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The Relationship of Serum 25-Hydroxyvitamin D Levels with Disease Activity in Upper Egyptian Patients with Rheumatoid Arthritis

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Abstract

Aim of the work: To assess the serum 25-hydroxyvitamin D concentrations [25(OH)D] and their relationship with parameters of disease activity in upper Egyptian patients with rheumatoid arthritis (RA).

Patients and methods: A case-control study was made on 34 patients with RA and 34 healthy control subjects. The following values were assessed for each patient: erythrocyte sedimentation rate (ESR), C reactive protein (CRP), rheumatoid factor (RF), anti-cyclic citrullinated peptide antibodies (Anti-CCP), visual analogue scale of pain (VAS), disease activity score 28 (DAS28), and serum 25-hydroxyvitamin D concentrations.

Results: Patients with RA had mild to moderate (DAS28 < 5.1) disease activity. The mean serum level of 25(OH)D in patients with RA (24.35±5.66 ng/ml) was significantly lower (P< 0.001) than controls (42.46±11.33 ng/ml). Serum 25(OH)D levels did not show correlation with disease duration, ESR, CRP, VASor DAS28 in patients with RA.Serum 25(OH)D levels were significantly correlated with age in RA patients (P< 0.01).Serum 25(OH)D levels had no relation to RF or anti-CCP positivity.

Conclusion: Although serum 25(OH)D levels were lower in RA patients of upper Egypt, there was no correlation with disease activity parameters, therefore, serum 25(OH)D concentrations cannot be used to reflect disease activity.

Keywords: Disease activity, Rheumatoid arthritis, Vitamin D

Introduction

Rheumatoid arthritis (RA) is a systemic connective tissue autoimmune disease which is characterized by inflammation of synovial joints which can lead to cartilage destruction as well as bone erosion (1).Although its etiology is unknown, the interactions between both genetic and environmental factors have been demonstrated in RA(2).

Vitamin D has a broad range of biological effects that ranges fromits classical role as a mediator of phosphorus and calcium metabolism which promotes the healthy mineralization, growth and remodeling of the bone, to the modulation of cellular differentiation and anti-microbial activity(3).

Vitamin D and its analogues suppress T-cell proliferation as well as they inhibit the expression of pro-inflammatory cytokines involved in the pathogenesis of RAwhich include interleukin (IL)-2 and interferon- γ(4).

Epidemiological studies concerned with the relationship between serum 25(OH)D concentrations and RA have conflicting results(1, 5). Several studies demonstrated a reverse relationship between serum 25(OH)D concentrations and activity of RA, however, studies contradictory to these observations are also found (6-13).

Because of these contradictory results regarding the effect of serum 25(OH)D concentrations on the severity of RA, the present study performedto estimatethe serum 25(OH)D concentrations and their relationship with parameters of disease activity in patients with RA living in upper Egypt.

Patients and methods

This case-control study was performed on RA patients coming to the outpatient clinic of Rheumatology and Rehabilitation Department, Sohag University Hospital. Thirty-four female patients with definite RA diagnosed according to the 2010 American College of Rheumatology (ACR) /European League Against Rheumatism (EULAR) classification criteria (14) were included in this study.Exclusion criteria were as follows: history of liver or kidney disease, diabetes mellitus, uncontrolled arterial hypertension, thyroid dysfunction, Cushing's syndrome, dyslipidemia, pregnancy and patients taking vitamin D replacement therapy. Thirty-four apparently healthy females matched in age were also included as controls. None of the controls were taking vitamin D. All participants signed their informed consent according to Declaration of Helsinki. The study approval by the local ethics committee was done.

For all patients, full history –taking and clinical examination was performed. Age and disease duration were recorded.Visual analogue scale of pain (VAS) (15), disease activity index 28 (DAS28) (16), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were used to assess disease activity. DAS28 was calculated based on ESR, tender joint count (28 joints), swollen joint count (28 joints), and the patient's assessment of global well-being (100 mm visual analogue scale). Serum rheumatoid factor (RF) and CRP concentrations were determined by immune-nephelometry methods on a Turboxnephelometer(Orion Diagnostica, Finland). The concentrations were expressed as IU/ml for RF and mg/l for CRP. RF concentration ≥ 25 IU/ml and CRP concentration ≥ 6 mg/l were considered positive for RF and CRP respectively. The anti-cyclic citrullinated peptide (anti-CCP) was tested using Microparticle Enzyme Immunoassay (MEIA) for the semi-quantitative determination of IgG class of antibodies specific to cyclic citrullinated peptide in patients' serum samples on the AXSYM System (Abbott diagnostics, Dallas, USA), according to the manufacturer's instructions. The concentrations of anti-CCP were expressed as U/ml and values ≥ 5 U/ml were considered as positive. The ESR was measured by westergren method.

Detection of serum 25(OH)D.

Serum levels of 25(OH)D was measured by the use of Architect-1000 (Abbott Diagnostics, Dallas, USA). The architect 25(OH)D assay is a chemiluminescentmicroparticle immunoassay (CMIA) for the quantitative detection of 25(OH)D in human serum and plasma.

The definition of vitamin D deficiency,vitamin D insufficiency and normal vitamin Dlevels are defined as the serum 25(OH)D concentration≤ 20 ng/ml, between 20–30 ng/ml and ≥ 30 ng/ml,respectively. All patients with RA in this study were treated by methotrexate (15 mg/week) and leflunomide (20 mg/day). Non-steroidal anti-inflammatory drugs were prescribed only on demand for pain.

Statistical analysis.

Statistical package for social sciences (IBM-SPSS), version 24 IBM-Chicago, USA (May 2016) was used for statistical data analysis. Data expressed as mean, standard deviation (SD), number and percentage. Mean and standard deviation were used as descriptive value for quantitative data, while number and percentage were used to describe qualitative data. Student *t* test was used to compare the

means between two groups, and Pearson correlation test was used to compare two quantitative variables. The level of significance was considered when the *p* value is < 0.05.

Results

This study included 34 female RA patients from upper Egypt with a mean age of 34.21±6.06 (range; 22-45) years and 34 female controls with a mean age of 34.63±7.38 (range; 24-44) years. The demographic and clinical characteristics of patients with RA and of control subjects are shown in Table 1.

Age did not show statistically significant difference between RA patients and control subjects (*P* = 0.814). Patients with RA had mild to moderate (DAS28 < 5.1) disease activity. The mean serum 25(OH) D in patients with RA (24.35±5.66 ng/ml) was significantly lower (*p*< 0.001) than controls (42.46±11.33 ng/ml) (Table 1 and Fig. 1). Serum 25(OH)D concentrations did not show significant correlation with age, disease duration, ESR, CRP, VAS, or DAS28 in patients with RA (Table 2). Serum 25(OH)D levels had no relation to rheumatoid factor or anti CCP (Table 3).

Table 1. Demographic and clinical characteristics of RA patients and control.

Characteristics (mean ± SD)	RA patients (34)	Control (34)	T test	*P* value
Age (years)	34.21±6.06	34.63±7.38	0.237	0.814(NS)
Disease duration (years)	5.77±1.84	-		
Rheumatoid factor n(%)	23(67.6%)	-		
Anti CCP n(%)	20(58.8%)	-		
VAS (0-100)	46.47±10.98	-		
DAS28 score	4.34±0.39	-		
ESR (mm/1sthr)	31.03±4.21	-		
CRP (mg/l)	22.32±14.94	-		
25(OH)D (ng/ml)	24.35±5.66	42.46±11.33	7.220	< 0.001(HS)

RF: rheumatoid factor; VAS: visual analogue scale of pain; DAS28: disease activity for 28 joint indices score; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.
(NS)= non significant. (HS) = Highly significant.

Table 2. Correlations between 25(OH)D levels and patients' characteristics.

Patients' characteristics	Pearson Correlation	*P* value
Age	0.423	0.013 (S)
Disease duration	-0.012	0.946 (NS)
ESR	-0.205	0.244 (NS)
CRP	-0.123*	0.489 (NS)
VAS	0.123	0.488 (NS)
DAS28	-0.264	0.131 (NS)

* Spearman Correlation was used in stead of Pearson Correlation due to non parametric values

Table 3. Relation between 25(OH) Vitamin D and serology (RF and anti-CCP) in RA patients

Serology		Vitamin D		T test	P value
		(Mean±SD)	Median(range)		
RF	Positive	23.87±5.77	23(15-36)	0.715	0.480(NS)
	Negative	25.36±5.54	25(19-38)		
Anti CCP	Positive	24.80±5.63	25(15-36)	0.545	0.590(NS)
	Negative	23.71±5.85	22(18-38)		

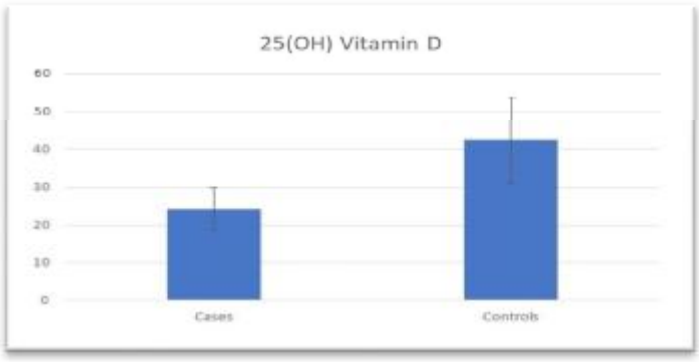

Figure 1.25(OH)D levels in RA patients and control groups

Discussion

Rheumatoid arthritis affects up to 1 % of adults worldwide. It represents a serious health problem due to articular and extra-articular involvement. To maintain the physiological innate as well as adaptive immune responses and the immune tolerance of self antigen, normal concentrations of vitamin D are required(8). Because of the immunosuppressive effects of serum 25(OH)D and the potential link between serum 25(OH)D deficiency and autoimmune diseases(17), 25(OH)D has been studied as a potential factor in the pathogenesis of autoimmune diseases including RA(18). Further studies are needed to confirm that vitamin D status directly contribute to the pathogenesis of RA.

In the present study, we showed that the serum 25(OH)D concentrations were significantly lower in the RA group compared to the control group ($P < 0.001$). These results are in agreement with other studies (9, 19-21).In contrast to these results, other studies reported that the levels of serum 25(OH)Din RA patients were not different from that of controls (11, 22, 23). This discrepancy in results might be attributed to the difference in the level of vitamin D in healthy people of different populations inhabiting different latitudes. All patients in the present study had only insufficient levels of Serum 25(OH)D (between 20–30 ng/mL) which might be attributed to the climate of upper Egypt being characterized by plenty of sunny days most of the year.

In the current study, Serum 25(OH)D concentrations did not show significant correlation with DAS28 in patients with RA.Theseresults were in agreement with other studies(23, 24) and contradictory to others (11, 13, 19-22, 25). The risk of RA may be increased by a low vitamin D level (18). Little information is known about vitamin D intake and its role in the modificationof the risk and activity of RA (17). Progression of collagen – induced arthritis in mice is prevented by vitamin D supplementation (26). Further studies are needed to demonstrate the clinical benefits of vitamin D intake in the management of RA.

In the present study, serum 25(OH)D concentrationswere not correlated with disease duration which was in agreement with other study(27). In the current study age was significantly correlated with serum 25(OH)D levelswhich was in contrast to other study (27).In our study, Serum 25(OH)D levels had no relation to RF or anti-CCP positivity.

Many limitations are present to the current study that may lead to the contradictory results between this study and other previous ones. Of these are, the small sample size, absence of RA patients with deficient serum 25(OH)D levels and lack of information about sun exposure time. Further studies are required to yield more information about the effects of vitamin D in patients with RA.

In conclusion,Serum25(OH)D levels are lower in RA patients compared to controls. There are no association between Serum25(OH)D levels and disease activity in patients with RA living in upper Egypt.

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