

ASTHMA CONTROL

Vitamin D deficiency and level of asthma control in women from North of Jordan: a case–control study

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Abstract

Introduction: Reduced vitamin-D levels in patients with asthma have been associated with impaired lung function, increased airway hyper-responsiveness, and reduced glucocorticoid responsiveness. Nationwide studies revealed a considerable prevalence of vitamin-D deficiency (VDD) in Jordanian women. **Objective:** A case–control study was conducted to determine the relationship between serum vitamin A and D levels and asthma among women in North of Jordan. **Methods:** Sixty-eight asthmatics, age range between 14 and 65 years and 77 healthy women, age range between 19 and 51 years, were enrolled. Asthma severity was classified using Global Initiative for Asthma (GINA) guidelines and Asthma Control Test (ACT) questionnaire. Serum vitamin-A and 25-hydroxyvitamin-D (25(OH)D3) levels were measured using high-performance liquid chromatography (HPLC) and liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods, respectively. **Results:** The prevalence of VDD (<15 ng/ml) was higher but not statistically significant for women with asthma compared with controls (95.6% vs. 87.0%; $p = 0.070$). The severity of VDD correlated with the number of asthma medications ($p = 0.020$). 25(OH)-D3 serum levels directly correlated with asthma control level using ACT score ($p = 0.012$) and GINA classification ($p = 0.046$). After adjusting for age, the odds of having VDD for asthmatic women were 35.9 times higher than that for women with no asthma. There was no difference in serum vitamin-A level between healthy and asthmatic women ($p = 0.214$) and none had vitamin-A deficiency (<200 µg/dl). **Conclusions:** VDD is prevalent in women with asthma in northern Jordan. The severity of VDD correlated with poor asthma control and a need for more medications to control asthma. There was no association between vitamin-A and asthma.

Keywords

ACT score, asthma, GINA, Jordan, vitamin A, vitamin D

History

Received 3 March 2014

Revised 14 April 2014

Accepted 25 April 2014

Published online 20 May 2014

Introduction

Asthma is an inflammatory disorder of the airways associated with airflow obstruction and bronchial hyperresponsiveness that varies in severity across the spectrum of the disease. It is recognized that a subgroup of asthmatics show reduced responsiveness to standard therapy and experience greater morbidity and lower quality of life than those asthmatics whose disease is adequately controlled [1,2]. Little is known about the distribution of asthma severity in men and women in the general population. Many studies concluded that there is no gender differences observed in the crude prevalence of asthma or in asthma severity but indicated women to have considerably higher risk of being admitted to the hospital for asthma-related illnesses than men [3–5]. International studies reported females to constitute the majority of the severe asthma cases. In an European multicenter study, females dominated the severe asthma group with a female-to-male

ratio of 4.4:1 compared with 1.6:1 in the controlled asthmatics [2]. A study by Skobeloff et al. [6] reported a higher asthma severity in women. At the adult pulmonary clinic at King Abdullah University Hospital (KAUH), asthma cases visiting with refractory uncontrolled asthma were in majority females in their childbearing age. The female-to-male ratio of this subgroup of asthma phenotype was estimated to be around 7:1 (unpublished data), which is higher than that reported in the literature. This subgroup represented patients whose asthma remains uncontrolled despite using Global Initiative for Asthma (GINA) guidelines for treatment [7]. This is a cause of concern with potential complications of uncontrolled disease including fatal or near fatal asthma, in this subgroup.

In contrast, vitamin-D deficiency (VDD) has been reported worldwide and is linked to many diseases including asthma [8]. Reduced vitamin-D levels have been associated with increased airway hyperresponsiveness, reduced response to glucocorticoids, and severe asthma exacerbations in asthmatic children [9–14]. Few studies have examined vitamin-D levels and asthma severity in adults [15–18]. In Jordan, low vitamin-D status is more prevalent in females in contrast to males.

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This was attributed to lack of direct sunlight exposure mainly because of the dress styles that cover most or all of women’s skin [19–21]. A recent nationwide study found 95.7% of women vitamin-D insufficient, and 63.0% of women deficient [20]. Another study by Batieha et al. [19–21] found higher prevalence of low vitamin-D status in Jordanians females (37.3%) compared with males (5.1%). These percentages translate to a female-to-male ratio of 7.4:1 which is close to our estimated female-to-male ratio of the refractory uncontrolled asthma subgroup visiting the adult pulmonary clinic at KAUH.

Antioxidant vitamins, including vitamin-A, may have protective effect against oxidative stress and its manifestation in bronchial asthma. Serum vitamin-A concentration was significantly lower in asthmatics compared with control subjects ($p<0.01$) [22]. Many studies have shown a significant increase in odds of asthma and wheeze with a decrease in the dietary intake of vitamins A and C [23]. Other studies suggested that a reduction of vitamin-A in asthmatic children may have etiological implications [24], and may be involved in the acute phase response and various degrees of chronic epithelial damage of airways [25]. In Jordan, vitamin-A has been studied in schoolchildren in North Badia of Jordan and revealed significantly low vitamin-A level in this area with poor income with under-nutrition conditions. This finding was anticipated to be reflected in adult population [26,27]. Vitamin-A status in the adult Jordanian population has not been investigated yet.

The purpose of this study was to determine the relationship between serum vitamin A and D levels and asthma among women in Northern Jordan.

Methods

Participants

All women with asthma, who visited the adult pulmonary clinic at KAUH in Irbid, Jordan, during the period between June 2011 and January 2013, were eligible for the study. The presence of asthma was defined by at least one attack with typical asthma symptoms such as cough, chest tightness, dyspnea, and wheezes during the previous 12 months of the study enrollment. All asthma cases had to have previous evidence of variable airways obstruction, as documented by at least one of the followings. (1) Reversibility in forced expiratory volume in one second (FEV1) by an increase of >12% and 200 ml predicted after four puffs of a 100 mg salbutamol dose-aerosol administered via a spacer. (2) An improvement of 60 L/min or ≥20% of the pre-bronchodilator

peak expiratory flow rate (PEFR), or a diurnal variation in PEFR of >20%. (3) A provocative concentration causing a 20% fall in FEV1 with methacholine <8 mg/ml. Patients with exercise induced asthma, asthma exacerbation within 1 month of the study requiring systemic glucocorticosteroids, or cases required hospitalization to control asthma for up to 3 months prior to enrollment were excluded from the study. We also excluded asthma cases who did not take their medications or inhalers regularly as prescribed or demonstrated difficulty in performing inhaler technique that would result in inadequate delivery of the inhaled medication. Healthy volunteers, mainly hospital and university employees, were screened for asthma symptoms using life quality (LQ) test questionnaire [28] and had to have a normal range flow spirometry test prior to inclusion in the study to exclude undiagnosed asthma or other subclinical lung diseases.

Women with any disorder that can affect the level of vitamin-D were excluded from our study including, upper airway respiratory infection within 4 weeks, presence of chronic bronchitis, emphysema or bronchiectasis, presence of diabetes mellitus, cancer or autoimmune disorders, presence of cardiovascular disease including uncontrolled or hard to control hypertension, uncontrolled gastroesophageal reflux disease, history of malabsorption, history of drug abuse or any alcohol intake, current or past history of active smoking, pregnancy or lactation, actively on weight loosing diet program, and current or past history of vitamin-D supplement intake.

Out of 249 women with asthma screened for the study, 181 cases were excluded from the study. The most common reasons for exclusion were non-compliance with prescribed asthma therapy or difficulty in performing inhaler technique that would result in inadequate delivery of the inhaled medication (43 cases), asthma with atypical symptoms (36 cases), and history of vitamin-D supplement intake (29 cases). A total of 28 patients were excluded because of recent use of systemic glucocorticosteroids. A total of 23 cases had diabetes mellitus.

A total of 145 women (68 patients with asthma and 77 healthy volunteers), aged between 14- and 65-year old, were enrolled in the study. The level of asthma control was assessed using Asthma Control Test (ACT) questionnaire [29], and classified into controlled, partly controlled, or uncontrolled according to 2012, GINA guidelines [7] (Table 1). Asthma medication lines required to control asthma and taken within 4 weeks prior to study enrollment were counted individually. Cases with controlled asthma that are neither requiring nor taking any asthma treatments within 4 weeks of the study

Table 1. Classification of asthma by level of control, GINA guidelines (2012).

Characteristic	Controlled (all the followings)	Partly controlled (any measure present in any week)	Uncontrolled
Daytime symptoms	None (twice or less/week)	More than twice/week	Three or more features of partly controlled asthma present in any week
Limitation of activities	None	Any	
Nocturnal symptoms/awakening	None	Any	
Need for reliever/rescue treatment	None (twice or less/week)	More than twice/week	
Lung function (PEF or FEV ₁)	Normal	< 80% predicted or personal best (if known)	One in any week
Exacerbations	None	One or more/year	

PEF, peak expiratory flow rate. FEV, forced expiratory volume in one second.

were included and considered as asthma in remission and were included in the asthma group. Lines of asthma treatments encountered in our study included as needed rapid-acting β_2 -agonist, (low, medium, or high)-dose inhaled glucocorticosteroids, long acting β_2 -agonist, leukotriene modifier, theophylline, inhaled anticholinergic agents, and anti-IgE treatment [28].

All participants included in the study were informed about the study details, goals, and requirements and provided a signed consent form approved by the institutional review board (IRB) and local research ethic committee at Jordan University of Science and Technology (JUST) and KAUH prior to their inclusion (IRB number 2010/4-session-21).

Data collection

Both groups underwent a complete clinical and physical evaluation and completed a general information questionnaire about income, marital status, number of children, work environment, average number of daily meals, degree of sun exposure (including questions about dress cover style and average of total daily hours of sun exposure), past medical history, and medication intake including over the counter medications asking specifically for vitamins and nutritional supplements.

Laboratory measurements

During a routine clinic visit, a trained phlebotomist collected venous blood samples from the participants in polypropylene tubes containing ethylene–diamine–tetraacetic acid (EDTA). Samples were centrifuged immediately after drawing and then transported (4–10 °C in a cold box containing frozen gel packs) to JUST laboratory and kept frozen under –20 °C until the time of biochemical analysis. The collected samples were shielded from direct light exposure. Serum vitamin-A and 25-hydroxyvitamin-D (25(OH)D3) concentrations were measured using high-performance liquid chromatography (HPLC) and gold-standard liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods, respectively, at Micronutrient Laboratory at JUST. The imprecision was accepted since it was <3%. Using vitamin-D level values from the most recent nationwide study [20], results of serum 25(OH)D3 concentration (ng/ml) were classified into four categories: normal (20–40), insufficient (15–20), deficient (10–15), and severely deficient (<10). Serum level of vitamin-A ($\mu\text{g/dl}$) results was classified into three categories: normal (>300), insufficient (200–300), and deficient (<200).

Statistical analysis

Data were analyzed using the Statistical Package for Social Science (SPSS version 15, SPSS Inc., Chicago, IL). The characteristics of the participants were described using means and standard deviations for quantitative variables and using percentages for qualitative variables. Independent *t*-test was used to test for the statistical differences between means. Spearman's correlation coefficient was used to test for the correlation between the serum 25(OH)D3 concentration and the number of asthma treatments and ACT scores. The General Linear Procedure was used to assess the

significance of the association between asthma and 25(OH)D3 level after adjusting for age. Multivariate logistic regression was used to assess the significance of the association between asthma and VDD after adjusting for potential confounders. A *p* value of <0.05 was considered statistically significant.

Results

The study included a total of 68 women with asthma (asthma group) and 77 healthy women without asthma (control group). Table 2 shows the socio-demographic and relevant characteristics of the two groups. Women with asthma were significantly older than women with no asthma. The age of the asthma group ranged from 14 to 65 year and control group ranged from 19 to 51 year. Compared with controls, women with asthma had a significantly lower income, higher number of children, and higher body mass index. There was no statistical difference in the total hours of daily sunlight exposure between asthma group [mean(SD) = 2.3(2.2) hours] and healthy group [mean(SD) = 2.3(2.2) hours] (*p* = 0.062). There is significant weak and direct correlation between vitamin-A and 25(OH)D3 level (*r* = 0.21, *p* = 0.010).

Vitamin-A was slightly higher but not statistically significant (*p* = 0.214) in the asthma group compared with the control group. Vitamin-A insufficiency (<300 $\mu\text{g/dl}$) was present in 16% of the asthma group and about 9% of the control group. None of the women enrolled was found to have vitamin-A deficiency (<200 $\mu\text{g/dl}$). Serum 25(OH)D3 level was significantly lower (*p* = 0.027) in the asthma group compared with the control group. In the general linear model analysis, 25(OH)D3 in its continuous form was only associated with age and asthma. The age-adjusted mean of 25(OH)D3 was 7.8 ng/ml (95% confidence interval: 6.2, 9.2) for the asthma group and 11.1 ng/ml (95% confidence interval: 9.7, 12.5) for the control group (*p* = 0.002).

The prevalence of VDD (<15 ng/ml) was higher but not statistically significant for the asthma group compared with the control group (95.6% vs. 87.0%; *p* = 0.070). The distribution of 25(OH)D3 categories for women with asthma and without asthma is shown in Figure 1. In the univariate analysis using logistic regression, VDD was not significantly associated with any of the studied variables including age (*p* = 0.090), asthma (*p* = 0.070), body mass index (*p* = 0.759), monthly income (*p* = 0.117), or parity (*p* = 0.092). However, the association between VDD and asthma became significant when adjusted for age in the multivariate analysis (Table 3).

Table 2. The socio-demographic and vitamins D and A status of women with and without asthma.

	Control (<i>n</i> = 77)		Asthma (<i>n</i> = 68)		<i>p</i> Value
	Mean	SD	Mean	SD	
Age (year)	30.7	6.4	41.0	13.7	<0.005
Body mass index (kg/m ²)	25.9	4.4	29.3	6.0	<0.005
Monthly income (JD)	597.2	312.5	425.7	231.5	<0.005
Parity	1.6	1.7	3.6	2.9	<0.005
Hours of daily exposure to the sun	1.6	2.2	2.3	2.2	0.062
Vitamin A ($\mu\text{g/dl}$)	418.6	95.6	441.2	121.7	0.214
25(OH)D3 (ng/ml)	10.5	7.6	8.3	3.2	0.027

Figure 1. The distribution of 25(OH)D level using different cutoff values in asthma and control groups.

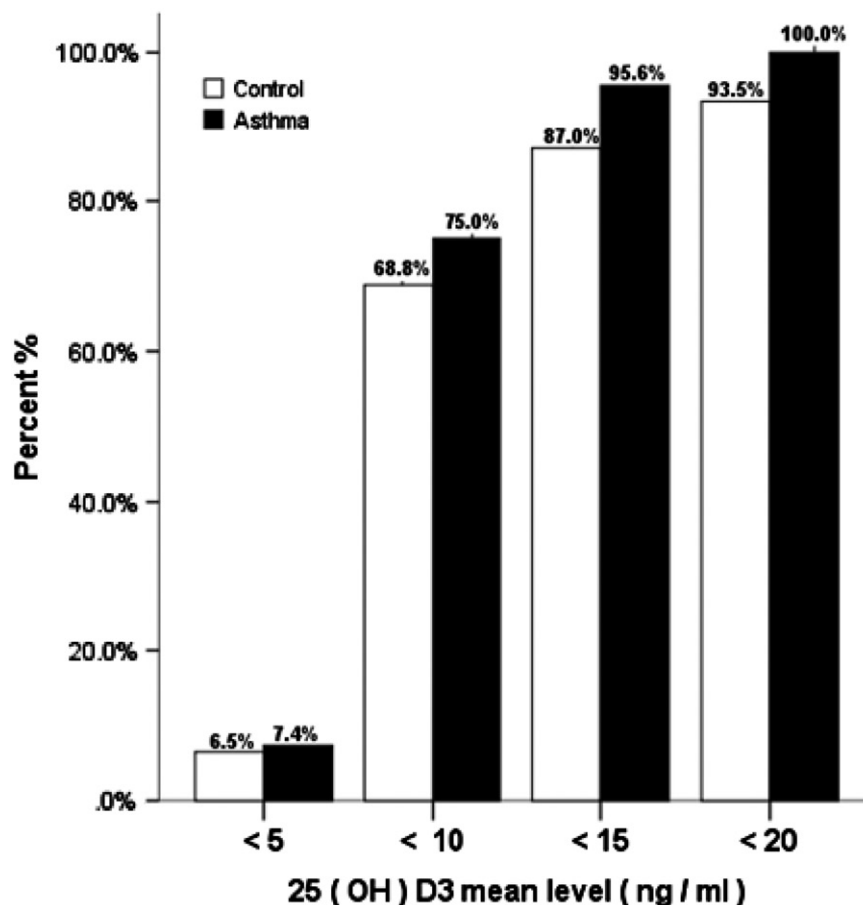


Table 3. The age-adjusted association between VDD and asthma in the multivariate analysis.

Variable	OR	95% confidence interval	p Value	
Age (year)	0.9	0.002	0.8	0.901
Group (asthma vs. control)	35.9	3.4	378.8	0.003

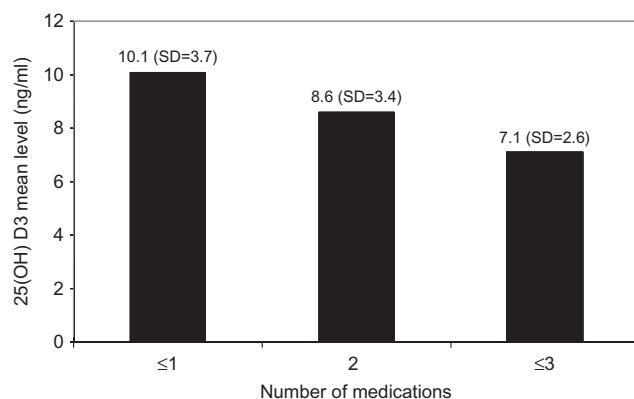


Figure 2. Relationship between the serum concentration level of 25(OH)D3 and the number of treatments required to control asthma.

After adjusting for age, the odds of having VDD for asthmatic women were 35.9 times higher than that for women with no asthma. Figure 2 shows the mean of 25(OH)D3 according to the number of asthma treatments. Among patients with asthma, the levels of 25(OH)D3 were inversely associated

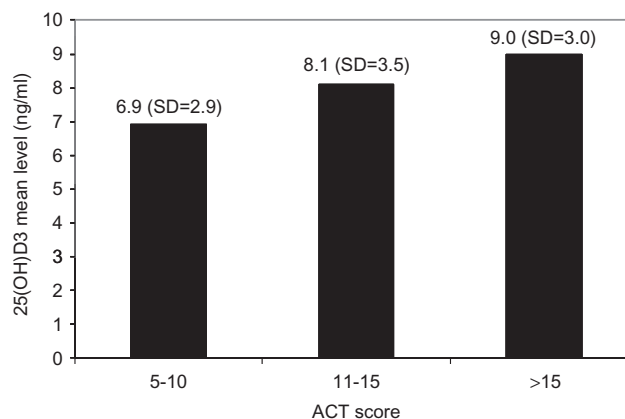


Figure 3. Relationship between 25(OH)D3 serum level and control of asthma (ACT score).

with the number of asthma medications ($r=-0.28$, $p=0.020$) and directly with ACT scores ($r=0.30$, $p=0.012$) (Figure 3). The mean of vitamin-D level differed between asthma categories using GINA classification for the level of asthma control ($p=0.046$). Cases with controlled asthma had higher mean level of vitamin-D (mean = 9.4 ng/ml) than patients with partly controlled asthma (mean = 8.4 ng/ml) and those with uncontrolled asthma (mean = 7.9 ng/ml) (Figure 4). In contrast, vitamin-A was not significantly associated with the number of asthma medications ($r=-0.05$, $p=0.674$) or ACT score ($r=0.04$, $p=0.688$). The mean of

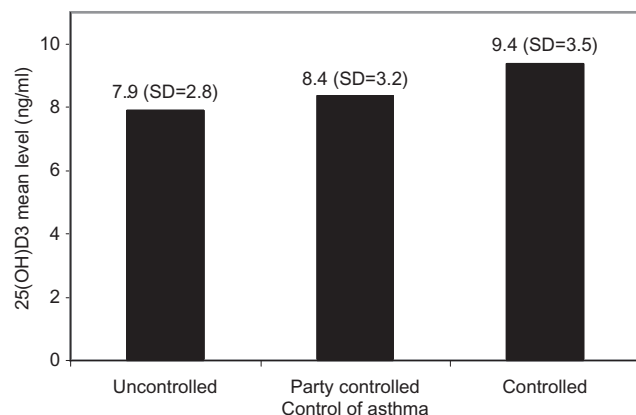


Figure 4. Relationship between 25(OH)D3 serum level and control of asthma (GINA classification).

vitamin-A level did not differ significantly between asthma categories using GINA classification.

Discussion

To date, three other studies have reported results regarding vitamin-D in adult asthmatics [15–18]. In this study, there was no statistical difference in the prevalence rates of VDD (<15 ng/ml) between asthma and control groups ($p=0.070$) in the univariate analysis. The lack of statistical significance in the univariate analysis can be explained by the fact that the majority of subjects in both groups had VDD. This finding correlates with nationwide studies which revealed a significant prevalence for VDD among Jordanian women [19,20]. Only few cases from our study population were found to have vitamin-A insufficiency <300 μ g/dl ($n=7$ (9%) from the control group) and ($n=11$ (16%) from the asthma group) with no difference between both groups ($p=0.214$). No association among level of vitamin-A and asthma symptoms, level of asthma control, or number of medications was found. This finding might be explained by the fact that the majority of women with asthma and healthy controls have normal vitamin-A level and none of the women had vitamin-A deficiency (<200 μ g/dl).

The ability to convert previtamin-D3 to 25(OH)D3 is diminished with aging [30]. In our study, a significant difference in the age between asthma and control groups was present. The age mismatch might have confounded the association between asthma and vitamin-D. After adjusting for age, asthma patients were found to have a more severe form of VDD compared with control subjects, and the risk of developing asthma is much more with a more severe form of VDD. An important finding from our study that was not affected by the age mismatch is how the level of VDD significantly correlates with the number of asthma medication lines required to control asthma and asthma control level. This indicates that a severe asthma phenotype is found in the subgroup with a more VDD requiring more medications to control asthma symptoms. This study showed that there are statistically significant differences in the levels of vitamin-D among the three different categories of asthma control level using both GINA and ACT scores, with the higher level of vitamin-D being associated with better asthma

control. However, although this difference is beyond chance, it appears to be small. Therefore, the association between vitamin-D and asthma control is better to be studied in populations with higher variability in vitamin-D level and lower prevalence rate of VDD.

The study included cases with persistent refractory uncontrolled asthma that did not require recent use of systemic glucocorticoids. Although systemic glucocorticoids have been reported to affect vitamin-D level, the effect of using short-term courses of systemic glucocorticosteroids on vitamin-D level is not clear [31,32]. Asthmatic cases that required taking systemic glucocorticoids within 1 month of the study were excluded to avoid any confounding effect of systemic glucocorticoids on vitamin-D serum level that would interfere with the evaluation of asthma and vitamin-D level association. These excluded cases constitute in majority cases with severe uncontrolled asthma phenotype with recurrent asthma exacerbations with probably lower vitamin-D levels. Excluding these asthma cases is another limitation of our study.

Low vitamin-D level can be attributed to limited sunlight exposure due to limited out-door activities in asthmatics. In this study, the length of daily sun-light exposure was slightly higher but not significant for the asthma group [mean(SD) = 2.3(2.2) hours] compared with the healthy group [mean(SD) = 1.6(2.2) hours] ($p=0.062$). Hence, we suggest a possible cause-effect link between VDD and asthma phenotype, or a likely possibility that vitamin-D has a role and is required during asthma inflammation and/or healing processes. Increased demand and consumption of vitamin-D during the chronic course of asthma, with frequent episodes of inflammation and healing processes, might lead to a greater degree of VDD in uncontrolled asthma cases. If this conclusion is true, VDD would contribute to a cycle of further uncontrolled asthma status that requires higher number of treatments to control symptoms of asthma and further VDD.

There is mounting evidence that vitamin-D plays a beneficial role in the prevention and treatment of a wide range of diseases outside bone health and calcium homeostasis [33–37]. Many studies have suggested the role of VDD in both T-helper-1 and T-helper-2 related diseases; however, the association among vitamin-D, allergy, and asthma remains uncertain [38–40]. Recent recognition and identification of vitamin-D receptor on many cells have implicated vitamin-D as a potential therapeutic target for many disorders including asthma [34,41–44]. Others suggested a potential use of vitamin-D as a new treatment for airway remodeling in asthma by inhibiting growth of human airway smooth muscle cells through growth factor-induced phosphorylation of retinoblastoma protein and checkpoint kinase-1 [37].

The inverse correlation observed from this study between reduced serum vitamin-D levels and the number of asthma medication lines required to control asthma suggests that measuring serum vitamin-D concentrations might be beneficial in evaluating adults with persistent refractory uncontrolled asthma despite using usual asthma therapeutic options or those with poor response to usual pharmacologic treatment lines. This study also raise a possibility that vitamin-D supplementation would help in improving asthma symptoms in cases with uncontrolled asthma who are vitamin-D

deficient. Ongoing clinical trials should yield valuable insights into the role of vitamin-D supplementation in preventing asthma or reducing asthma morbidity [45].

Conclusions

VDD is prevalent in women with asthma in Northern Jordan. The severity of VDD correlates with poor asthma control and with the number of medication lines required to control asthma symptoms. Measuring serum vitamin-D might be beneficial in evaluating high-risk adults with persistent uncontrolled asthma. Further studies to investigate a possible therapeutic effect of vitamin-D supplementation on cases with uncontrolled asthma and VDD might be beneficial.

Author contributions

Dr. Samrah contributed to study conception and design of the research questions, provision of substantive content, and the drafting and revision of the manuscript.

Dr. Khatib contributed to laboratory analysis of serum samples, and the drafting and revision of the manuscript.

Dr. Omari contributed to data extraction, analysis, and the drafting and revision of the manuscript.

Dr. Khassawneh contributed to data extraction, analysis, and the drafting and revision of the manuscript.

Dr. Momany contributed to data extraction, analysis, and the drafting and revision of the manuscript.

Dr. Daoud contributed to data extraction, analysis, and the drafting and revision of the manuscript.

Dr. Malkawi contributed to data extraction, analysis, and the drafting and revision of the manuscript.

Dr. Khader contributed to design of the research questions, statistical analysis, and the drafting and revision of the manuscript.

Declaration of interest

The authors report no conflicts of interest in this work. The study was fully funded by the Deanship of Scientific Research of JUST.

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