Serum 25-Hydroxy Vitamin D Concentration in Patients with Rheumatoid Arthritis and Its Association with Disease Activity in Adult Saudi Arabian Women

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Abstract

Background: Vitamin D deficiency has been linked to increased susceptibility to the development of rheumatoid arthritis (RA) and may be associated with disease activity in patients with RA. Vitamin D deficiency is common in healthy Saudi Arabian women. The objective of this study was to evaluate vitamin D status in patients with RA and to assess the relationship between vitamin D levels and disease activity in adult Saudi Arabian women.
Subjects and method: This study was conducted at King Saud Hospital, AL-Qassem area, Saudi Arabia between January 2012 and May 2013 and had been carried out on 40 patients diagnosed as having RA and 40 healthy adult females matched for age as a control group. All participants were subjected to full history taking, clinical examination, laboratory investigations including assessment of serum calcium, serum phosphorus, and 25-hydroxy vitamin D3 (25(OH)D3). Disease activity of RA was assessed using Disease Activity Score Index of a 28 joint count (DAS28), CRP and ESR.
Results: There was a highly significant difference between RA patients and healthy controls as regarding the mean 25(OH)D3 (10.8±4.8 vs 19±7.96 ng/ml; $p< 0.001$) and both were below the reference range . We found that 25(OH)D3 was not correlated with DAS28, the correlation coefficient being -0.14, and was also not correlated with CRP or ESR in RA patients.
Conclusion: Vitamin D deficiency is prevalent in healthy Saudi women and highly prevalent in Saudi women with RA, but vitamin D deficiency is not linked to disease activity in RA. These results may raise our important rationale for vitamin D supplementation to decrease the risk of development of rheumatoid arthritis, but more definitive evidence is also required to demonstrate the clinical benefit of vitamin D supplementation in the treatment of RA.

Keywords: rheumatoid arthritis, disease activity, vitamin D status.

INTRODUCTION

Vitamin D is a steroid hormone involved in bone and calcium metabolism. It is involved in the regulation of calcium homeostasis [1]. Vitamin D has extra-skeletal effects as well [2,3]. The non classical actions of vitamin D are currently under discussion. Vitamin D has been found to have immune-modulatory actions [4,5]. Patients with vitamin D deficiency may have an increased risk of developing some immune-mediated diseases, such as diabetes mellitus type 1 and multiple sclerosis [6].
Vitamin D deficiency is very prevalent in the general population [7] and is common in healthy Saudi adults and this is more pronounced in females and in the younger age groups [8]. Wearing of traditional clothes, deliberate avoidance of the sun and inadequate dietary intake are likely to be the principal causes of low vitamin D levels. [9].

Rheumatoid arthritis (RA) is an autoimmune disease of unknown aetiology [10]. Both T and B lymphocytes are involved in the pathogenesis of the disease [11]. Vitamin D deficiency may increase the risk for the development of RA [12]. Epidemiological, genetic, and basic studies indicated a potential role of vitamin D in the pathogenesis of certain systemic and organ-specific autoimmune diseases. These studies demonstrate correlation between low vitamin D and prevalence of diseases. [13-15] including an elevated risk of RA development [14]. Recently, the role of vitamin D deficiency in the pathogenesis of RA, as well as the relationship between vitamin D deficiency and the activity of RA is discussed [16,17]. RA is an inflammatory disease characterized by flares and remissions, flares being characterized by pain. Vitamin D deficiency is also known to be associated with diffuse musculoskeletal pain [18].

The objective of this study was to evaluate vitamin D status in adult Saudi Arabian female patients with RA and to assess the relationship between vitamin D levels and disease activity.

SUBJECTS AND METHODS

This study had been carried out on 40 patients diagnosed as having RA attending the outpatient clinic of rheumatology, King Saud Hospital, AL-Qassem area, Saudi Arabia between January 2012 and May 2013. Their age ranged from 18-55 years, with a mean of 35.7 ±9.75 years. All patients fulfilled the 2010 American College of Rheumatology / European League Against Rheumatism RA classification criteria [19].
A control group of 40 Saudi Arabian healthy adult females matched for age (the mean age was 35.5 ±10.86) was evaluated as well.
The following were excluded from the study: (a) subjets who had been pregnant and/or lactated within the previous 2 years; (b) any chronic illness as: liver, renal, endocrine or malignant disease, (c) those taking anticonvulsants.
All participants gave their informed consent, and the local ethical committee approved the protocol. All subjects were subjected to:

1- Full history taking.
2- Thorough clinical examination.
3- Laboratory investigations:

- Serum calcium using automated analyser [20].
- Serum phosphorus using automated analyser [21].

- Serum 25(OH)D3 levels using electrochemo-illuminescence immunoassay [22]. 25(OH)D3 is considered normal at 30 ng/ml or above, Insufficient at 20–29 ng/ml and Vitamin D Deficient below 20 ng/ml [23].

In the cohort of 40 patients with RA additional investigations included:
- Erythrocyte sedimentation rate (ESR) using Westergren's method [24].
- C-reactive protein (CRP) using single immmunodiffusion method [25].
- Serum rheumatoid factor using latex fixation test [26].
- Disease activity was evaluated by calculating the 28-joint Disease Activity Score (DAS28) [27].

Disease Activity Score of 28 joints (DAS28) is widely used as an indicator of RA disease activity and response to treatment. The joints included in DAS28 are (bilaterally): proximal interphalangeal joints (10 joints), metacarpophalangeal joints (10), wrists (2), elbows (2), shoulders (2) and knees (2). When looking at these joints, both the number of joints with tenderness upon touching (TEN28) and swelling (SW28) are counted. In addition, the erythrocyte sedimentation rate (ESR) is measured. Also, the patient makes a subjective assessment (SA) of disease activity during the preceding 7 days on a scale between 0 and 100, where 0 is "no activity" and 100 is "highest activity possible".
With these parameters, DAS28 is calculated as:
DAS28=$0.56\times\sqrt{TEN28}+0.28\times\sqrt{SW28}+0.70\times \ln(ESR)+0.014\times SA$
Or from the website: http://www.das-score.nl/das28/en/

Statistical analysis
Statistical analysis of the results was performed using SPSS software version 16.0 (statistical package for social science,
SPSS inc. Chicago, USA). Student's t test and Kruskal–Wallis test were used. Regression analysis was performed to analyze the relationship between indices of disease activity and 25(OH)D3 levels. Differences of $P < 0.05$ were considered significant.

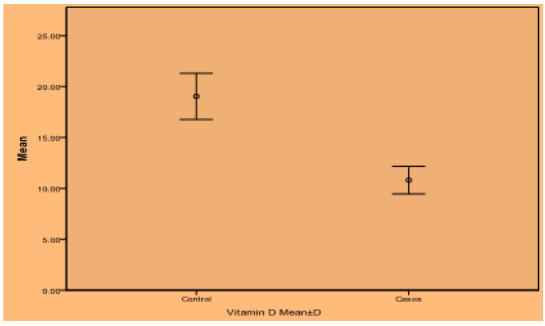
RESULTS:
The characteristic and clinical data of RA patients and controls (age, 25(OH)D3, Calcium, and Phosphorus levels) are shown in table 1.

Table (l) Characteristic and clinical data of RA patients and controls

	Controls N=40	Cases N=40	P-value
Age (years) mean ± SD	35.5 ±10.86	35.7 ±9.75	0.9
25(OH)D3 (ng/ml) mean ± SD	19±7.96	10.8±4.8	< 0.001
Ca (nmol/L) mean ± SD	2.3±0.11	2.27±0.12	0.27
Phosphorus (nmol/L) mean ± SD	1.2±0.27	1.16±0.21	0.4

There was no significant deference in age, serum calcium and serum phosphorus between the studied groups.
The levels of 25(OH)D3 were found to be low in RA patients and controls than normal reference range and in the cohort of 40 patients with RA 25(OH)D3 levels were found to be highly significant lower compared with the control group, being 10.8±4.8 ng/ml vs 19±7.96 ng/ml [mean ± SD], in the patient and control group respectively (Student's *t*-test, $p < 0.001$).

Figure (1): 25(OH)D3 levels [ng/ml, mean ± SD] in the group of patients with rheumatoid arthritis (RA) and controls.



In RA patients, DAS 28 was 4.43±0.92, CRP levels were 7.16±3.68 mg/liter (normal values < 3 mg/liter) and ESR was 50.6±19.9 mm/hour.

In RA patients, the levels of 25(OH)D3 were found to be not correlated to the DAS28 score, the correlation coefficient being -0.14, *r* being -0.14. The levels of 25(OH)D3 were also found to be not correlated to CRP and ESR, the correlation coefficient being-0.23 and -0.1and *r* being-0.23 and -0.1, respectively (table 2).

Table (2): Correlation between 25(OH)D3 and disease activity parameters in RA patients.

Disease Activity Parameters	25(OH)D3		
	r	P	
DAS28	-0.14	> 0.05	NS
ESR	-0.1	> 0.05	NS
CRP	-0.23	> 0.05	NS

DISCUSSION

In the present study vitamin D levels were found to be lower than normal reference range in the healthy control group of adult Saudi women and this consistent with other studies that showed high prevalence of vitamin D deficiency in Saudi Arabia [8,9].
Vitamin D deficiency is very prevalent in the general population [7]. The incidence of vitamin D deficiency may also be increasing [28], and vitamin D deficiency is common in healthy Saudi adults. This is more pronounced in females and in the younger age groups. Wearing of traditional clothes, deliberate avoidance of the sun and inadequate dietary intake are likely to be the principal causes of low vitamin D levels. [8,9]. Vitamin D deficiency is a major public health problem in Saudi population as the prevalence of vitamin D deficiency/insufficiency among healthy Saudi population residing in Al-Qassem region is 67.8% [29].

In the present study we found that, vitamin D levels were significantly lower in the group of female Saudi Arabian patients with RA than control subjects

Similarly, several studies have evaluated the association between vitamin D levels and RA. In a recent study by Rossini and colleagues include 581 RA from 22 Italian rheumatology centers, they found that, vitamin D deficiency is very common in Italian patients with RA [30].
Similarly, the Iowa Women's Health Study by Merlino and colleagues analyzed data from a prospective cohort study of 29,368 women aged 55–69 years, Merlino and colleagues found that greater intake of vitamin D might be associated with a lower risk of RA [12].
Our results were in agreement with those of Kostoglou-Athanassiou and colleagues, who found that vitamin D deficiency is highly prevalent in patients with RA [31] and there may be a potential role of vitamin D in the pathogenesis of certain systemic and organ-specific autoimmune diseases [13]. Including an elevated risk of RA development [14].

The importance of 25(OH)D3 deficiency *per se* for the pathogenesis and development of RA is still unclear [32]. Yazmalar and colleagues suggested that: 25(OH)D3 is an immune modulator and regulator of various immune-mediated processes through its effects on monocytes, macrophages and dendritic cells by activation of its receptors on these cells[33]. Other research found that 25(OH)D3 may induce innate tolerance by promoting tolerogenic dendritic cells and increase the macrophagic response to infections [34], and intake of 25(OH)D3 has also been demonstrated to reduce the antibody production by B cells [35].

In contrast to our results, a cohort study conducted by Costenbader and colleagues, included 91,739 women followed from 1980 to 2002 in the Nurses' Health Study, vitamin D intake was not found to be associated with the risk of RA and they observed no associations between cumulative average vitamin D intake and the risk of RA [36]. Another study by Baker and colleagues included 499 patients with RA and they did not found any association between vitamin D intake and the risk of RA [37].
These contradictory results may be explained by the sample size or the high prevalence of vitamin D deficiency in some study populations.

In the current study we found no correlation between vitamin D levels and disease activity parameters including Disease Activity Score-28 (DAS28), CRP and ESR.
Other studies, were in agreement of our results, did not found a relationship between vitamin D deficiency and disease activity in RA [37, 38]. In the study done by Braun-Moscovici and colleagues they found no correlation between vitamin D levels and disease activity among 85 patients with RA [39].

Similarly Yazmalar and colleagues did not found any correlation between serum 25(OH)D3 levels and DAS28 [33]. Higgins and colleagues studied 176 RA patients and found that vitamin D deficiency is common in RA but no significant correlation between vitamin D and DAS28 [40].

In contrast, Kostoglou-Athanassiou and colleagues studied 44 RA patients and found vitamin D deficiency may be linked to disease severity in RA[31]. Sabbagh and colleagues found strong association between inadequate vitamin D with disease activity in RA cases [41]. Welsh and colleagues found that vitamin D deficiency is linked with disease activity in RA [42]. Also Haque and Bartlett found an inverse relationship between vitamin D levels and disease activity in RA[43].
An Italian study including 1191 patients with RA and 1019 controls recruited from 22 rheumatology centers, concluding that lower serum 25(OH)D levels were associated with active disease defined by a DAS28 score > 3.1 , lack of remission and poor response to therapy, even after adjusting for sun light exposure and body mass index [44].

Studies evaluating the association between serum level of 25(OH)D3 and disease activity are not entirely clear and have unequivocal and conflicting results as some studies showed evidence that RA disease activity, as assessed by DAS28, can be influenced by vitamin D levels. It is difficult to know whether this is due to a true immune-modulatory effect of vitamin D or a more subjective effect of low vitamin D on pain perception [45].

Although there may be no overall correlation between vitamin D levels and DAS28, RA patients may perceive themselves or be perceived by assessors as having responded less well to disease modification in the presence of vitamin D deficiency. This could have major implications for subsequent management, and clinicians need to be aware of the potential confounding effect of vitamin D deficiency in assessing RA disease activity using the full DAS28 tool.

It has even been suggested that the 25(OH)D3 level may decrease in the acute phase response, thereby explaining the low levels in patients with high disease activity [46].
25(OH)D3 level may therefore be low for reasons other than lack of exposure to 25(OH)D3 and may result from the disease rather than produce the disease. Patients with RA are prone to osteoporosis [47] and suffer from pain when the disease is in flare. Vitamin D supplementation has been proposed for patients with RA for the prevention and treatment of osteoporosis [48].
In conclusion, it appears that vitamin D deficiency is prevalent in healthy Saudi women and vitamin D deficiency is highly prevalent in Saudi women with RA, but vitamin D deficiency is not linked to disease activity in RA.These results may rise our important rationale for vitamin D supplementation to decrease the risk of development of Rheumatoid arthritis, but more definitive evidence is also required to demonstrate the clinical benefit of vitamin D supplementation in the treatment of RA. Appropriate training should be given to the patients to ensure the intake of the recommended amount of vitamin D per day through diet or supplement.

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