**
	5.88 ± 2.2	10.91±0.93		24.38±3.1		33.69±2.3	

Data presented as number (percentage), Endogenous vitamin D measured as (25-OH vitamin D). NS: No significant differences (P>0.05), (*) Significant difference (P<0.05), (**) Highly Significant difference (P<0.01).

Correlation between body mass index (BMI), endogenous vitamin D level, and asthma control test (ACT) in asthmatic patients treated with conventional therapy and with vitamin D_3 supplement.

Table (4) and figure (1, 2, and 3) shows that at baseline there was a negative correlation between body mass index and vitamin D level, though not reaching significant result (P>0.05), and no significant correlation was present between body mass index and asthma control test at baseline (P>0.05).

After three months treatment body mass index still inversely correlated with vitamin D level reaching nearly significant level in groups 1 patients than in groups 2 patients (P>0.05), nevertheless, in group 2 patients the change in the body mass index after vitamin D₃ treatment was parallel to the improvement in endogenous vitamin D level compared to group 1 patients on conventional therapy alone where the negative correlation nearly significant in the later group, figure (1).

Moreover, after treatment significant negative correlation between body mass index and asthma control test was noticed in group 1 patient (P<0.05), meanwhile in group 2 patient, the reduction in the body mass index after vitamin D₃ treatment produce a positive correlation with asthma control test, though no significant (P>0.05), figure (2). No direct correlation was found between endogenous vitamin D level and asthma control test in both study groups, figure (3).

Table (4) Correlation between body mass index (BMI), endogenous vitamin D level, and asthma control test (ACT) at baseline and after three months in asthmatic patients treated with conventional therapy alone or with vitamin D_3 supplement.

	Pre-treatment G1+G2 (n=44)			
BMI	ACT	Vitamin D		
Pearson Correlation	0.033	-0.189		
<i>P</i> -value	0.831^{NS}	$0.220^{ m NS}$		
	Post-treatment G1 (n=20)			
Pearson Correlation	-0.489	-0.430		
<i>P</i> -value	0.029^{*}	0.059^{NS}		
	Post-treatment G2 (n=24)			
Pearson Correlation	0.290	-0.264		
P-value	0.170^{NS}	0.213 ^{NS}		

G1: group 1, G2: group 2, Pearson correlation coefficient (r).

NS: No significant differences (P>0.05), (*) Significant difference (P<0.05), (**) Highly Significant difference (P<0.01).

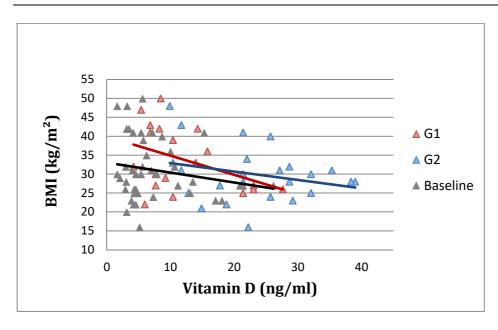


Figure (1) Correlation between body mass index (BMI) and endogenous vitamin D level in asthmatic patients at baseline and after three months treatment

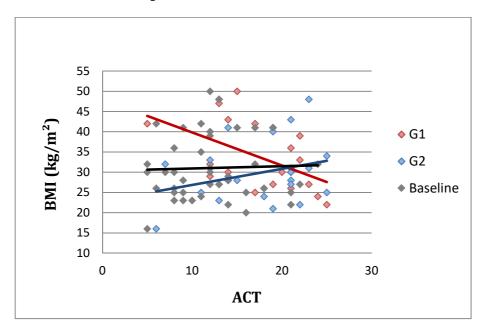


Figure (2) Correlation between body mass index (BMI) and asthma control test (ACT) in asthmatic patients at baseline and after three months treatment

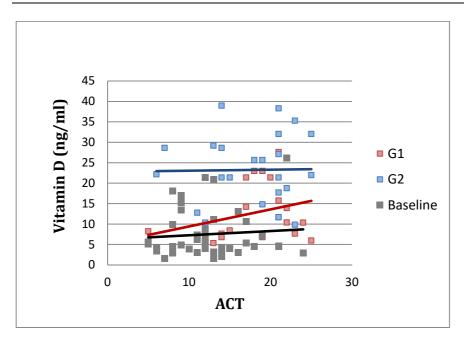


Figure (3) Correlation between endogenous vitamin D level and asthma control test (ACT) in asthmatic patients at baseline and after three months treatment

4. DISSCUSION

Most prospective studies including large number of patients showed that obesity is a risk factor for asthma, and found a positive correlation between baseline body mass index and the subsequent development of asthma [2]. In general, the more BMI increases, the more the incidence of asthma rises, and this effect is generally stronger among women than among men and this may be related to the degree of adiposity in women, although this effect appears to be modest and depends on factors such as age and sex [5,17]. All asthmatic patients in the present study were overweight or obese and predominantly female patients.

Different measurements, including BMI or other adiposity indexes, was used as a significant determinants of adults asthma control in some studies, even when adjusting for other confounders [18-20]. Inversely, other studies failed to show this trend. Such as in a predominantly African American adult, increasing BMI was not shown to be independently associated with decrements in the asthma control questionnaire (ACQ) or asthma control test (ACT) [21]. In the present study no clear correlation was present between body mass index and asthma control test at baseline (P>0.05).

There are many theories that involve mediating factors linking obese state include abnormal circulating inflammation and oxidant stress, chest restriction with airway narrowing, and obesity-related co morbidities, and the obesity-related systemic

inflammation triggers exaggerated lung responses to environmental factors, leading to asthma-like symptoms [22].

Treatment of obese asthmatics must include a weight control program, in the current study, most of asthmatic patient were treated with reliever medication, inhaled preventer medication, and leukotriene antagonist as a conventional therapy, hence they show marked but not significant changes in asthma control in all patients with different disease severity after 3 months of treatment according to asthma control test (ACT). In a previous study, asthma conventional treatment was begun or increased in 20 out of 29 patients with ACT score less than 19 and, in 10 out of 31 patients with ACT score > 20, and in both treatment groups ("Initiated or increased therapy" and "No change in therapy") the clinical and functional findings were significantly better in patients with higher ACT score [23]. Moreover, in the current study significant inverse correlation was found after treatment between body mass index and asthma control test in those patient on conventional treatment (P<0.05). The impact of increasing body weight on asthma control or response to therapy is not consistently reported in the literature and the relationship between obesity and asthma severity as classified in published asthma guidelines is controversial [24], however, a possible explanation may be that obesity can lead to a reduction in pulmonary compliance caused by fat compression and infiltration of the thorax or the increase in lung blood volumes or reduction in lung volumes, and the diameter of peripheral airways that can affect the volume of blood in the lungs and the ventilation perfusion relationship resulting in a subjective increase in dyspnea [2, 4]. Moreover, adiponectin receptors are down regulated with increased adiposity particularly in females, and that adiponectin was found to be protective against current asthma prevalence [24] .In contrast, leptin was associated with poorer asthma control, but an independent effect could not be demonstrated because of the high correlation between adiposity measures and leptin [24]. The present study is also compatible with a cross-sectional study on urban adults with asthma which found no differences in asthma control as measured by 4 validated asthma control questionnaires with changes in BMI [21]. In a another study comparing obese and non-obese adult asthmatics presenting to emergency rooms, the severity of the asthma exacerbations were found to be similar [25].

While there are no pharmacologic strategies to specifically treat obese asthmatics, weight loss interventions, both surgical and nutritional, have been tested and shown to have varying degrees of effectiveness in improving the respiratory health of these patients, however, vitamin D deficiency has been proposed as a risk factor of increased pattern of asthma prevalence as mentioned earlier [12, 13].

In the current study following conventional therapy, it was found that among the 12 obese patients with vitamin D deficiency, only 1 patients presented with significant vitamin D insufficiency (P<0.05). Previous study mentioned that those patients with high BMI who received montelukast, the clinical benefit was greater than in lean patients, which suggests that leukotrienes play a more important role as mediators of symptoms in obese patients[26]. Also in the current study the body mass index still

inversely correlated with endogenous vitamin D about to reaching significant level before and after treatment, this is probably due to the minimum impact of the conventional treatment on endogenous vitamin D level.

In the recent National Institutes of Health (NIH) Asthma Net Clinical Trial of Vitamin D Supplementation in Asthma (VIDA), vitamin D was not more effective on obese asthmatics, specifically, the VIDA study was designed to determine if vitamin supplementation in asthmatics using inhaled corticosteroids improved asthma outcomes with a primary outcome of time to first asthma treatment failure (based on decline in lung function and increased use of beta agonists or systemic corticosteroids, and increased healthcare utilization)[27]. In other study, when comparing those asthmatics with BMI < 25 versus BMI \geq 25, vitamin D supplementation did not show a reduction in asthma treatment failures in the obese group [28]. One study concluded that 25(OH)D levels below 30 ng/ml are common in adult asthma and most pronounced in patients with severe and/or uncontrolled asthma, supporting the hypothesis that improving suboptimal vitamin D status might be effective in prevention and treatment of asthma [29].

In this study, a 12 week 2000 IU vitamin D_3 supplement therapy produced a highly significant improvement in asthma control was noticed post treatment (P<0.01), mainly in the well controlled (score \geq 20) and uncontrolled (score<16) asthmatic patients. Similar finding was reviewed in recent study which showed no variation in ACT scores after a 12 week 2000 IU vitamin D_3 adjuvant therapy, but a significant improvement of the ACT scores at the end of the study in the subjects with uncontrolled asthma (ACT < 19)[30]. The incidence of severe vitamin D deficiency was high in adult Turkish asthmatics, and the lower vitamin D levels were associated with poor asthma control and decreased pulmonary function [31].

On the other hand, vitamin D_3 supplement in this study significantly improved endogenous vitamin D status in obese patients with vitamin D deficiency(P<0.01). It is well reviewed previously that obese individuals, as a group, have low plasma concentrations of 25-hydroxyvitamin D (25(OH)D) [9-11], and regardless of the possible underlying mechanisms, it may be relevant to take adiposity into account when assessing vitamin D requirements. In the previous review, the possible mechanisms for lower vitamin D concentrations in obese individuals which may explained by lower dietary intake, reduced cutaneous synthesis, altered behavior, reduced synthetic capacity, reduced intestinal absorption, altered metabolism which may include either reduced activation and/or increased catabolism, sequestration in adipose tissue [32]. It has also been suggested that the metabolic clearance of vitamin D may increase in obesity, possibly with enhanced uptake by adipose tissue [10].

Additionally, inverse correlation between BMI and endogenous vitamin D level in asthmatic patients was noticed [33], as in the present study. After vitamin D₃ supplement in the current study, the change in the body mass index was parallel to the improvement in endogenous vitamin D level, though no clear positive correlation was produced probably due to the small scale study, and also no correlation was found

between endogenous vitamin D level and asthma control test was found. The trial linking asthma control, obesity, and vitamin D deficiency was well reviewed recently in children, and stated that obese individuals have low vitamin D status, and emerging evidence suggests vitamin D affects risk of acute respiratory infection and corticosteroid responsiveness in individuals with asthma [34].

All these observations suggested that evaluation of serum vitamin D concentrations should be considered in obese asthmatic patients that responds suboptimally to inhaled corticosteroid (ICS), and recently give promising preventive strategy that anti-inflammatory and antioxidant effect of vitamin D_3 supplementation could result in improvement of these phenotypic variables in the subset of subjects with asthma who are vitamin D deficient [35, 36].

5. CONCLUSION

After vitamin D_3 supplement in the current study, the change in the body mass index produce improvement in endogenous vitamin D status parallel to the change in the body mass index and markedly improvement in asthma control. Also the reduction in the body mass index after vitamin D_3 treatment was positively correlated with asthma control.

Acknowledgment

The author would like to thank Mustansiriyah University (www.uomustansiriyah.edu.iq) Baghdad - Iraq for its support in the present work and special thanks to Al-Yarmouk Teaching Hospital for their help in providing the practical platform of this study.

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