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Relationship Between Vitamin D and Rheumatoid Arthritis Activity

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Abstract

Objectives: Deficiency of vitamin D has been involved in the pathogenesis of many auto-immune diseases, as diabetes mellitus type 1 and multiple sclerosis. Reduction of the intake of vitamin D has been associated with high susceptibility of the development of rheumatoid arthritis (RA) and also with increased disease activity in patients with RA. The objective of this study was to evaluate the status of vitamin D in patients with RA, assess the correlation between serum level of vitamin D and disease activity and its association to the pathogenesis of RA.

Methods: 60 female patients with RA, 25-hydroxyvitamin D3 [25(OH)D3] levels, Para-thyroid hormone levels, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were measured. Disease activity was evaluated by calculating the 28-joint Disease Activity Score (DAS28). A control group (n=30), matched for age, was evaluated as well.

Results: There is a significant decrease in the mean vitamin D serum levels in RA patients compared to control group (F test, p 0.031). We did not find any correlation between DAS28 score and vitamin D levels in controls (p=0.871), low active RA patients (p=0.722) and high active RA patients (P=0.428).

Conclusion: No association was found between vitamin D and disease activity. However, the deficiency of vitamin D may have a negative impact on bone health in patients in the course of the disease. Vitamin D supplementation may be needed to prevent the osteoporosis and for the relief of pain in patients with RA.

Keywords: Vitamin D; Rheumatoid arthritis; Antibodies; Minerals; Blood Biochemistry

Introduction

Rheumatoid arthritis (RA) is an auto-immune disease that makes synovium inflammation with continuous bone erosion leading to joint loss [1]. The etiology of RA could be due to genetic and non-genetic factors such as hormonal, environmental, and infectious factors [2]. Vitamin D might be one of the environmental factors related to RA disease [3]. The immune-modulatory effects of vitamin D and the detection of vitamin D receptors in the immune system cells may suggest the relation between vitamin D and RA [4].

There is a great concern for public health for vitamin D deficiency or insufficiency; vitamin D deficiency has a role in the pathogenesis of many chronic diseases. There is a link between 25-hydroxy vitamin D status and the overall mortality. Low 25-hydoxy vitamin D serum levels were associated with a significant high risk of all-cause mortality. Individuals with severe vitamin D deficiency have almost twice the mortality rate as those with 25-hydoxy vitamin D level ≥ 30 ng/mL, (≥ 75 nmol/L) [5].

Vitamin D has a great role in proliferation, differentiation and survival of cells in immunity disorders [6]. Also, vitamin D hormone production after immune dendritic cells activation may prove the immune regulatory properties of vitamin D [7].

Vitamin D deficiency is common in RA patients [8], also there is an inverse correlation between serum vitamin D levels and RA activity [9,10]. Diagnosis of RA disease could be performed by symptoms, antibodies, and inflammatory biomarkers, while it is more useful to assess the genetic and environmental factors for early prognosis of the disease [11].

Materials and Methods

This study included 60 adult patients, presenting at Rheumatology department of Zagazig University Hospitals. These patients met the American College of Rheumatology (ACR) RA classification criteria. Thirty apparently healthy individuals matched in age were also included as controls. The laboratory work was conducted at Clinical Pathology Department, Zagazig University Hospital after taking informed consent from all subjects. Physical examination, a medical history of patients, and blood biochemistry were evaluated in all patients to exclude chronic diseases affecting the bone and mineral metabolism. Also, treatment with vitamin D and/or calcium supplementation or drugs which affect the bone and mineral metabolism is excluded.

Disease activity was determined using the Disease Activity Score including 28 joint counts (DAS28). Components of DAS28 are CRP, and swollen and tender joint counts (both 0–28). DAS28 >5.1 reffers to high active RA, 3.21<DAS28 ≤ 5.1 indicates a moderate active RA, DAS28 ≤ 3.21indicates low active RA.

The serum of the collected blood from patients and controls was used for the detection of rheumatoid factor (RF), C-reactive protein (CRP) and vitamin D. CRP and RF was assessed with using Cobas Integra 400 analyzer, and erythrocyte sedimentation rate (ESR, mm/h) was assessed with the Westergren method. Serum 25(OH)D

concentration and PTH were analyzed using Cobas e 602 analyzer (Roche diagnostics GmbH, Mannheim, Germany). Ionized calcium determination using Cobas 121 blood gases analyzer (Roche diagnostics GmbH, Mannheim, Germany).

Statistical analysis

Data was analyzed using SPSS V20 (IBM Corp, Armonk, NY, USA). Mean values were calculated for all continuous findings of the values, along with their standard deviations. In order to study associations between two continuous variables, a Pearson's correlation coefficient was calculated. To study differences in mean findings of related continuous interval groups, an unpaired Student's t-test or a one-way analysis of variance (ANOVA) was performed when relevant. Differences were considered to be of statistical significance at $P<0.05$.

Results

The mean age was 39.0 years in the patients with low active RA, 41.0 years in the patients with high active RA and 37.36667 years in the healthy controls. There was no significant difference between the groups as regards age ($p>0.05$). The mean of the 25-OH Vitamin D levels was 17.16033 ng/ml in patients with low active RA (n=30), 16.45667 ng/ml in patients with high active RA (n=30) and 21.74133 ng/ml in healthy controls (n=30). We found that the mean of the 25-OH D vitamin levels of the patients with RA was significantly lower than that of controls (p=0.031) (Table 1).

Parameter	Controls n=30 X ± SD	Low active RF patients n=30 X ± SD	High active RF patients n=30 X ± SD	F test	P
VIT. D	21.74133 ± 10.75196	17.16033 ± 6.78284	16.45667 ±8.75506	3.69	0.031

Table 1: Statistical comparison between patients and control groups as regards Vitamin D.

The mean of the 25-OH D vitamin levels of the patients with RA was significantly lower than that of controls (p=0.031). Additionally, we examined the prevalence of vitamin D deficiency and insufficiency defined as a 25(OH)-D level <20 ng/ml and < less than 30 ng/ml (Table 2).

Vitamin D	Controls N=30 No. %		Low active RA Patients N=30 No. %		Low active RA Patients N=30 No. %		Chi-Square P value
Deficient	15	50.0	23	67.7	21	70.0	-
Insufficient	9	30.0	6	20.0	7	23.3	0.134
Sufficient	6	20.0	1	3.3	2	6.7	-

Table 2: Prevalence of vitamin D deficiency and insufficiency in patients and controls group.

Prevalence of vitamin D deficiency and insufficiency in patients and controls group was not significant. Our study revealed that there is no correlation between vitamin D level and DAS 28/CRP score in controls (p=0.871), low active RA patients (p=0.722) and high active RA patients (P=0.428) (Table 3).

Parameter	DAS28 score n=30 X ± SD (range)	Vitamin D level n=30 X ± SD	Pearson's r correlation	P value
Control	0.74 ± 0.23	21.74 ± 10.75	0.0311	0.871
Low active RA	3.57 ± 0.39	17.16 ± 6.78	-0.0678	0.722
High active RA	5.73 ± 0.39	16.45 ± 8.75	0.1503	0.428

Table 3: Correlation between DAS28 score and vitamin D levels in controls and RA patients.

The statistical results did not show any significant correlation.

Discussion

Vitamin D is one of the environmental factors contributed to RA [3]. There is a high incidence of osteoporosis in RA patients [12,13], deficiency of vitamin D has been linked to diffuse musculoskeletal pain, and these results have therapeutic indication [14]. There have been conflicting results regarding the correlation between RA and blood levels of vitamin D [15]. This confliction may be due to a lot of factors such as design, study population, analytical methods, testing tools and sample size. A meta- analysis performed five years ago showed that vitamin D supplementation was inversely related to the risk of RA [16].

Our results show that serum levels of vitamin D are significantly lower in patients with RA compared to healthy controls. Additionally, vitamin D levels are lower in the high active RA patients than those with low active RA. But, we found that there was not a correlation between serum 25-OH vitamin D levels and rheumatoid arthritis disease activity as assessed by DAS28 score. Other studies have evaluated the association between vitamin D levels and RA activity. Some studies showed that there is no correlation between vitamin D serum level and DAS28 score [17-19]. These results are suggested to be due to the small sample study [18]. Other studies revealed that there is an inverse correlation between vitamin D serum level and DAS28 score [20-22]. In this study, we can't find any correlation between vitamin D

serum level and the activity of RA. That may be due to a lot of reasons in proving the relationship between vitamin D deficiency and disease activity in rheumatologic disorders in humans, as the low incidence of the diseases which makes it hard to obtain large samples of patients. There are also other factors associated with those diseases and vitamin D level such as various drugs intake, inflammatory processes, sun exposure, seasonal vitamin D variations and the degree of physical activity.

It is obvious that both of environmental and genetic factors are involved in the etiology of rheumatoid arthritis. The immune regulatory role of vitamin D and its relation to auto-immunity suggests that vitamin D might be one of the environmental factor that participates in the control of self-tolerance in autoimmune rheumatic diseases. In conclusion vitamin D is not related to etiology of RA but is essential in combination with traditional drugs therapy. The role of vitamin D is anti-inflammatory i.e., used only in active form of diseases. So, we recommended correcting 28-DAS parameter to differentiate between RA diseases activity and vitamin D deficiency disease (osteoporosis). A meta-analysis on larger participants of RA is recommended. Additionally, it is recommended to do a long follow up study to evaluate the serum level of vitamin D from the beginning of the disease, also before and after treatment in order to monitor the effect of the type and intensity of therapy on the level of vitamin D.

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