

Prevalence of vitamin D deficiency in Egyptian rheumatoid arthritis patients: correlation with disease activity, functional disability, and bone mineral density

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Aim of Work

To detect the prevalence of 25-hydroxyvitamin D₃ [25(OH)D₃] deficiency in rheumatoid arthritis (RA) patients and its correlation with disease activity, functional disability and bone mineral density (BMD).

Patients and Methods

Cross-sectional case control study included 104 RA patients and 60 matched controls. All patients were subjected to full history taking, clinical examination and routine laboratory investigations in addition to measurements of serum 25(OH)D₃. Disease activity was assessed by 28-Disease Activity Score (DAS-28) with three variables; tender and swollen 28-joints (T-28 and S-28) and erythrocyte sedimentation rate (ESR). Functional disability was assessed by Modified Health Assessment Questionnaire (M-HAQ). BMD was measured by dual energy x-ray absorptiometry.

Results

25(OH)D₃ deficiency was similar in both RA patients and controls (99.1% versus 100%). Although, the mean serum 25(OH)D₃ level was less among RA patients than among controls but there was no statistical significant difference (5.98 ± 6.8 nmol/l versus 8.4 ± 9.6 nmol/l, *p* = 0.06). There were statistically significant correlations between 25(OH)D₃ and body weight (*r* = -0.256, *p* < 0.009), T-28 (*r* = -0.559, *p* < 0.001), S-28 (*r* = -0.631, *p* < 0.001), DAS-28 (*p* < 0.001), M-HAQ (*p* < 0.001) scores, ESR (*r* = -0.39, *p* < 0.001) and hemoglobin (*r* = 0.28, *p* = 0.004). No significant correlation was found between 25(OH)D₃ level and BMD or drug intake.

Conclusion

Although the prevalence of 25(OH)D₃ deficiency is similar in both RA patients and controls but its deficiency is significantly correlated with increased disease activity and disability but not with BMD.

Keywords:

25(OH)D₃, DAS-28, M-HAQ, Rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease of unknown etiology [1]. It is characterized by synovitis, cartilage damage, and bone resorption, resulting in structural damage and significant morbidity and mortality [2]. The role of T and B lymphocytes in the disease pathogenesis has been proven [3]. Vitamin D is a steroid hormone synthesized in the skin by the action of ultraviolet irradiation [4]. It plays a major role in the maintenance of proper bone metabolism [5] because it regulates calcium absorption from the gastrointestinal tract [6]. However, the discovery of the vitamin D receptor in nonskeletal tissue, particularly in immune cells, indicated a possible role for vitamin D in maintaining its normal function [7,8]. Interestingly, vitamin D deficiency has been linked to an increased susceptibility to develop autoimmune diseases such as RA [9], systemic lupus erythematosus, multiple sclerosis, and type-1 diabetes

in large population studies [10,11]. A low vitamin D level is also linked to increased disease activity in RA patients [12]. However, the exact mechanism for the inverse relationship between low vitamin D level and increased inflammatory disease activity is still under investigation [12–14].

The aim of the present study was to detect the prevalence of 25-hydroxyvitamin D₃ [25(OH)D₃] deficiency in RA patients and its correlation with disease activity, functional disability, and bone mineral density (BMD).

Patients and methods

Patients

A cross-sectional, case-control study was carried out that included 104 RA patients who fulfilled the 2010 American College of Rheumatology/European

League Against Rheumatism (ACR-EULAR) classification criteria for RA [15] in addition to 60 healthy age-matched and sex-matched controls. All participants were recruited from the Rheumatology and Rehabilitation Clinic, Kasr Alainy Hospitals, Cairo University. Full assessment of history and detailed clinical examination were performed for all patients. Demographic data including patients' age and disease duration were reported. Body weight, height, and BMI (kg/m^2) were measured and calculated for all participants. The inclusion criteria were the diagnosis of established RA, age at disease onset above 18 years, and at least 1-year disease duration. Patients or controls on vitamin D supplement or those with endocrine, hepatic, or renal diseases were excluded. Participants provided written informed consent before their inclusion. The current study was approved by the local ethical committees and was carried out in accordance with the ethical standards established in the 1964 Declaration of Helsinki.

Disease activity assessment

Modified 28-joints Disease Activity Score (DAS-28) was calculated using three variables: the 28-tender and swollen joints count (TJC-28 and SJC-28) and erythrocyte sedimentation rate (ESR) (mm/h) according to Prevoo and colleagues' formula: $\text{DAS-28} = (0.56 \times \sqrt{\text{TJC-28}} + 0.28 \times \sqrt{\text{SJC-28}} + 0.70 \times \text{Ln ESR}) \times 1.08 + 0.16$. Patients were considered to be in remission if DAS-28 is less than 2.6, to have low disease activity if DAS-28 is less than 3.2, moderate disease activity if DAS-28 is between 3.2 and 5.1, and high disease activity if DAS-28 is greater than 5.1 [16].

Functional disability assessment

The modified-health assessment questionnaire (M-HAQ) was used. Patients were considered normal if the M-HAQ score was 0.3 or less [17].

Treatment

RA-specific treatments were reported for all patients. These drugs were glucocorticoids and disease-modifying antirheumatic drugs.

Laboratory measurements

Serum $25(\text{OH})\text{D}_3$ was measured using an enzyme-linked immunosorbent assay. Its level was considered sufficient if it was greater than 75 nmol/l (>30 ng/ml), insufficient if it was between 50 and 75 nmol/l (20–30 ng/ml), and deficient if it was less than 50 nmol/l (<20 ng/ml) [18,19]. ESR (mm/h) was determined using the Westergren method; rheumatoid factor (considered positive if it is >20 IU/ml) was

determined using the nephelometric method; and anticyclic citrullinated polypeptide (considered positive if ≥ 5 U/ml) was determined using a microparticle enzyme immunoassay for all patients.

Radiological investigations

Plain radiography of the hands and wrists, posteroanterior view, was performed for all patients to detect radiological signs of RA.

High-resolution computed tomography of the chest was used to diagnose interstitial pulmonary fibrosis (IPF).

Dual-energy X-ray absorptiometry with advanced fan-beam technology was used to measure BMD according to diagnostic categories proposed by the WHO [20] and modified by the International Osteoporosis Foundation [21]: 1 — normal BMD, hip BMD greater than 1 SD below the young adult female reference mean (T score > -1); 2 — low bone mass (osteopenia), hip BMD greater than 1 SD below the young adult mean, but less than 2.5 SD below this value (T score < -1 and > -2.5); 3 — osteoporosis, hip BMD 2.5 SD or more below the young adult female mean (T score < -2.5); 4 — severe osteoporosis (established osteoporosis), hip BMD 2.5 SD or more below the young adult mean in the presence of one or more fragility fractures.

Statistical analysis

The statistical package for social sciences SPSS (Statistical Package for the Social Sciences; SPSS Inc, Chicago, IL, USA) version 15 for Microsoft windows, version 18 was used to analyze data. Continuous variables were summarized as mean \pm SD and categorical variables as frequency (percentage). An independent t -test compared two independent groups and the analysis of variance test compared more than two groups. Associations between categorical groups were tested using the χ^2 -test with Yates correction or Fisher's exact test as appropriate. The Pearson correlation test was used as a measure of the association of quantitative variables. Two-tailed P values of 0.05 or less were considered to be statistically significant.

Results

Demographic, clinical, radiologic, and laboratory features of RA patients

Among RA patients, there were 82 (78.8%) women and 22 (21.2%) men. The demographic, clinical, radiologic, and laboratory features of the RA patients at the time of the study are shown in Table 1.

Table 1 Demographic, clinical, radiological, and laboratory features of RA patients

Patients' characteristic features	<i>n</i> (%) / mean \pm SD
Demographic features	
Age (years)	46.39 \pm 10.43
Weight (kg)	73.72 \pm 12.77
Height (m)	1.59 \pm 0.8
BMI (kg/m ²)	29.2 \pm 5
Disease duration (years)	6.61 \pm 5.77
Clinical articular features	
Morning stiffness	56 (53.85)
Symmetric arthritis	88 (84.61)
SJC-28	2.67 \pm 2.63
TJC-28	4.78 \pm 4.18
Deformities	19 (18.3)
Radiological features	
Erosions	83 (79.8)
IPF	7 (6.7)
Laboratory features	
ESR (mm/h)	37.63 \pm 19.89
Positive RF	83 (79.8)
Positive anti-CCP	68 (65.4)

Anti-CCP, anticyclic citrullinated polypeptide; ESR, erythrocyte sedimentation rate; IPF, interstitial pulmonary fibrosis; RA, rheumatoid arthritis; RF, rheumatoid factor; SJC-28, 28 swollen joint count; TJC-28, 28-tender joint count.

At the time of the study, all patients were on methotrexate at a dose ranging from 12.5 to 20 mg/week, with a mean of 15 ± 2.31 mg/week, 26 (25%) patients were taking leflunomide (20 mg/day), 46 (44.2%) patients were taking hydroxychloroquine (400 mg/day) divided into two doses per day, and 21 (20.2%) patients were on prednisone at a dose ranging from 5 to 10 mg/day, with a mean of 6.5 ± 1.88 mg/day. None of our patients was treated by tumor necrosis factor- α blockers.

Disease activity score and functional disability index

The DAS-28 score ranged from 2.06 to 7.22, with a mean of 4.34 ± 1.03 . Nine (8.65%) patients had disease remission, whereas nine (8.65%), 61 (58.65%), and 25 (24.03%) patients had low, moderate, and high disease activity, respectively. SJC-28 ranged from 0 to 12, with a mean of 2.67 ± 2.63 . TJC-28 ranged from 0 to 20, with a mean of 4.78 ± 4.18 . The M-HAQ score was ranged from 0 to 2.1, with a mean of 0.58 ± 0.59 . The M-HAQ score was 0.3 or less in 53 (50.96%) patients and greater than 0.3 in 51 (49.04%) patients.

BMD

BMD was normal, osteopenic, and osteoporotic in 36 (34.6%), 47 (45.2%), and 21 (20.2%) patients, respectively.

Serum 25(OH)D₃ level

The mean serum 25(OH)D₃ level among RA patients was 5.98 ± 6.8 nmol/l, deficient in 103 (99.1%) patients

and insufficient in one (0.9%) patient. However, the mean serum 25(OH)D₃ level among the controls was 8.4 ± 9.6 nmol/l and all had 25(OH)D₃ deficiency. Although the mean serum 25(OH)D₃ level was lower in RA patients than in the controls, the difference was statistically insignificant ($P = 0.06$).

Correlation between serum 25(OH)D₃ level and the disease parameters studied

The correlation between serum 25(OH)D₃ level and the demographic, clinical, radiological, and laboratory features of RA patients is shown in Table 2.

The mean serum 25(OH)D₃ level showed a mild negative correlation with weight and IPF ($r = -0.256$ and -0.234 with $P = 0.009$ and 0.017 , respectively) and moderate negative correlations with morning stiffness, symmetric arthritis, SJC-28, TJC-28, and ESR ($r = 0.398, -0.333, 0.631, -0.559$, and -0.39 , with $P < 0.001$ for all, except for arthritis, which was 0.001).

Correlation between serum 25(OH)D₃ level and DAS-28 and M-HAQ

Serum 25(OH)D₃ level showed a strong negative correlation with the DAS-28 score ($r = -0.794$, $P < 0.001$) and moderate negative correlations with M-HAQ ($r = -0.562$, $P < 0.001$). Although almost all RA patients had 25(OH)D₃ deficiency, it was found that the mean 25(OH)D₃ level was relatively higher in patients with disease remission and its level was significantly decreased as the disease became more active ($P < 0.001$; Table 3 and Fig. 1). Also, the mean serum 25(OH)D₃ was significantly higher in patients without functional disability in comparison with those with disability ($P < 0.001$; Table 3 and Fig. 2).

Correlation between serum 25(OH)D₃ level and treatment

There was an insignificant correlation between serum 25(OH)D₃ and leflunomide ($P = 0.57$), hydroxychloroquine ($P = 0.45$), or prednisone ($P = 0.16$).

Correlation between serum 25(OH)D₃ level and BMD

Also, there was an insignificant correlation between serum 25(OH)D₃ and BMD of the hip ($P = 0.11$), spine ($P = 0.74$), or distal radius ($P = 0.24$).

Discussion

The prevalence and association between vitamin D deficiency and the outcome of various autoimmune diseases are the most evolving topics. The present

Table 2 Correlation between mean serum 25(OH)D₃ level and demographic, clinical, radiologic, and laboratory features of RA patients

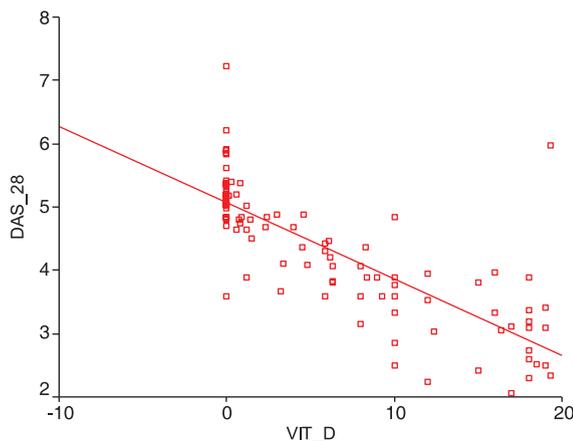
Features of RA patients	<i>r</i>	<i>P</i> value
Demographic data		
Age	-0.162	0.101
Weight	-0.256	0.009
Height	-0.141	0.153
BMI	-0.167	0.09
Disease duration	-0.166	0.091
Clinical features		
Morning stiffness	-0.398	<0.001
Symmetric arthritis	-0.333	0.001
SJC-28	-0.631	<0.001
TJC-28	-0.559	<0.001
Deformities	-0.134	0.176
Radiologic features		
Erosive arthritis	0.035	0.725
IPF	-0.234	0.017
Laboratory features		
ESR	-0.39	<0.001
RF	-0.211	0.032
Anti-CCP	-0.073	0.469

Anti-CCP, anticyclic citrullinated polypeptide; ESR, erythrocyte sedimentation rate; IPF, interstitial pulmonary fibrosis; 25(OH)D₃, 25-hydroxyvitamin D₃; RA, rheumatoid arthritis; RF, rheumatoid factor; SJC-28, 28 swollen joint count; TJC-28, 28-tender joint count.

Table 3 Comparison between the mean serum 25(OH)D₃ and DAS-28 and M-HAQ

Parameters	25(OH)D ₃ (mean ± SD)	<i>P</i> value
DAS-28<2.6	16.31 ± 3.3	
DAS-28<3.2	15.2 ± 4.02	
DAS-28 3.2-5.1	5.2 ± 5.4	<0.001
DAS-28>5.1	0.84 ± 6.78	
M-HAQ ≤ 0.3	9.7 ± 6.25	<0.001
M-HAQ > 0.3	2.12 ± 4.93	

DAS-28, 28-joints disease activity score; M-HAQ, modified-health assessment questionnaire; 25(OH)D₃, 25-hydroxyvitamin D₃.

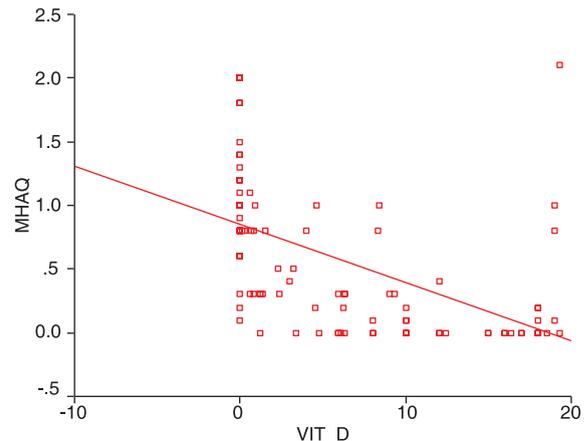
Figure 1

Correlation between the serum 25(OH)D₃ level in nmol/l and the DAS-28 score. DAS-28, 28-joints Disease Activity Score; 25(OH)D₃, 25-hydroxyvitamin D₃.

study showed that 25(OH)D₃ deficiency was prevalent among RA patients as well as among the controls (99.1 and 100%, respectively), without a significant difference, indicating that vitamin D deficiency might be endemic in our country. Surprisingly, the high prevalence of 25(OH)D₃ deficiency that was found in our country, which has abundant sunshine, may be attributed to decreased sun exposure (conservative dressing culture, wearing of veil and muffler, and/or avoidance of exposure to hot sunny weather). Another explanation may be our predisposition as an Arab population for 25(OH)D₃ deficiency as a result of certain intrinsic factors related to ethnicity as reported by Braun-Moscovici *et al.* [22], who found that the prevalence of 25(OH)D₃ deficiency was 76.6% in Arab RA patients compared with 35% in Jewish RA patients, with a statistically significant difference ($P < 0.001$). The low socioeconomic status and educational level of our participants, who were recruited from the rural and slums area near Cairo, may be another contributing factor toward 25(OH)D₃ deficiency.

Although the mean serum 25(OH)D₃ level of our RA patients was lower than that of the controls, there was no statistically significant difference (5.98 ± 6.8 vs. 8.4 ± 9.6 nmol/l, $P = 0.06$), and this is in agreement with the study of Turhanoglu *et al.* [23]. However, the prevalence of 25(OH)D₃ deficiency in our study was much higher (99.1%) compared with that found by Rossini *et al.* [18] (52%), Haque and Bartlett [19] (61%), and Braun-Moscovici *et al.* [22] (42%).

The present study showed an inverse correlation between serum vitamin D level and DAS-28 as well as with its three components: S-28, T-28, and ESR. Our study found a statistically significant moderate inverse correlation between 25(OH)D₃ and both

Figure 2

Correlation between the serum 25(OH)D₃ level in nmol/l and the M-HAQ score. M-HAQ, modified-health assessment questionnaire; 25(OH)D₃, 25-hydroxyvitamin D₃.

S-28 and T-28 ($r = -0.631, -0.559$, respectively, with $P < 0.001$ for both), which is in agreement with the study of Zakeri *et al.* [24], but in contrast to the study of Pakchotanon *et al.* [25], who found an insignificant correlation between 25(OH)D₃ and S-28 and T-28. Also, the present study found a statistically significant mild inverse correlation between 25(OH)D₃ and ESR ($r = -0.39, P < 0.001$) that was in agreement with the study of Kostoglou-Athanassiou *et al.* [13]. Moreover, the current study found a statistically significant strong inverse correlation between 25(OH)D₃ and DAS-28 ($r = -0.794, P < 0.001$) and this is in agreement with several previous studies. In a study involving 158 RA patients, Moghimi *et al.* [10] found an inverse correlation between serum vitamin D and DAS. Kostoglou-Athanassiou *et al.* [13], Rossini *et al.* [18], and Haque and Bartlett [19] found the same inverse correlation between vitamin D level and disease activity score in RA patients. Also, Turhanoglu *et al.* [23], Zakeri *et al.* [24], and Chen *et al.* [26] found that vitamin D deficiency was associated with the RA activity score. Welsh *et al.* [27] and Kerr *et al.* [28] found a significant correlation between vitamin D deficiency and increased disease activity in RA. However, other studies did not find such a significant correlation between vitamin D level and RA activity [22,25,29–31].

Moreover, there was a statistically significant moderate inverse correlation between 25(OH)D₃ and M-HAQ ($r = -0.562, P < 0.001$) that was in agreement with other previous studies [18,23]. In contrast, other studies showed an insignificant correlation between vitamin D and RA functional disability [26,32]. There was a statistically significant mild inverse correlation between 25(OH)D₃ and body weight ($r = -0.256, P < 0.009$). Body weight is part of the BMI calculation formula and according to this formula and the WHO classification, the mean BMI of our patients (29.2 kg/m²) was within the overweight range [33]. This significant correlation is in agreement with previous studies that reported an inverse correlation between 25(OH)D₃ and obesity [34,35].

Our present study found a statistically significant mild inverse correlation between vitamin D and IPF ($r = -0.234, P = 0.017$). In a previous study of 67 patients with interstitial lung disease (ILD) secondary to connective tissue disease including RA and 51 patients with other causes of ILD, significant vitamin D deficiency (52 vs. 20%, $P < 0.0001$) and insufficiency (79 vs. 31%, $P < 0.0001$) were found among those with connective tissue disease-ILD than those with other forms of ILD [36].

No significant correlation was found between 25(OH)D₃ and BMD. In contrast to our results, Chen

et al. [26] found a significant positive correlation between 25(OH)D₃ and BMD.

No significant correlation was found between 25(OH)D₃ and drug intake. This finding is in agreement with the study of Baker *et al.* [37].

Vitamin D is known to induce immunologic tolerance [32] and its deficiency may increase the risk of development of autoimmune diseases such as RA. Also, vitamin D has immunomodulatory properties [38,39]. It appears to regulate the immune response by decreasing antigen presentation [40], inhibiting the T-helper type-1 (Th-1) cell that is directed against self-antigens [41], and decreases the production of interleukin-2 and interleukin-5 [42]. 1,25(OH)₂D₃ suppresses proliferation and immunoglobulin production and retards differentiation of B-cell precursors into plasma cells [43]. Varenna *et al.* [44] reported that vitamin D supplementation may be recommended for RA patients for the prevention and treatment of osteoporosis as well as for its possible effects on disease activity.

Conclusion

Our results showed a high prevalence of vitamin D deficiency among RA patients as well as among the controls, indicating that vitamin D deficiency might be endemic among our population. Although the mean serum level of vitamin D was lower in RA patients, it was insignificantly different from that among the controls. However, there were statistically significant inverse correlations between vitamin D and both RA disease activity and functional disability. Vitamin D deficiency also correlated inversely with IPF, but not with BMD. Our finding justifies the inclusion of vitamin D in the routine RA laboratory workup because of its possible effects on disease activity and disability outcome.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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