Predictors of reduced serum vitamin D levels among Egyptian children with interstitial lung disease

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Background/aim

Patients with interstitial lung disease (ILD) appear to be at an increased risk of vitamin D deficiency for reasons that are not clear. This study was designed to determine the serum vitamin D level and to evaluate the relationship between the serum level of vitamin D and the underlying etiology, the clinical severity, and pulmonary functions among children with ILD.

Patients and methods

This cross-sectional case–control study was conducted on 40 patients aged 4–16 years with ILD from those regularly attending the Pediatric Chest Clinic and Pediatric Allergy and Immunology Clinic, Children's Hospital, Ain Shams University. They were divided into two subgroups: 20 patients with nonconnective tissue disease-associated ILD constituted group I and 20 patients with connective tissue disease-associated ILD constituted group II. Twenty apparently healthy children of matched age and sex were recruited as the control group.

Results

The mean serum vitamin D (25-hydroxyvitamin D) level was significantly lower among patients with ILDs compared with controls (21.15 ± 4.6 vs. 48 ± 40.76 ng/ml, respectively, $P < 0.05$), and there was no significant difference between patients' subgroups. The mean alkaline phosphatase level was significantly higher in patients with ILDs compared with controls ($P < 0.05$). Our patients had a highly significant increase in the total leukocytic count, erythrocyte sedimentation rate, and C-reactive protein in connective tissue disease-associated ILD as compared with nonconnective tissue disease-associated ILD. Serum vitamin D levels showed a significant positive correlation with forced vital capacity and significant negative correlations with the age and the duration of steroid therapy. By linear regression analysis, patients' age and the duration of steroid therapy were significant predictors of low serum vitamin D levels (at $P = 0.045$ and 0.01, respectively).

Conclusion

Children with ILD appear to be at an increased risk of vitamin D deficiency and insufficiency, particularly those with reduced lung function. All patients with ILD receiving long-term corticosteroid therapy should be considered at increased risk for bone fracture. Preventive measures and routine estimation of vitamin D (25-hydroxyvitamin D) should be recommended and vitamin D supplementation is advised on an individual basis.

Keywords:
Egyptian children, interstitial lung disease, predictors, serum vitamin D levels

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Introduction

Interstitial lung disease (ILD) is rarely cured and is an ultimately fatal disease, and the life expectancy of patients after diagnosis is ~5–10 years. It is characterized by irreversible and progressive replacement of the normal lung tissue with fibrous tissue, leading to derangement of gas exchange, restrictive lung physiology, and diffuse infiltrates on radiographs. It occurs in children as young as 3 years of age [1]. The disease may be idiopathic or it can be triggered by a severe viral infection. It can be caused by autoimmune diseases (lupus, rheumatoid arthritis) or through occupational exposure to molds, gases, fumes, or ionizing radiation (such as radiation therapy to treat tumors of the chest) [2]. Genetic factors are taken into consideration due to various reports of cases in the same family and due to new information regarding genetic surfactant dysfunction [3].

Vitamin D is a steroid hormone with pleiotropic effects including calcium homeostasis and bone mineralization. The most important source of vitamin D is its natural cutaneous production due to the sun's ultraviolet radiation [4]. Recent studies suggest that vitamin D plays a role in lung tissue remodeling, preserving lung function, immune system modulation, and preventing pulmonary infection [5,6]. Infants and children with vitamin D deficiency had been associated with a higher risk of and more severe respiratory infections [7,8]. In adults with ILD, the National Health and Nutrition Examination Survey III showed an association between the forced vital capacity (FVC), the forced expiratory volume in 1 s (FEV_1), and 25-hydroxyvitamin D_3 [9]. The connection between the vitamin D status and lung function is unclear; the mechanism by which vitamin D improves lung function may be through its action on regulating inflammation [10], inducing antimicrobial peptides [11], and/or its action on muscle [12]. Various cytokines, cellular elements, oxidative stress, and protease/antiprotease levels appear to affect lung fibroproliferation, remodeling, and function, which may be influenced by the vitamin D status [13].

Lung involvement is common in many types of connective tissue diseases (CTDs) with prevalence estimates of up to 80%, with diffuse ILD being the most common pulmonary manifestation [14]. The general mechanism of injury is the interaction of autoantibodies produced by the body with either the lung parenchyma or the vasculature within the lung, resulting in disease [15]. Moreover, corticosteroids are a mainstay of treatment regimens in patients with ILD, especially in those with CTD-ILD, and the detrimental effects of long-term usage on vitamin D and bone health are well documented [16]. Arnson *et al.* [17] suggest that vitamin D may be involved in the pathogenesis and the development of end-organ dysfunction of autoimmune disorders. Therefore, our study aimed to determine the relationship between the serum level of 25-hydroxyvitamin D (25-OHD) and the underlying etiology, the clinical severity, and lung function among Egyptian children with ILDs.

Patients and methods

This cross-sectional case–control study was conducted on 40 patients aged 4–16 years with ILD. The inclusion criteria for selection included all children regularly attending the Pediatric Chest Clinic and Pediatric Allergy and Immunology Clinic within a period of 1 year starting from October 2012 to September 2013. Exclusion criteria included (a) any conditions known to affect bone metabolism (e.g. renal disease, hyperparathyroidism) and (b) intake of dietary supplements containing calcium or vitamin D.

Children were diagnosed according to a multidisciplinary clinical, radiological consensus conference with input from pulmonologists, rheumatologists, and radiologists [18]. Children were diagnosed to have ILD and possible etiology according to Vece and Fan [19]. They were classified as having CTD-ILD when they met the diagnostic criteria according to the American College of Rheumatology criteria for the diagnosis of the following conditions: rheumatoid arthritis, systemic lupus, scleroderma, polymyositis/dermatomyositis, mixed CTD, Wegener granulomatosis, and Sjögren disease [15,20]. Each patient with ILD was assigned a clinical ILD score based on the severity of illness as follows: 1, asymptomatic; 2, symptomatic under all conditions; 3, symptomatic with desaturation during sleep or with exercise; 4, symptomatic with desaturation at rest; or 5, symptomatic with pulmonary hypertension. In pediatric ILD, an increased score has been associated with a higher probability of decreased survival [21].

They were divided into two subgroups: 20 patients with non-CTD-ILD constituted group I and 20 patients had CTD-ILD constituted group II. Twenty apparently healthy children of matched age and sex were recruited as the control group. A written informed consent was obtained from the study participants' parents. The study was conducted in accordance to the ethical procedures and policies approved by the ethical committee of the Ain Shams Pediatric Hospital, Ain Shams University, Cairo, Egypt.

Methods

Information on age, sex, parental consanguinity, family history of interstitial lung and autoimmune diseases, the duration of illness, and treatment modalities were collected through a questionnaire. Each child was subjected to a complete physical examination and anthropometric measurements. Their weight was measured using a digital scale (Seca, Hamburg, Germany) to the nearest 0.1 kg. Their height was measured using a Seca 225 stadiometer to the nearest 0.1 cm, with the children dressed in minimal clothes and without shoes [22]. The BMI was calculated as the weight (kg) divided by the height (m) squared. BMI and growth percentiles were calculated using CDC-2000 reference values [23].

Dynamic spirometry, a high-resolution computed tomography (HRCT) scan, and serologic tests were performed for the clinical evaluation of the patients. Computed tomographic findings were graded according to the severity and the extent of pulmonary disease as follows: grade 0, normal findings; grade 1, minimal disease (thickened interlobular septa, reticular disease, subpleural cysts, and areas of ground glass pattern); grade 2, moderate disease (traction bronchiectasis, peribronchovascular thickening, tracheal retraction involving one or two zones of the lungs, and the findings present in grade 1); and grade 3, severe disease (the findings in grades 1 and 2 involving all three zones) [24].

Dynamic spirometry (Master screen Pneumo, Erich Jaeger GmbH, Germany) was performed in all patients and healthy controls. A forced expiratory maneuver was carried out in which the child takes full inspiration to the total lung capacity followed by forceful, rapid, and maximal expiration to the residual volume. The display was plotted with volume in liters and flow in liters/second. The following data were obtained: the FVC (l), the FEV_1 (l), and the FEV_1% (FEV_1/FVC or FEV_1%). For every parameter obtained, the actual and the predicted values for age, sex, height, weight, and percentage (%) of the predicted were calculated [25].

An overnight fasting venous blood sample was collected from all patients, and the separated serum was stored at −20°C. Quantitative determination of 25-OHD in serum samples was performed using the enzyme-linked immunosorbent assay (ELISA) (Immundiagnostik EIA, Bensheim and Biomedica, Wien, Austria) according to the manufacturer's guidelines [26]. All wash steps were performed using an ELISA washer (Robonik ELISA plate washer, Mahape, Navi Mumbai, India), whereas the absorbance of all samples was read using the ELISA reader (Biotek EL×800, Mumbai, India) at 450 nm. A standard curve of the absorbance versus concentration was plotted using the calibrators. The concentration of vitamin D in samples was determined directly from the curve. A cutoff value of less than 20 ng/ml for serum 25-OHD was considered as vitamin D deficiency, and 25-OHD less than 30 ng/ml was considered as insufficient, whereas a truly normal 25-OHD level is 30 ng/ml [27]. Serum C-reactive protein was also estimated using an ELISA kit [28].

Another fresh serum sample was analyzed for the measurement of calcium according to the manufacturer's guidelines (Analyticon Biotechnologies AG, Germany) by a colorimetric assay with endpoint determination and a sample blank. The detection limit was 0.05 mmol/l (0.2 mg/dl) using the cresolphtalein complex one method, where the color intensity was measured photometrically at 580 nm. The serum phosphorus was assayed by the measurement of the colorless phosphomolybdate complex at 340 nm by a spectrophotometer with respect to special sample precautions [29].

In addition, samples for alkaline phosphatase were kept at room temperature and assayed within 4 h for biochemical assessment by the popular 4-nitrophenyl phosphate method according to the manufacturer's guidelines (Centronic GmbH, Germany). The enzyme activity was monitored by a spectrophotometer as the increase in absorbance per minute at 405 nm for 3 min [30]. In addition, the complete blood picture and erythrocyte sedimentation rate were also assayed for all children.

Statistical analysis

Statistical analyses were performed using the SPSS statistical package software for Windows version 20 (SSPS Inc., Chicago, Illinois, USA). Parametric variables are expressed as the mean ± SD. Differences between parametric variables among the two groups were evaluated using the two-tailed unpaired *t*-test. Pearson's correlation coefficients were used to evaluate correlations between the data exhibiting parametric distribution. Linear logistic regression analysis was carried out. *P*-value less than 0.05 was considered as a significant difference and *P*-value less than 0.005 was considered as a highly significant difference.

Results

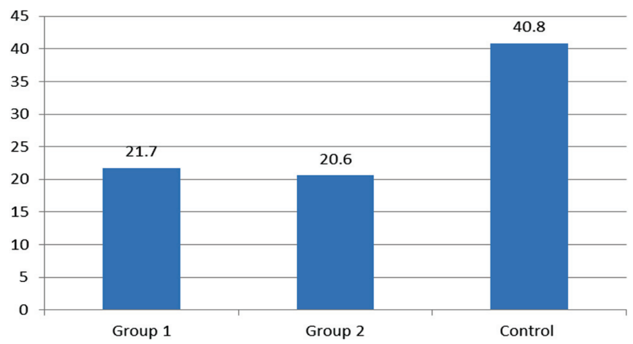
A total of 40 children aged between 4 and 16 years (mean 10.35 ± 3.53 years) were studied. The study included 30 girls (75%) and 10 boys (25%), with a female-to-male ratio of 3 : 1. They were divided into two subgroups: 20 patients with non-CTD-ILD constituted group I and 20 patients with CTD-ILD constituted group II. Sixty percent of the patients were living in urban areas. Passive smoking was found in 10 cases (25%), positive consanguinity in 10 patients (25%), and a positive family history in 10 patients (25%). A positive history of bone fracture was present in two patients, and recurrent history of hospitalization was present in 18 cases. The children with CTD-ILD included 10 patients with SLE, six patients with mixed collagen disease, and four patients diagnosed to have systemic-onset juvenile rheumatoid arthritis. The HRCT findings were graded according to the severity in CTD-ILD as follows: 12 patients were grade 2 (moderate disease), four patients were grade 3 (severe disease), and four patients were grade 1 (minimal disease). However, among the non-CTD-ILD patients, only four patients were grade 2 (moderate disease), five were grade 3 (severe disease), and 11 patients were grade 1 (minimal disease). The demographic and clinical characteristics and the computed tomographic findings are shown in Table 1.

The symptoms score and the duration of systemic steroid therapy were significantly higher among CTD-ILD in group II compared with non-CTD-ILD in group I. The clinical characteristics and comparisons between the patients with CTD-ILD and other forms of ILD are shown in Table 2.

Although the mean BMI, the weight, and the height for age percentiles of the studied patients were within the normal range, the mean weight for the age percentile and the BMI of the total patient group were significantly higher compared with those of the control group ($P < 0.05$), and both were significantly increased in patients with CTD-ILD in group II compared with patients with non-CTD-ILD in group I ($P < 0.05$). The height of our patients was markedly affected and lower compared with their weight. The mean height for the age percentile of the studied patients' group was highly significantly lower compared with that of the control group ($P < 0.005$); however, there was no significant difference between the patients' subgroups ($P > 0.05$). The mean FVC and the FEV_1 of the total patient group was significantly lower compared with those of the control group ($P < 0.05$); however, there was no significant difference between the patient subgroups ($P > 0.05$). Anthropometric measures and pulmonary functions of the studied patients and controls are shown in Table 3.

The mean serum 25-OHD level was significantly lower among the patients with ILD compared with controls (21.15 ± 4.6 vs. 48 ± 40.76 ng/ml, respectively, $P < 0.05$), and there was no significant difference between the patients' subgroups ($P > 0.05$) as shown in Table 4 and Fig. 1. The mean alkaline phosphatase level was significantly higher in patients with ILD compared with controls (252.35 ± 126.9 vs. 144 ± 24.55 ng/ml, respectively, $P < 0.05$). Patients in group II had a highly significant increase in the mean of the total leukocytic count, erythrocyte sedimentation rate, and C-reactive protein as compared with group I and the control group, whereas the mean hemoglobin and platelet count were significantly lower among patients with ILD compared with controls ($P < 0.05$), and there was no significant

Figure 1



A histogram of serum vitamin D levels of the studied patient and control groups.

Table 1 Demographic and clinical characteristics and computed tomographic findings of the studied patients

Variables	Non-CT-IPF (group I) (N = 20) [n (%)]	CT-IPF (group II) (N = 20) [n (%)]	Total patients group (N = 40) [n (%)]
Sex			
Male	10 (50)	0 (0)	10 (25)
Female	10 (50)	20 (100)	30 (75)
Residence			
Urban	12 (60)	12 (60)	24 (60)
Rural	8 (40)	8 (40)	16 (40)
Positive consanguinity	2 (10)	8 (40)	10 (25)
Positive family history	10 (50)	0 (0)	10 (25)
Passive smoking	2 (10)	8 (40)	10 (25)
Clubbing	4 (20)	0 (0)	4 (10)
Positive history of bone fracture	2 (10)	0 (0)	2 (5)
Recurrent history of hospitalization	8 (40)	10 (20)	18 (45)
HRCT scan findings			
Ground glass opacity	16 (80)	10 (50)	26 (65)
Reticular opacities	11 (55)	14 (70)	25 (62.5)
Honeycombing	2 (10)	3 (15)	5 (12.5)

CTD, connective tissue disease; HRCT, high-resolution computed tomography; ILD, interstitial lung disease.

Table 2 Comparison of some clinical characteristics of the studied patients

Variables	Non-CT-IPF (group I) (N = 20) (mean ± SD)	CT-IPF (group II) (N = 20) (mean ± SD)	Total patients group (N = 40) (mean ± SD)	P-value
Age (years)	10.5 ± 4.86	10.2 ± 0.61	10.35 ± 3.53	0.834
Symptoms score	1.3 ± 0.85	3.1 ± 0.88	2.2 ± 0.85	0.03*
Crowding index	1.1 ± 0.32	1.0 ± 0.1	1.05 ± 0.22	0.343
Duration of therapy (years)				
Inhaled corticosteroids	7.75 ± 3.71	3.87 ± 1.08	5.8 ± 3.33	0.007**
Systemic corticosteroids	2.3 ± 0.67	5.87 ± 1.68	3.6 ± 1.6	0.00**

CTD, connective tissue disease; ILD, interstitial lung disease; *Significant difference at $P < 0.05$; **Highly significant difference at $P < 0.005$.

Table 3 Anthropometric measures and pulmonary functions of the studied patients and controls

Variables	Non-CT-IPF (group I) (*N* = 20) (mean ± SD)	CT-IPF (group II) (*N* = 20) (mean ± SD)	Total patients group (*N* = 40) (mean ± SD)	Control Group (*N* = 20) (mean ± SD)	Group I vs. group II (*P*-value)	Patients vs. controls (*P*-value)
Anthropometric measures						
Weight/age percentile	30.06 ± 25.23	69.75 ± 17.36	49.91 ± 29.3	41.56 ± 13.5	0.008**	0.046*
Height/age percentile	13.98 ± 16.36	14.36 ± 14.66	14.17 ± 15.12	40.0 ± 5.5	0.959	0.003**
BMI	19.27 ± 3.18	22.4 ± 2.32	20.84 ± 3.15	15.2 ± 2.06	0.017*	0.048*
Pulmonary functions						
FVC (% of predicted)	74.6 ± 1.51	70 ± 2.4	73.3 ± 2.08	95.28 ± 2.65	0.138	0.04*
FEV_1 (% of predicted)	74.9 ± 1.37	71.4 ± 3.1	72.15 ± 2.35	95.4 ± 2.47	0.685	0.01*
FEV_1/FVC ratio	97.4 ± 4.01	97.69 ± 6.04	97.55 ± 4.1	94.96 ± 2.73	0.919	0.48

CTD, connective tissue disease; ILD, interstitial lung disease; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; *Significant difference at $P < 0.05$; **Highly significant difference at P < 0.005.

Table 4 Laboratory findings of the studied patient and control groups

Variables	Non-CT-IPF (group I) (*N* = 20) (mean ± SD)	CT-IPF (group II) (*N* = 20) (mean ± SD)	Total patients group (*N* = 40) (mean ± SD)	Control group (*N* = 20) (mean ± SD)	Group I vs. group II (*P*-value)	Patients vs. controls (*P*-value)
Serum vitamin D (ng/ml)	21.7 ± 5.36	20.6 ± 3.92	21.15 ± 4.6	48.0 ± 40.76	0.59	0.046*
Serum alkaline phosphatase (IU/l)	293.4 ± 144.38	211.3 ± 70.48	252.35 ± 126.9	144 ± 24.55	0.159	0.027*
Serum phosphorus (mg/dl)	6.22 ± 0.58	6.41 ± 0.85	6.40 ± 0.68	7 ± 6.2	0.443	0.635
Serum calcium (mg/dl)	8.12 ± 0.23	8.14 ± 0.35	8.05 ± 0.22	10 ± 9.36	0.343	0.429
ESR	18 ± 3.56	24.65 ± 5.42	21.3 ± 5.6	10 ± 16	0.026*	0.004*
CRP	3.7 ± 1.16	9.6 ± 6.47	6.6 ± 6.5	3.4 ± 2.5	0.000**	0.04*
Hemoglobin (g/dl)	10.82 ± 1.34	9.71 ± 0.76	10.2 ± 1.2	15 ± 13.56	0.47	0.01*
White blood cells (×1000/μl)	6.5 ± 2.15	17.00 ± 3.8	11.9 ± 6.22	7.5 ± 6.4	0.038*	0.047*
Platelets (×100 000/μl)	341 ± 76.59	322.3 ± 71.11	332 ± 31.65	512 ± 339.8	0.124	0.008**
Eosinophils	3.7 ± 1.6	5.67 ± 1.54	4.8 ± 1.73	3 ± 2.04	0.565	0.115

CRP, C-reactive protein; CTD, connective tissue disease; ESR, erythrocyte sedimentation rate; ILD, interstitial lung disease; *Significant difference at $P < 0.05$; **Highly significant difference at $P < 0.005$.

difference between the patients' subgroups ($P > 0.05$). Laboratory findings of the studied patient and control groups are shown in Table 4.

The serum vitamin D level showed a significant positive correlation with FVC and significant negative correlations with the age and the duration of steroid therapy. Correlations between the serum 25-OHD level, the age, the duration of steroid therapy, and FVC are shown in Table 5.

By linear regression analysis, the age and the duration of steroid therapy were significant predictors of low serum vitamin D levels (at $P = 0.045$ and 0.01, respectively, as shown in Table 6).

Discussion

The incidence of interstitial pulmonary fibrosis is approximately five cases per 100 000. The prevalence of idiopathic lung disease (ILD) is increasing in the UK and USA among children. In developing countries, the prevalence of ILD among children is not well known. It is probably underdiagnosed and under-reported [31]. Pulmonary involvement is common in many types of CTDs. The impact of pulmonary involvement is underscored and it is now the leading cause of death in several CTDs [32].

In the present study, shortness of breath, particularly with exertion, chronic dry, hacking coughing, fatigue and weakness, chest discomfort, loss of appetite, and rapid weight loss were the main symptoms among children with ILD. Sometimes fine inspiratory crackles can be heard at the lung bases on auscultation. A chest radiograph may or may not be abnormal, but HRCT will frequently demonstrate abnormalities. This is in the agreement with Fan *et al.* [33].

The recent literature suggests that vitamin D has an effect on the lung function and on the lung's ability to fight infection. It has complex effects on the pulmonary cell biology and immunity with an impact on inflammation, host defense, wound healing, repair, and other processes. Vitamin D has also been implicated in the development of lung diseases, whereas the knowledge of direct mechanistic links between vitamin D and lung diseases is limited [34]. Hagaman *et al.* [35] reported that vitamin D deficiency may play a role in the development of CTD-ILD and worsening lung function in adult patients.

To the best of our knowledge, there is no available information in the literature regarding the prevalence of vitamin D deficiency and insufficiency among children with ILD. Therefore, our study aimed to determine the presence of vitamin D deficiency and insufficiency among children with ILD and the relationship between the serum level of 25-OHD and the underlying etiology, the clinical severity, and the lung function among children with ILD in Egypt.

Our present study demonstrated significantly lower serum 25-OHD levels among children with ILD compared with controls (21.15 ± 4.6 vs. 48 ± 40.76 ng/ml, respectively, $P < 0.05$). About 60% of children with non-CTD-ILD had 25-OHD insufficiency and 40% of them had 25-OHD deficiency, whereas 35% of the children with CTD-ILD had vitamin D insufficiency and 65% of them had vitamin D deficiency. However, no statistically significant difference was present between patients' subgroups. This is in agreement with Hagaman *et al.* [35] who found that most patients with ILD, particularly those with autoimmune-related CTDs, had insufficient 25-OHD in adults over 20 years old.

Van Etten and Mathieu [36] frequently noted deficiency of vitamin D in patients with autoimmune disease, and that it may contribute to the autoimmune disease process. Baeke *et al.* [37] reported that all cells of the adaptive immune system express vitamin D receptors and are sensitive to the action of vitamin D. High levels of vitamin D are potent inhibitors of dendritic cell maturation, with lower expression of major histocompatibility complex class 2 molecules, cause downregulation of costimulatory molecules, and lower the production of proinflammatory cytokines. Vitamin D might play a role in regulating autoantibody production by B cells, inhibiting the ongoing proliferation of activated B cells and inducing their apoptosis [38]. However, Marshall *et al.* [39] explain that these low levels of vitamin D are a result, rather than a cause, of the disease process. Indeed, Marshall's research shows that in autoimmune disease, vitamin D levels are naturally downregulated in response to vitamin D receptor (VDR) dysregulation by chronic pathogens.

Table 5 Correlations between serum vitamin D levels, age, the duration of steroid therapy, and the forced vital capacity

Variables	Age	Duration of steroid therapy	Forced vital capacity
Serum vitamin D (ng/ml)	−0.447*	−0.737**	0.387*

*Significant difference at $P < 0.05$; **Highly significant difference at $P < 0.005$.

Vitamin D has recently been implicated in the development of lung disease. The best evidence to date regarding the connection between vitamin D deficiency and lung function is the Third National Health and Nutrition Examination Survey (NHANES III). NHANES III was an observational, cross-sectional survey that analyzed data collected from more than 14 000 noninstitutionalized adults older than 20 years of age. Analysis of the data revealed a number of interesting findings, including a significant association between serum vitamin D (25-OHD) levels and pulmonary function tests, specifically FEV_1 and the FVC [9].

To our knowledge, the present study is the first to document hypovitaminosis D in children with diffuse parenchymal lung disease. The present study demonstrated a strong association between the lung function and the serum vitamin D level in patients with ILD. A significant positive correlation was found between the FVC% predicted and the serum 25-OHD among children with ILD ($r = 0.25$, $P = 0.04$). This is in agreement with Glady *et al.* [40] and Swanney *et al.* [41], who reported that serum 25-OHD levels are reduced in adults with diffuse parenchymal lung disease.

We report that the serum vitamin D level showed significant negative correlations with the duration of corticosteroid therapy. Furthermore, by linear regression analysis, the duration of systemic steroid therapy was a statistically significant predictor of low serum vitamin D (25-OHD) levels among children with ILDs ($P = 0.01$). It means that the reduced 25-OHD levels were strongly associated with a long duration of systemic corticosteroid therapy among patients with

Table 6 Predictors of reduced serum vitamin D levels using multivariate linear regression analysis

Variables	Coefficients			*t*	*P*-value
	Unstandardized coefficients		Standardized coefficients		
	B	SE	β		
Constant	44.517	40.303		1.105	0.289
Age (years)	−0.747	0.341	−0.573	−2.192	0.047*
Duration of systemic steroid therapy	0.357	0.943	0.122	0.37	0.01*
Forced vital capacity	−0.416	0.596	−0.188	−0.697	0.498

*Significant difference at $P < 0.05$.

ILD. This is in agreement with Zhou *et al.* [42] who suggested that corticosteroid usage reduces 25-OHD levels. However, their results showed no statistically significant association between 25-OHD levels and prednisone use.

Corticosteroids are the mainstay of treatment for ILD. A favorable response occurs in less than 25% of patients; however, and it is desirable to wean the individual to low-dose steroids after 6 months to a year. In patients who are not responsive to corticosteroids, immunosuppression therapy to suppress the action of the body's immune system may be considered. Corticosteroids reduce bone mineral accretion and contribute to corticosteroid-induced osteoporosis by impairing the function and the differentiation of osteoblasts and by increasing osteoclast activity [43]. Furthermore, they induce the apoptosis of osteoblasts while having an antiapoptotic effect on osteoclasts, resulting in accelerated bone resorption [44]. At the intestinal level, corticosteroids inhibit vitamin D-dependent intestinal calcium absorption and decrease the expression of specific duodenal calcium transporters [45]. Vitamin D insufficiency has been associated with a compensatory increase in parathyroid hormone secretion, which can lead to bone resorption and reduced bone mineral density [46].

In the present study, a positive history of bone fracture after trauma was present in two cases out of 40. This is consistent with Bischoff-Ferrari *et al.* [45] and Carnevale *et al.* [46], who found that patients with ILD, particularly those who had taken corticosteroids, were at a high risk of bone demineralization.

Although the mean BMI, the weight, and the height for the age percentiles of the studied patients were within the normal range, the mean weight for the age percentile and the BMI of the total patient group were significantly higher compared with those of the control group ($P < 0.05$), and both were significantly increased in patients with CTD-ILD compared with patients with non-CTD-ILD ($P < 0.05$). This could be explained by the long duration of systemic corticosteroid therapy of the patients with CTD-ILD compared with the patients with non-CTD-ILD. The height of our patients was markedly affected and lower compared with their weight. Stunting could be due to the chronic disease condition and the effect of corticosteroid therapy on the bone.

Conclusion

All patients with ILD receiving long-term corticosteroid therapy should be considered at increased risk for vitamin D deficiency and insufficiency, particularly those with reduced lung function. Preventive measures and routine estimation of serum vitamin D (25-OHD) levels should be recommended. Vitamin D supplementation is advised on an individual basis. The exact mechanisms of autoimmune parenchymal lung injury and whether supplementation with vitamin D is associated with improved clinical outcomes, including lung function and other systemic disease manifestations, need to be investigated.

Acknowledgements

Conflicts of interest

None declared.

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