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Hypo-vitaminosis D in Patients with Rheumatoid Arthritis, Systemic Lupus Erythematosus and Ankylosing Spondylitis

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Abstract

Hypo-vitaminosis D and its relevance to the stability of the immune system represent an interesting investigational topic in the field of rheumatology.

Objectives: survey hypo-vitaminosis D and its relation to disease activity parameters in a population of patients with autoimmune diseases.

Materials and methods: case control study including 70 patients: 30 patients with rheumatoid arthritis (RA), 30 patients with systemic lupus erythematosus (SLE) and 10 patients with ankylosing spondylitis (AS). In vitro quantitative determination of serum 25-hydroxyvitamin D3 using the electro-chemi-luminescence immunoassay "ECLIA" was done. Serum concentrations ≥ 30 ng/ml has been considered sufficient and levels between 11 ng/ml-29 ng/ml has been considered insufficient, whilst patients with levels ≤ 10 ng/ml has been considered deficient. Fifty healthy control subjects were included.

Results: Hypo-vitaminosis D was reported in 91.4% of the patients vs. 68% of the control group. The mean values of vitamin D in the population with AID was significantly lower than in controls (16.14 ± 9.32 ng/ml vs 24.61 ± 8.36 ng/ml, t=-5.05, P<0.01**, 95% CI=-12.31-5.31). The majority of patients (57.1%) had insufficiency vs 34.3% with vitamin D deficiency. Vitamin D levels inversely correlated with the ESR (r=-0.23, P=0.04) and with the SLEDAI score in SLE (r=-0.419, P=0.02). Regression analysis identified the presence of an autoimmune disease as a potentially significant risk factor for vitamin D deficiency (P<0.001).

Conclusion: The study reported a higher prevalence of hypo-vitaminosis D with autoimmune diseases. Lower levels of vitamin D correlated with higher ESR in all patients and with the SLEDAI score.

Keywords: Hypo-vitaminosis D; Autoimmune diseases; Systemic lupus erythematosus; Rheumatoid arthritis; Ankylosing spondylitis; Disease activity score

Introduction

The hypo-vitaminosis D and its contribution to immune competence and stability are being increasingly considered a clinical problem of significant importance. [1]. The fundamental role of Vitamin D was recognized for long as regulator of the calcium homeostasis and bone metabolism, that was recently modified following the discovery of the vitamin D receptor (VDR) in the cells of the immune system suggesting a possible immune-regulatory function role of vitamin D. Multiple recent studies have illustrated how the 1,25-dihydroxyvitamin D3 1,25(OH)2D3 which the recognized biologically active metabolite of Vitamin D3 possessed an immune modulatory function achieved via the nuclear VDR expressed in antigen-presenting cells and activated T/B cells [2-4]. The aim of the current study was to investigate the prevalence of hypo-vitaminosis D and its relation to disease activity parameters in a population of patients with autoimmune diseases.

Patients and Methods

This is a clinical case control study conducted over a period of one year. The study enrolled 70 patients with the diagnosis of autoimmune diseases including 30 patients with the diagnosis of rheumatoid arthritis (RA), 30 patients with the diagnosis of systemic lupus erythematosus (SLE) and 10 patients with the diagnosis of ankylosing spondylitis (AS). Patients were recruited from the outpatient Rheumatology clinic of a governmental teaching hospital.

Inclusion criteria

Patients who satisfied the American College of Rheumatology criteria as well as the international study groups diagnostic criteria for RA, SLE and AS [5-7].

Exclusion criteria

The study excluded patients with history of parathyroid disease, renal disease, hepatic disease, gastrointestinal, metabolic disorders, history of granulomatous diseases and patients on vitamin D supplementation therapy.

Patients were subjected to history taking, full clinical assessment and routine laboratory assessment including biomarkers of inflammation. The disease activity in the different target groups was assessed using disease activity score (DAS-28) for RA patients, systemic lupus erythematosus disease activity index [8], (SLEDAI) score for SLE patients [9], BASDAI for the AS patients [10].

Fifty healthy control subjects were included for comparison. The study was approved by the organizational research committee. All participants gave informed consents prior to enrollment.

Methods

Assessment of 25-OH Vitamin D3 status in the sera of patients and controls was accomplished by *in vitro* quantitative determination of 25-hydroxyvitamin D3 in human serum using the electro-chemi-luminescence immunoassay "ECLIA" [11]. The Elecsys 2010 immunoassay system is an automated, random access, multichannel analyzer for the determination of immunological tests, intended for in vitro quantitative or qualitative determination of a wide range of analytes utilizing the electro-chemi-luminescent (ECL) technology.

Health based reference values for Vitamin D: Currently there is no standard definition for the optimal values of vitamin D required for general and bone health. Many specialists consider the commonly used population based reference values too low recommending the establishment and standardization of health based reference values to replace the population based ones [12]. Estimation of optimal serum In the current study serum concentrations of vitamin D ≥ 30 ng/ml will be considered sufficient whereas levels between 11 ng/ml-29 ng/ml will be considered insufficient, whilst patients with vitamin D levels ≤ 10 ng/ml will be considered deficient [13].

Descriptive	Patients	Controls	Significance (P-value)
	Number (%)	Number (%)	
Total	70 (100%)	50 (100%)	>0.05
RA	30		
SLE	30		
AS	10		
Gender			
Females	43 (61.4%)	25 (50%)	>0.05
Males	27 (38.6%)	25 (50%)	
Smoking History			
Smoker	19 (27.1%)	30 (60%)	>0.05
Non-smoker	51 (72.9%)		
Age (years)			
Range	14-70	17-61	>0.05
Mean ± SD	39.64 ±12.67	40.05 ± 13.25	
ESR			
Range	8-95 mm/hour	8-41 mm/hour	0.001*
Mean ± SD	49.81 ± 22.34	24.05±10.38	
Disease Status			
Active	27 (38.6)	-	-
Inactive	43 (61.4)		

Table 1: Demographic and clinical features of the study population.

Statistical analysis

Statistical analysis was done using SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 19 for Microsoft Windows.

Quantitative data were statistically described in terms of mean and standard deviations (± SD); qualitative data were presented as frequencies (number of cases) and percentages. Comparison of quantitative variables between the study groups was done using Mann Whitney U test for independent samples when not normally distributed. Within group comparison of quantitative variables was done using Freidman's test with posthoc multiple 2-group comparisons. For comparing categorical variables, Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. P values less than 0.05 was considered statistically significant. Pearson correlation was used for quantitative variables; spearman rank correlation was used for qualitative variables.

Results

The study enrolled 120 participants they included 70 patients (30 RA patients, 30 SLE patients, 10 AS patients, including a total of 43 females 61.45% and 27 males 38.6%, mean age 39.64 ± 12.67 years, 48.57% had active disease, 51.43% had inactive disease) and 50 healthy controls (25 females 50%, 25 males 50%, mean age 40.05 ± 13.25 years) were included (Table 1).

Surveying the vitamin D levels amongst the population with AID versus controls results revealed that the majority of the patients population (91.4%, n=64) had hypo-vitaminosis D distributed as 57.1% (40 patients) had vitamin D insufficiency (vitamin D 11 ng/ml-29 ng/ml) and 34.3% (24 patients) had vitamin D deficiency (vitamin D ≤ 10 ng/ml), while 8.6% (6 patients) only of the patients had normal vitamin D levels (≥ 30 ng/ml), On the other hand, in the studied controls results showed that 32% (n=16) of controls had normal serum levels of vitamin D, with 68% of the control population having hypo-vitaminosis D including 64% (n=32) with vitamin D insufficiency and 4% (n=2) with actual vitamin D deficiency according to the ranges used in the methodology.

Results of this clinical cohort study reported a significantly lower mean value of the measured 25(OH) vitamin D of 16.14 ng/ml ± 9.32 ng/ml in patients with AID compared to controls where the mean values for the measured 25 (OH) vitamin D were 24.61 ng/ml ± 8.36 ng/ml (t=-5.05, 95% CI=-12.31--5.31, P<0.01**) supporting a significantly higher prevalence of hypo-vitaminosis D in patients. The mean values of the measured vitamin D in patients with RA was 13.47 ng/ml ± 8.17 ng/ml, in SLE 17.94 ng/ml ± 10.24 ng/ml, and in AS 17.6427 ng/ml ± 7.70 ng/ml.

Subgroup analysis showed the following: In patients with RA (n=30) vitamin D was normal in one patient (3.3%), insufficient in 17 patients (56.7%), deficient in 12 patients (40%). For the SLE group (n=30) vitamin D was normal in 4 patients (13.3%), insufficient in 16 patients (53.3%), and deficient in 10 patients (33.3%). In AS where we had 10 patients only who were able to complete the survey vitamin D was normal in one patient (1%), insufficient in 7 patients (70%) and deficient in 2 patients (20%).

One way ANOVA illustrated such differences in the measured values of vitamin D to be of significant value between controls and each of the RA and SLE groups of patients (P=0.0001 and 0.015 respectively, 95% Confidence intervals=5.39-16.89 and 0.92-12.41 respectively), however, such significant differences weren't evident for patients with AS (P=0.13, 95% Confidence interval=-1.31-15.26) possibly due to the limited number of AS patients participating in the study (Tables 2 and 3, Figures 1and 2).

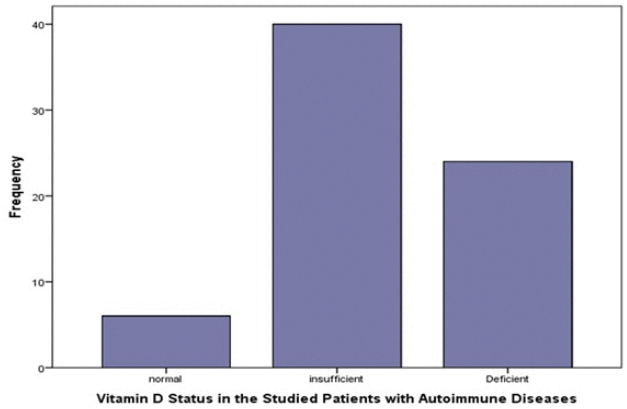

Figure 1: Displaying the differences in the mean values of vitamin D in the study population.

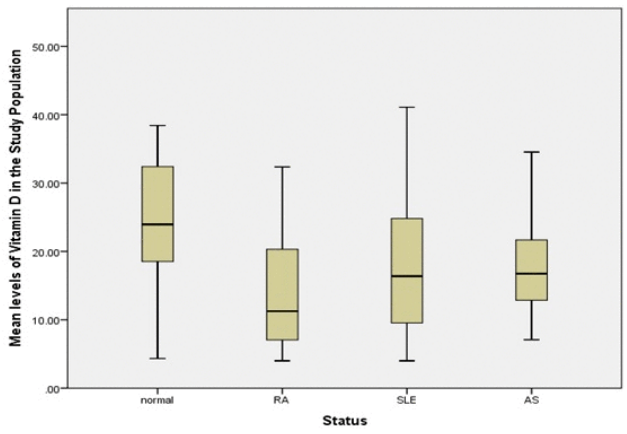

Figure2: Prevalence and distribution of hypo-vitaminosis D in patients with AID.

Investigating the possible variations in vitamin D levels with respect to disease status in the studied patients, results of the study showed lower values of the measured 25 (OH) vitamin D in the total population of patients with AID having active disease mean=17.82 ng/ml ± 9.45 ng/ml vs those with lesser disease activity mean=14.08 ng/ml ± 8.77 ng/ ml, however, such difference didn't reach statistical significance (P>0.05). On the other hand comparing means levels of vitamin D in each of the disease groups separately revealed a significantly lower vitamin D levels in SLE patients with active disease mean=16.17 ng/ml ± 10.09 ng/ml compared to those with quiescent disease mean=26.84 ng/ml ± 5.67 ng/ml (t=2.27, P=0.03, CI 95%=1.06-20.29) (Table 4), displays the results of comparison of mean differences in vitamin D levels in the disease population with respect to demographics and disease activity parameters.

	Patients	Controls	Significance (P-value)
Vitamin D			
Ranges	4-41 ng/ml	4.34-38.42 ng/ml	<0.01**
Mean ± SD	16.14 ± 9.32 ng/ml	24.61 ± 8.36 ng/ml	
Vitamin D			
Normal (≥ 30 ng/nl)	8.6% (6 patients)	32% (16 controls)	<0.05*
Insufficient (10-29 ng/ml)	57.1% (40 patients)	64% (32 controls)	
Deficient (<10 ng/ml)	34.3% (24 patients)	4% (2 controls)	

Table 2: Measured values of serum 25(OH) vitamin D3 the study group.

Disease Status (Number)	Mean ± S.D (ng/ml)	t	Significance
RA			
Total RA population	13.47 ± 8.17	0.74	0.46
Inactive/low DAS (n=18)	14.50 ± 9.58		
Moderate to high DAS (n=12)	11.70 ± 5.58		
SLE			
Total SLE population	17.94 ± 10.24	2.27	0.03
Inactive (n=18)	26.84 ± 5.67		
Active (n=12)	16.17 ± 10.09		
AS			
Total AS population	17.6427 ± 7.70	1.18	0.27
Inactive (n=1)	20.78 ± 8.48		
Active (n=9)	14.83 ± 7.33		
Total Population			
Inactive 38.6% (n=27)	14.08 ± 8.77	1.71	0.09
Active 61.4% (n=43)	17.82 ± 9.45		

Table 3: Comparing Vitamin D levels with variable disease activity in the population with AID. P<0.05 is considered statistically significant.

The presence of hypo-vitaminosis D significantly correlated with the presence of AID in the study population (r=0.21, P=0.01), results also revealed a significant negative correlation between vitamin D status and the ESR in the population with AID (r=-0.23, P=0.04).

The study revealed a significant correlation between disease activity score SLEDAI in patients with SLE and hypo-vitaminosis D (r=-0.419, P=0.02) however, statistical analysis revealed insignificant variations in the vitamin D levels relative to disease activity status in patients with RA and AS (r=0.003, P=0.98, r=-0.453, P=0.19 respectively). Hypo-vitaminosis D didn't show significant correlation with age (r=0.13, P=0.27), sex (r=0.20, P=0.08), smoking history (r=0.01, P=0.91), duration of illness (r=0.17, P=0.14), CRP (r=0.19, P=0.10), DAS-28 and sharp Score in RA patients (r=-0.03, P=0.85 & r=0.03, P=0.84, respectively) or BASDAI in AS (r=0.03, P=0.79).

Results of surveying the impact of smoking history, employment and the marital status on the measured values of vitamin D in patients with AID couldn't find any significant correlation between smoking history, occupational or the marital status and the abnormally low values of vitamin D in the studied patients (r=0.44, P=0.66, r=0.18, P=0.85, and r=1.09, P=0.28 respectively).

Discussion

The relationship between vitamin D and the immune system represents an emerging global problem of significant clinical impact. The current study is the first to screen for the prevalence as well as the risk of hypo-vitaminosis D among a population of Egyptian patients with different diagnoses of autoimmune diseases including RA, SLE and AS and correlate the findings with the different disease activity

scores and inflammatory markers in each group in the included population with AID. Multiple published researches have pointed to the possible role of vitamin D deficiency as a contributor to impaired tolerance [14,15].

Parameter	t-value	Significance (P-value)
Age	-0.69	>0.05 (-0.69)
Sex	1.66	>0.05 (0.10)
Smoking	-0.7	>0.05 (0.48)
Marital status	1.27	>0.05 (0.20)
Occupational status	1.48	>0.05 (0.23)
ESR	4.06	<0.05 (0.04)*
CRP	0.3	>0.05 (0.76)
DAS-28	-0.03	>0.05 (0.97)
Sharp Score	-0.12	>0.05 (0.90)
SLEDAI	-1.07	>0.05 (0.29)
BASDAI	-1.26	>0.05 (0.24)

Table 4: Results of comparison of mean differences in vitamin D levels in the disease population with respect to demographics and disease activity parameters. *P<0.05 is considered statistically significant.

In rheumatoid arthritis a study by Andjelkovic et al., authors reported an increased incidence of hypo-vitaminosis D in patients with RA that inversely related to the disease activity states, a conclusion that was later on supported by results from the studies published by Cutolo et al., and Rossini et al., showing a significant inverse relationship between hypo-vitaminosis D and disease activity as well as disability scores in their population of RA patients [16-18]. On the other hand, Cutolo et al., Nielen et al., as well as Rossini et al., reported that the incidence of hypo-vitaminosis D didn't vary significantly between their groups of RA patients and controls. Another interesting preliminary data reported by Frediani et al., pointed to a possible association between seasonal changes of Vitamin D serum levels, latitude and disease activity (DAS28) in RA patients [17-20]. On the other hand, Borba et al., found a higher incidence of hypovitaminosis D in SLE patients compared to controls and such deficiency inversely correlated with disease activity scores. A report that was further reinforced by the results of a late study from Bonakdar et al., showing a significant inverse relation between vitamin D levels in SLE patients and the disease activity score. Interestingly, in a recent study by Yap et al., the study found that low vitamin D was associated with a higher disease activity in SLE and an increase in serum vitamin D was associated with reduced disease activity over time [21-24].

In the present study the authors classified the patients into three groups according to their diagnoses in light of the identified international criteria; patients groups included 30 patients with RA, 30 patients with the diagnosis of SLA and 10 patients with the diagnosis of AS, with 50 healthy controls. The study enrolled patients who consented and succeeded to complete the assessment. The relation between autoimmune diseases and the vitamin D status was investigated in multiple ways first by exploring the vitamin D status whether deficiency or insufficiency in the population with autoimmune disease and comparing results to that of controls, estimation of relative risk of hypo-vitaminosis D in patients with the diagnosis of autoimmune disease, then investigate the influence of disease specific features in terms of the class of autoimmune disease, disease activity status and inflammatory biomarkers on the vitamin D status. The study revealed hypo-vitaminosis D in 91.4% of the population with autoimmune diseases (AID) using reference values previously provided with a mean value for the measured 25 (OH) vitamin D of 16.14 ng/ml ± 9.32 ng/ml compared to 68% of the control group where the mean values for the measured 25 (OH) vitamin D were 24.61 ng/ml ± 8.36 ng/ml displaying a significantly higher prevalence in the population with AID (t=-5.05, 95% CI=-12.31--5.31, P<0.01**). The majority of the patients had their vitamin D values within the insufficiency rather than the deficiency ranges, with a frequency of 57.1% within the insufficiency range 11 ng/ml-29 ng/ml versus 34.3% within the deficiency range ≤ 10 ng/ml. The mean values of the measured vitamin D in patients with RA was 13.47 ng/ml ± 8.17 ng/ml, in SLE 17.94 ng/ml ± 10.24 ng/ml, and in AS 17.6427 ng/ml ± 7.70 ng/ml. One way Anova for analysis of variants illustrated that the differences in the measured values of vitamin D were clearly significant between controls and each of the RA and SLE groups of patients (P=0.0001 & 0.015 respectively, 95% Confidence intervals=5.39-16.89 and 0.92-12.41 respectively), however, such significant differences weren't evident for patients with AS (P=0.13, 95% Confidence interval=-1.31-15.26) mostly because of the limited number of AS patients who succeeded to complete the study. Considering the possible impact of hypo-vitaminosis D on the inflammatory profile, authors in the current research investigated variations in the measured vitamin D levels with respect to ESR in the studied groups and results showed that hypo-vitaminosis D had significantly and inversely correlated with the ESR in the studied patients (r=-0.23, P=0.04) yet such correlation wasn't evident with respect to CRP (r=0.19, P=0.10). Furthermore, the study revealed that hypo-vitaminosis D inversely correlated with SLEDAI score in patients with SLE demonstrating that patients with higher disease activity scores SLEDAI had significantly lower levels of vitamin D which agrees with what has been published by Borba et al., 2009, Bonakdar et al., 2011 and Yap et al., 2015. On the other hand, RA patients with higher DAS score and/or sharp score didn't have synchronous significant decline in their vitamin D levels, neither did the BASDAI score in patients with AS.

The current study reported a higher prevalence of hypo-vitaminosis D with AID. Lower levels of vitamin D correlated with higher ESR in all patients and with the SLEDAI score. Does the current findings support the theory concerning the potential relationship between AID and hypo-vitaminosis D, authors believe this should be investigated in upcoming researches.

Study limitations and recommendations

Lack of financial support was a major limitation, the authors were aiming to include larger number of patients and to additionally investigate relation between vitamin D status and autoantibody profile which couldn't be performed in this study for organizational and financial issues with lack of compliance from the patients side.

The authors consider it a crucial issue and intend to assess it in upcoming studies.

The influence of medications whether steroids or immunosuppressive drugs as well as other medications on patient functional status and vitamin D status should be investigated.

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