

Vitamin D Level in Rheumatoid Arthritis Patients in Saudi Arabia and its Correlation with Disease Activity and Mood Changes

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Abstract

Background: Patients with rheumatoid arthritis (RA) are more susceptible for having psychological comorbidities than the normal population. This is due to many factors like pain, disability, and social impacts of the arthritis besides other metabolic co-factors like vitamin D deficiency. **Purpose:** To study the link between vitamin D level as a co-factor in mood changes outcome in RA patients and the extent of mood change variables affection as well as the relation to disease activity. **Patients and Methods:** This study included 100 adult RA patients divided into two groups; Group1(G1): RA patients with low vitamin D level and Group 2(G2):RA patients with normal vitamin level, both groups were subjected to assessment of mood change and disease activity. **Results:** This study found that total Beck scale for depression and mood change variables were significantly different between the two groups ($p < 0.001$). Significant correlation was also found between vitamin D level and total Beck scale and mood changes ($P, 0.001$). Disease activity index was in reverse correlation with vitamin D level in total patients' sample ($r = - 0.143$), but no significant difference was found between both groups ($p = 0.139$). **Conclusion:** Patients with rheumatoid arthritis who have vitamin D deficiencies are more prone to exhibit psychological and mood disorders regardless the status of disease activity

Keywords: Rheumatoid Arthritis, Vitamin D, Mood Changes, Rheumatoid Arthritis Disease Activity Score, Beck Scale.

Introduction:

Rheumatoid arthritis is an autoimmune disease of undefined etiology, it is one of the most famous and common autoimmune inflammatory arthritis over the world affecting nearly 1% of the population, it primarily affects the joints, yet multiple extra-articular manifestations can be representing serious comorbidity.⁽¹⁾

Mood changes are among the most common comorbidities in patients with rheumatoid arthritis and other inflammatory arthritis diseases. The incidence of a depressive disorder in RA is about 10 % - 42%.⁽²⁾

Psychological comorbidity adversely affects the outcomes in rheumatoid arthritis (RA). Mood changes, with RA, for example, might be associated with higher risk of incidental myocardial infarction, poor quality of life, and increased mortality.⁽³⁾

Vitamin D is a hormone synthesized in human skin under the stimulation of ultraviolet radiation. Beside its endocrine role in bone metabolism, Vitamin D has immunomodulatory effects which emphasizes on the immune system including the enhancement of microbicidal ability of monocytes/macrophages and the down-modulation of inflammatory cytokines produced by T lymphocytes. Vitamin D deficiency is involved in many health problems, including immune-mediated diseases such as autoimmune disorders.⁽⁴⁾

Vitamin D displays an immunologic effect which can modulate the function of Th17 - related cytokines and thereby prevent

perpetuation of inflammation in chronic disorders like rheumatoid arthritis.⁽⁵⁾ Interestingly, a possible association between depression and low vitamin D levels has been found in people with gout, chronic spinal cord injuries, stroke, and multiple sclerosis raising the susceptible role of the vitamin D in the joints and neurological health.^(6,7)

People with mood changes were found to have low circulating levels of Vitamin D in their blood. So, vitamin D deficiency may be linked to an increased risk or severity of depression.⁽⁸⁾

The importance of vitamin D to many brain processes including neuro-immunomodulation and neuroplasticity suggests that it might have a role in psychiatric illnesses such as mood changes and depression.⁽⁹⁾

The biological plausibility of the association between vitamin D and depressive illness has been strengthened by the identification of vitamin D receptors in areas of the brain implicated in depression.⁽¹⁰⁾

Patients and methods:

Objectives of the study:

This study aimed to study the correlation between vitamin D deficiency and mood changes, especially depression, in RA patients and its relationship with disease activity.

Study design:

This study is a prospective randomized clinical study of 100 adult patients of RA.

The study was conducted on rheumatology clinics of Dr. Soliman Fakeeh Hospital, Jeddah, Saudi Arabia. From February 2017 till July 2019.

Target population:

-Study was conducted on 100 adults RA patients diagnosed according to American college of rheumatology /European League Against Rheumatism (ACR/EULAR) rheumatoid arthritis classifications criteria.⁽¹¹⁾

-Disease activity of the RA was estimated according to Disease Activity Score 28(DAS 28).⁽¹²⁾

-All patients were subjected to BECK depression inventory score scale which is self-scored questionnaire consists of 21 items of variable mood changes , 6 items of them were chosen according to the most commonly affected items in RA patients experienced in our clinics, each has score from 0-3 . The chosen items were (sadness, discouraged about future, irritability, dissatisfaction, sleep disturbance and fatigability).⁽¹³⁾

-All patients were subjected to full history taking, clinical examination and laboratory tests: Erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), anti-citrullinated cyclic peptides (anti-CCP).

-All patients were subjected to quantitative serum vitamin D level estimated by radioimmunoassay method, considering the deficiency level is less than 30 nmol/L and the normal level is above 30 nmol/L.

-The patients were divided into 2 groups:

Group 1: consisted of 50 RA patients with low vitamin D level.

Group 2: consisted of 50 RA patients with normal vitamin D level.

Inclusion criteria:

-Age 18 years and above.

-RA patients who are under treatment with disease modifying antirheumatic drugs (DMARDs) and/or biological treatment.

Exclusion criteria:

-Age below 18.

-Overlapped other autoimmune disorders.

-Other chronic longstanding illness.

-Current use of antidepressants medications.

-Current use of vitamin D supplements.

-Pregnancy and breastfeeding.

Ethical considerations:

Written approvals permitting to the Helsinki declaration were taken from all patients before being included in this study. Local ethical committee approval NO.: DSFH-ECA-022.

Statistical methods:

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Categorical data were represented as numbers and percentages. Chi-square test was applied to compare between two groups. For continuous data, they were tested for normality by the Shapiro-Wilk test. Quantitative data were expressed as mean, standard deviation. Student t-test was used to compare two groups for normally distributed quantitative variables while one way ANOVA was used for comparing the different studied groups Mann Whitney test was used to compare two

groups for not normally distributed quantitative variable. Pearson coefficient was used to correlate between normally distributed quantitative variables while Spearman coefficient was used to correlate between not normally distributed quantitative variables. Significance of the obtained results was judged at the 5% level.

Results:

This study included 100 adult RA patients age range from 22-57years, G1 mean was (40.2±9) and G2 mean was (40.2±8.9) with 63 females (66% in G1 and 60% in G2) and 37 males (34% in G.1 and 40% in G2). They were divided into 50 patients with low vitamin D (G1) with mean level of (14.2±5.5) and 50 with normal vitamin D (G2) with mean level of (34.3±10.1)

Baseline demographics and characteristics were balanced between both groups for: age, sex, duration of illness with mean in G1 was (6.96±4.21) and (6.64±4.20) in G2, DAS score means were (3.3±0.9) in G1 and (3±0.8) in G2. Other parameters including RF, anti-CCP, ESR, total Beck scale and chosen variables of mood change were also studied for both groups. Significant relations were found as regards level of vitamin D (Figure 1) and total Beck scale (Figure 2) between both groups. While no significant relations were exhibited as regards DAS score (Figure 3) or other parameters. (Table 1)

When both groups were compared according to the variables of mood changes (Figure 4), significant relations were found as regards sadness, discouragement about future, irritability, dissatisfaction, and fatigability (p

<0.001). While no significance (p=0.559) as regard the sleep disturbance. (Table 2)

A highly significant inverse relation was found between vitamin D level and total Beck scale (Figure 5), sadness, irritability, dissatisfaction, and fatigability (p<0.05), while no significance was significant with discouragement about future and sleep disorder in total sample patients. (Figure 6)

When we studied the correlation between vitamin D level and disease activity score in total sample, a reverse relation was encountered but no significance was found (p=0.157). (Figure 7). As regards the laboratory tests reverse correlation and high significance were found only with the level of anti-CCP (p<0.001). (Table 3)

The relation of vitamin D level and DAS score degrees were studied (Figure 8). No significant relation to degree of disease activity was found for the group of patients with low vitamin D, while it was significant with patients with normal vitamin D level. (Table 4)

Most of the patients in the studied total sample and in G1 had a mild degree of disease activity. When disease activity was correlated with Beck scale a significant relation was found with the total sample (p=0.004) and G.2 (p=0.003), but no significant relation was found in G.1(p=0.098) (Table 5).

Study of the difference between both sexes in total sample group as regards: the vitamin D level ,total Beck scale score and DAS score ,showed significant result in the total Beck scale only (P<0.001)with mean in males(32.5 ± 8.9) and in females was(24.7 ± 10.3)

.Whereas , there was male predominance regarding both the lower vitamin D level, mean in males was (22.4 ± 15.3) and in females was(22.8 ± 15.8),and higher DAS

score, mean in males was(3.3 ± 1)and in females was (3.1 ± 0.7), but with no significant differences .(Table 6)

Table 1: Comparison between the two studied groups according to demographic data

	Group 1 (n=50)	Group 2 (n=50)	Test of sig.	p
Age (years)				
Mean ± SD.	40.2 ± 9	40.2 ± 8.9	t=	1.000
Median (Min. – Max.)	44 (22 – 57)	44 (24 – 55)	0.0	
Sex				
Male	17 (34%)	20 (40%)	$\chi^2=$ 0.386	0.534
Female	33 (66%)	30 (60%)		
Duration of illness				
Mean ± SD.	6.96 ± 4.21	6.64 ± 4.20	U=1182.0	0.635
Median (Min. – Max.)	5 (2 – 17)	5 (2 – 17)		
DAS score				
Mean ± SD.	3.3 ± 0.9	3 ± 0.8	U=1036.0	0.139
Median (Min. – Max.)	3 (2.5 – 5.1)	2.9 (1.6 – 5)		
RF				
Mean ± SD.	32.6 ± 11.8	32.4 ± 11.7	t=0.051	0.959
Median (Min. – Max.)	30 (14 – 55)	30 (14 – 55)		
Anti-CCP				
Mean ± SD.	9.17 ± 7.39	9.09 ± 7.28	U=1246.0	0.978
Median (Min. – Max.)	8 (0.40 – 25)	8 (0.40 – 25)		
ESR				
Mean ± SD.	35.7 ± 10.9	34.3 ± 10.1	U=1158.0	0.524
Median (Min. – Max.)	34 (24 – 60)	34 (20 – 60)		
Vit D level				
Mean ± SD.	14.2 ± 5.5	31.1 ± 17.7	U=562.0*	<0.001*
Median (Min. – Max.)	13 (5 – 24)	24 (9 – 60)		
Total beck scale				
Mean ± SD.	32.1 ± 7.2	23.1 ± 11.3	t=4.771*	<0.001*
Median (Min. – Max.)	33 (17 – 42)	23 (5 – 42)		

Notes: SD: Standard deviation. χ^2 : Chi square test. U: Mann Whitney test. t: Student t-test. p: p value for comparing between the studied groups *: Statistically significant at $p \leq 0.05$. Group 1: RA patients with low vit D level. Group 2: RA patients with normal vit D level

Abbreviations: DAS, disease activity score. RF, rheumatoid factor. Anti-CCP, anti-citrullinated cyclic peptides. ESR, erythrocyte sedimentation rate. vit d level, vitamin D level.

Table 2 Comparison between the two studied groups according to mood changes

	Group 1 (n=50)	Group 2 (n=50)	U	p
Sadness				
Mean ± SD.	1.96 ± 0.78	1.32 ± 0.74	724.0*	<0.001*
Median (Min. – Max.)	2 (1 – 3)	1 (0 – 3)		
Discouraged about future				
Mean ± SD.	2.2 ± 0.7	1.6 ± 0.6	682.0*	<0.001*
Median (Min. – Max.)	2 (1 – 3)	2 (0 – 2)		
Irritability				
Mean ± SD.	2.4 ± 0.5	1.6 ± 0.9	662.0*	<0.001*
Median (Min. – Max.)	2 (2 – 3)	2 (0 – 3)		
Dissatisfaction				
Mean ± SD.	2.3 ± 0.6	1.6 ± 0.8	604.0*	<0.001*
Median (Min. – Max.)	2 (1 – 3)	2 (0 – 3)		
Sleep disturbance				
Mean ± SD.	2.3 ± 0.6	2.2 ± 0.7	1174.0	0.559
Median (Min. – Max.)	2 (1 – 3)	2 (1 – 3)		
Fatigability				
Mean ± SD.	2.5 ± 0.5	1.6 ± 0.6	362.0*	<0.001*
Median (Min. – Max.)	3 (2 – 3)	2 (1 – 3)		

Notes: SD: Standard deviation; Mann Whitney test^p: p value for comparing between the studied groups *: Statistically significant at $p \leq 0.05$.

Group 1: RA patients with low vitamin D level. Group 2: RA patients with normal vitamin D level

Abbreviations: DAS, disease activity score. RF, rheumatoid factor. Anti-CCP, anti-citrullinated cyclic peptides. ESR, erythrocyte sedimentation rate. vit d level, vitamin D level.

Table 3 Correlation between Vitamin D level and different parameters in total sample (N=100)

	Vit D level	
	r_s	P
Age (years)	0.137	0.174
Duration of illness	-0.078	0.443
DAS score	-0.143	0.157
RF	0.112	0.267
Anti-CCP	-0.300*	0.002*
ESR	0.175	0.081
Vit D level	1.000	–
Total Beck scale	-0.695*	<0.001*
Sadness	-0.305*	0.002*
Discouraged about future	0.004	0.971
Irritability	-0.298*	0.003*
Dissatisfaction	-0.279*	0.005*
Sleep disturbance	-0.003	0.976
Fatigability	-0.249*	0.012*

Notes: r: Pearson coefficient. r_s : Spearman coefficient. *: Statistically significant at $p \leq 0.05$

Table 4 Relation between Vitamin D level and DAS score in each group and total sample

DAS score	N	Vitamin D level		H	p
		Mean ± SD.	Median (Min. – Max.)		
Total sample (n=100)					
≤2.6 (Remission)	30	25.9 ± 16.3	19 (10 – 60)	2.932	0.231
>2.6 – <3.2 (Mild)	40	18.1 ± 11.3	15 (8 – 54)		
>3.2 – <5.1 (Moderate)	30	25.5 ± 18.3	22 (5 – 60)		
Group 1 (n=50)					
≤2.6 (Remission)	12	15 ± 3.9	15 (10 – 19)	1.390	0.499
>2.6 – <3.2 (Mild)	22	14.5 ± 5.1	13 (8 – 22)		
>3.2 – <5.1 (Moderate)	16	13.3 ± 7.1	12 (5 – 24)		
Group 2 (n=50)					
≤2.6 (Remission)	18	33.2 ± 17.4	38 (12 – 60)	6.803*	0.033*
>2.6 – <3.2 (Mild)	18	22.3 ± 15.1	19 (9 – 54)		
>3.2 – <5.1 (Moderate)	14	39.6 ± 17.1	45 (9 – 60)		

Notes: SD: Standard deviation; F for One way ANOVA test. p: p value for comparing between DAS score categories. *: Statistically significant at $p \leq 0.05$

Abbreviations: DAS: disease activity index. N: number

Table 5: Relation between total Beck scale and DAS score in each group and total sample

DAS score	N	Total Beck scale		F	p
		Mean ± SD.	Median (Min. – Max.)		
Total sample (n=100)					
≤2.6 (Remission)	30	22.7 ± 13.8	17 (5 – 42)	5.831*	0.004*
>2.6 – <3.2 (Mild)	40	30.9 ± 3.8	32 (20 – 35)		
>3.2 – <5.1 (Moderate)	30	28.2 ± 11.1	26 (8 – 42)		
Group 1 (n=50)					
≤2.6 (Remission)	12	29.2 ± 12.4	29 (17 – 42)	2.445	0.098
>2.6 – <3.2 (Mild)	22	31.6 ± 2.2	32 (28 – 35)		
>3.2 – <5.1 (Moderate)	16	35 ± 6	37 (25 – 42)		
Group 2 (n=50)					
≤2.6 (Remission)	18	18.33 ± 13.33	12 (5 – 42)	6.439*	0.003*
>2.6 – <3.2 (Mild)	18	29.89 ± 4.96	32 (20 – 35)		
>3.2 – <5.1 (Moderate)	14	20.43 ± 10.55	18 (8 – 40)		

Notes: SD: Standard deviation; F for One way ANOVA test. p: p value for comparing between DAS score categories. *: Statistically significant at $p \leq 0.05$

Table 6: Relation between Sex and different parameters in total sample

Total sample (n=100)	Sex		Test of sig.	p
	Male (n=37)	Female (n=63)		
Vit D level				
Mean ± SD.	22.4 ± 15.3	22.8 ± 15.8	U=	0.971
Median (Min. – Max.)	19 (7 – 60)	19 (5 – 60)	1160.50	
Total beck scale				
Mean ± SD.	32.5 ± 8.9	24.7 ± 10.3	t=	<0.001*
Median (Min. – Max.)	34 (12 – 42)	26 (5 – 42)	3.792*	
DAS score				
Mean ± SD.	3.3 ± 1	3.1 ± 0.7	U=	0.892
Median (Min. – Max.)	2.8 (1.6 – 5.1)	3 (1.8 – 4.7)	1146.50	

Notes: SD: Standard deviation_U: Mann Whitney test t: Student t-test
 p: p value for comparing between DAS score categories*: Statistically significant at $p \leq 0.05$

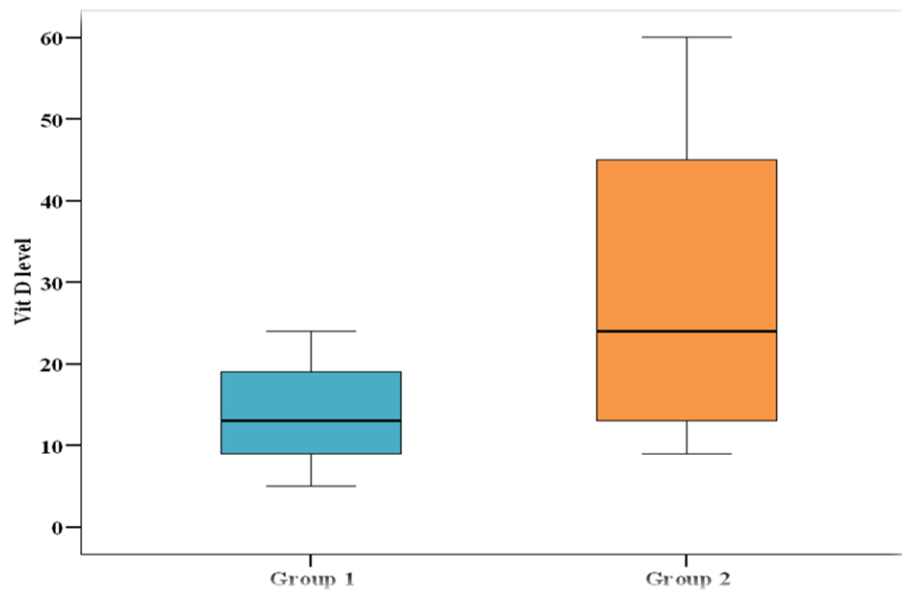


Fig. 1: Comparison between the two studied groups according to Vitamin D level

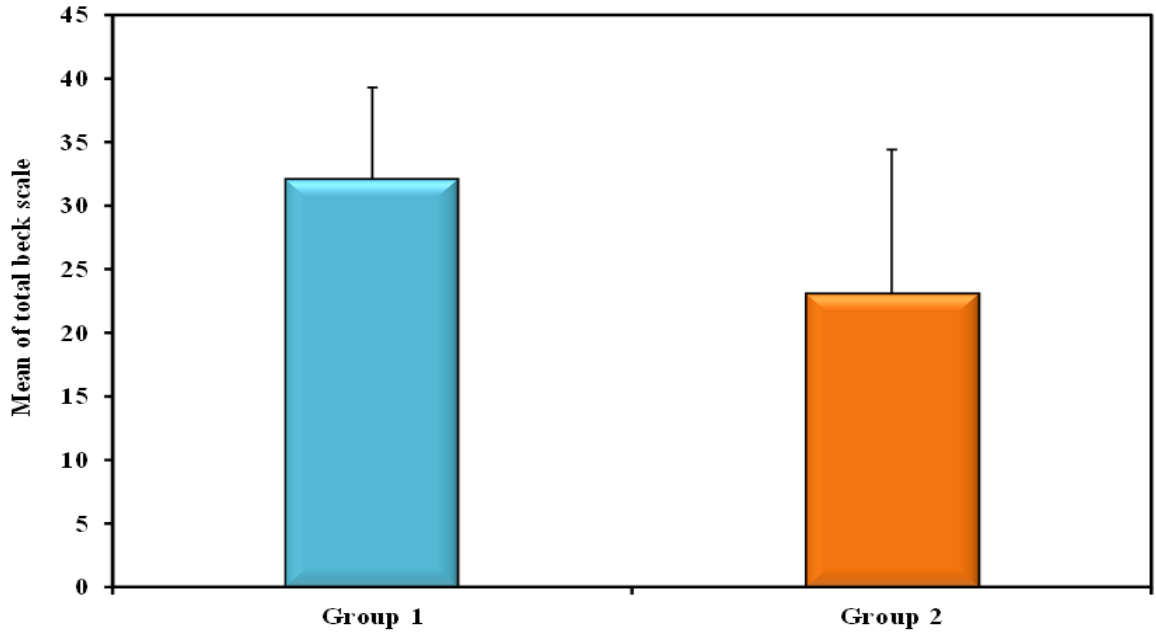


Fig. 2: Comparison between the two groups according to total Beck scale score

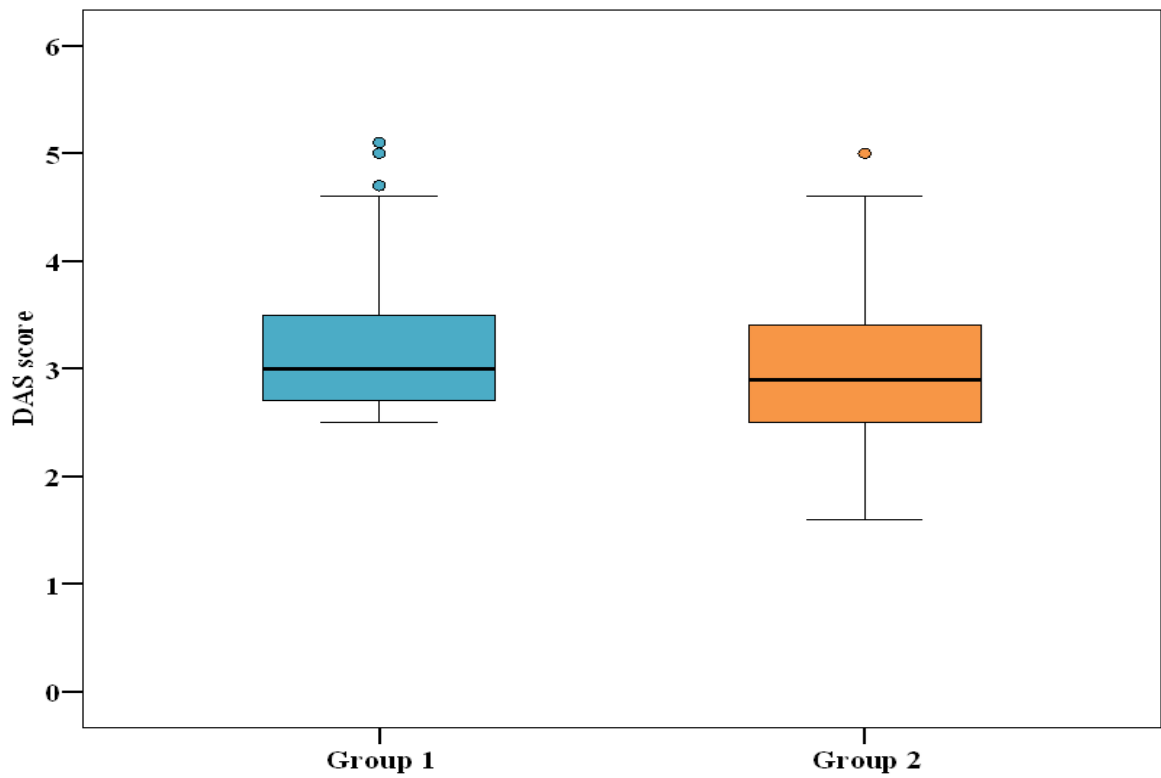


Fig. 3: Comparison between the two groups according to DAS score

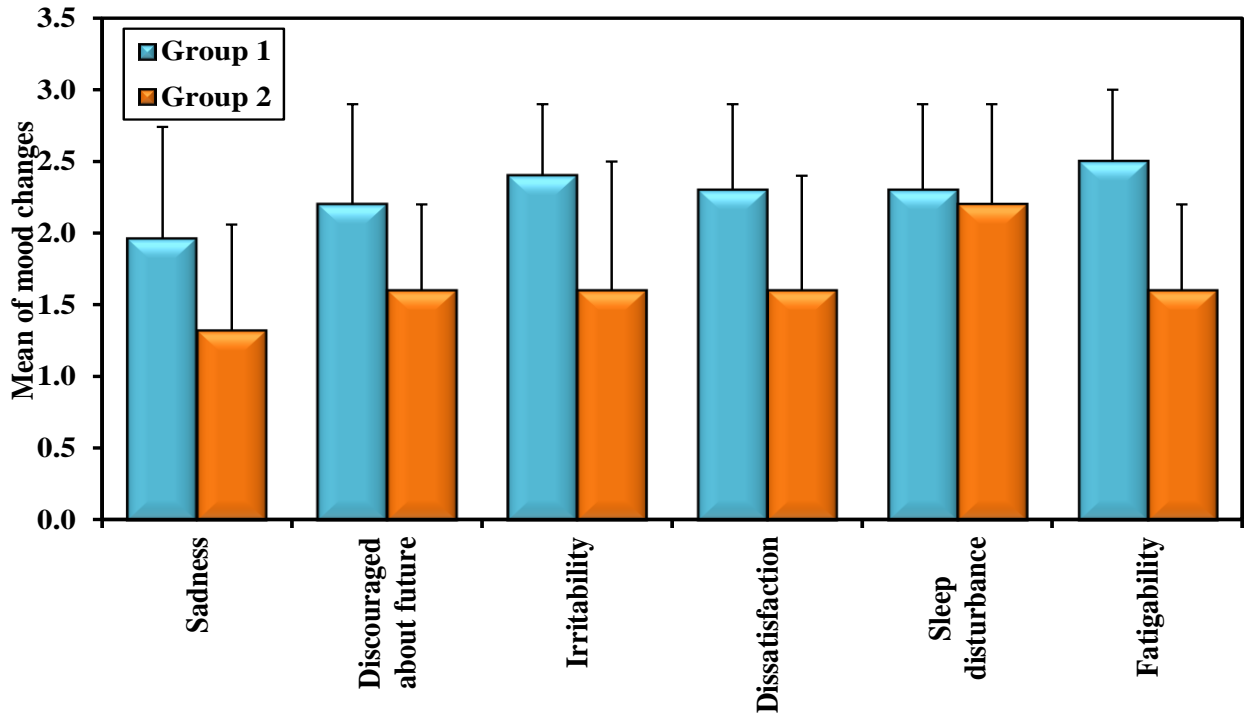


Fig. 4: Comparison between the two groups according to mood changes

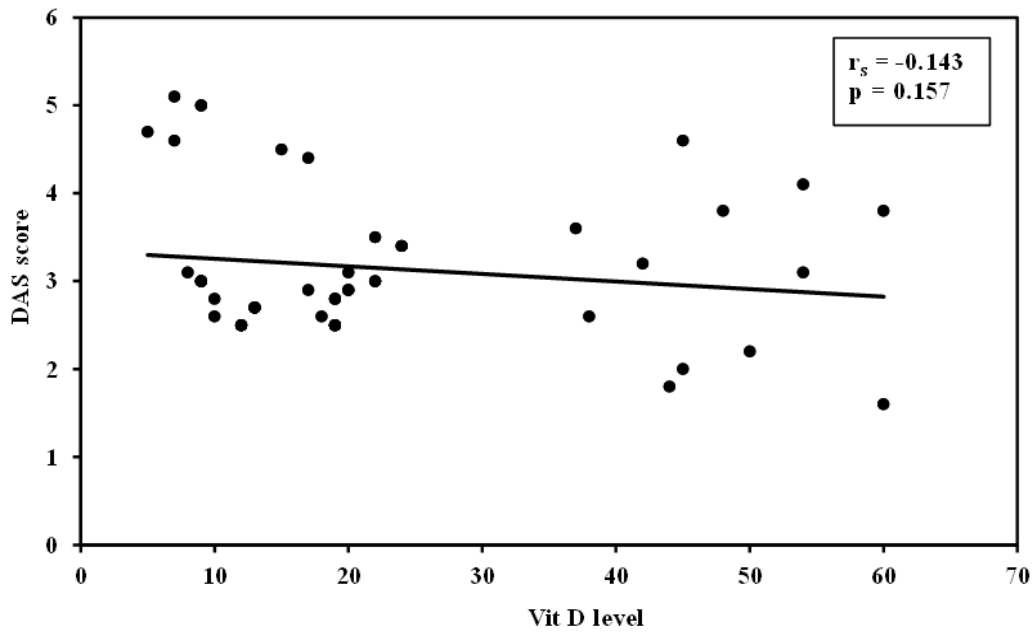


Fig. 5: Correlation between Vitamin D level and DAS score in total sample

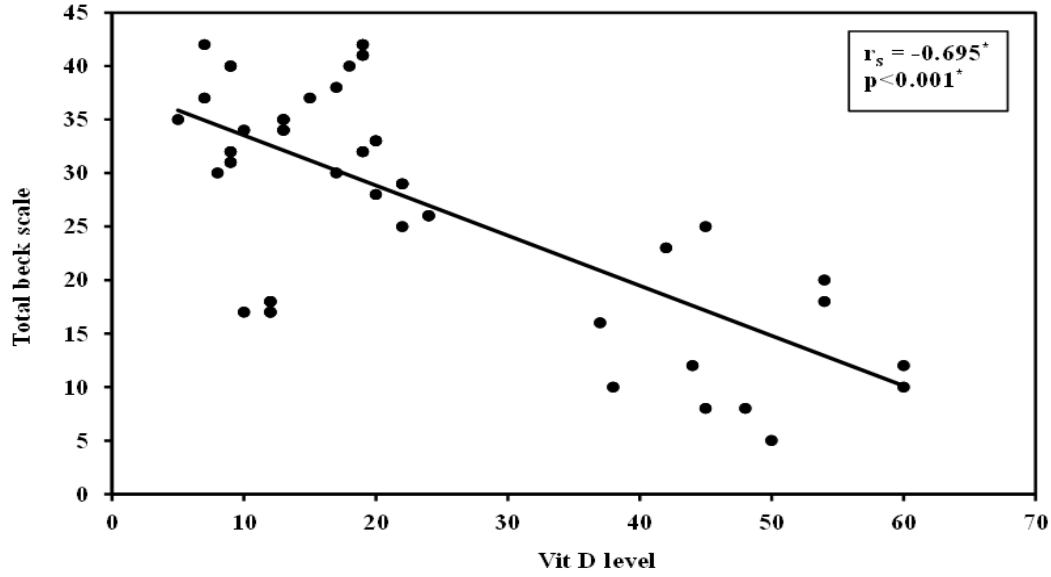


Fig. 6: Correlation between Vitamin D level and Total beck scale in total sample

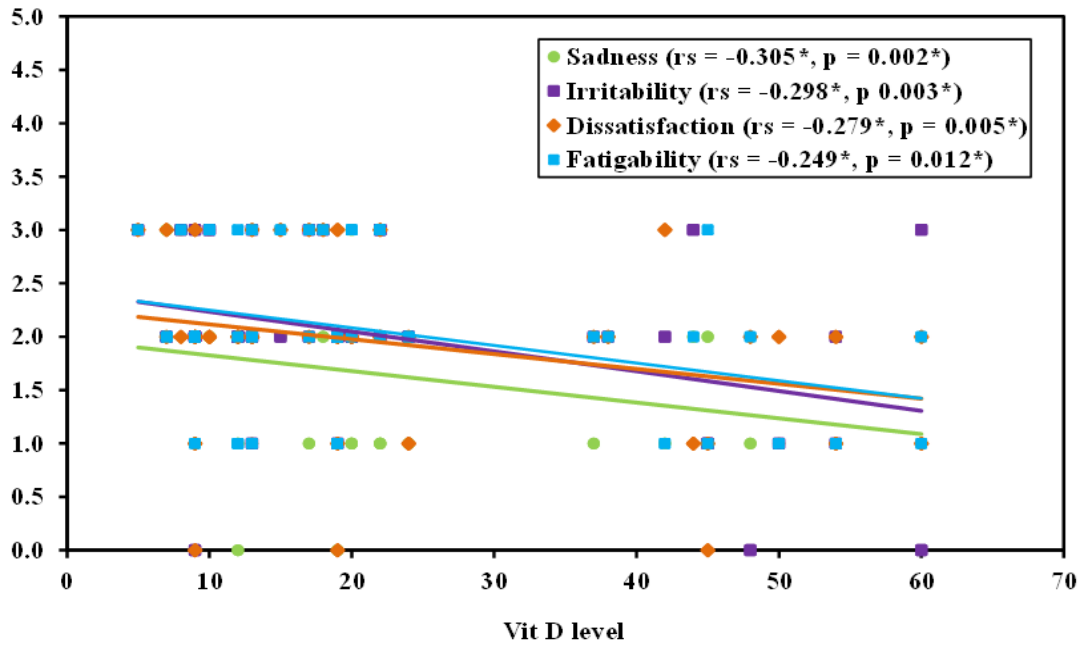


Fig. 7: Correlation between Vitamin D level and different mood parameters in total sample.

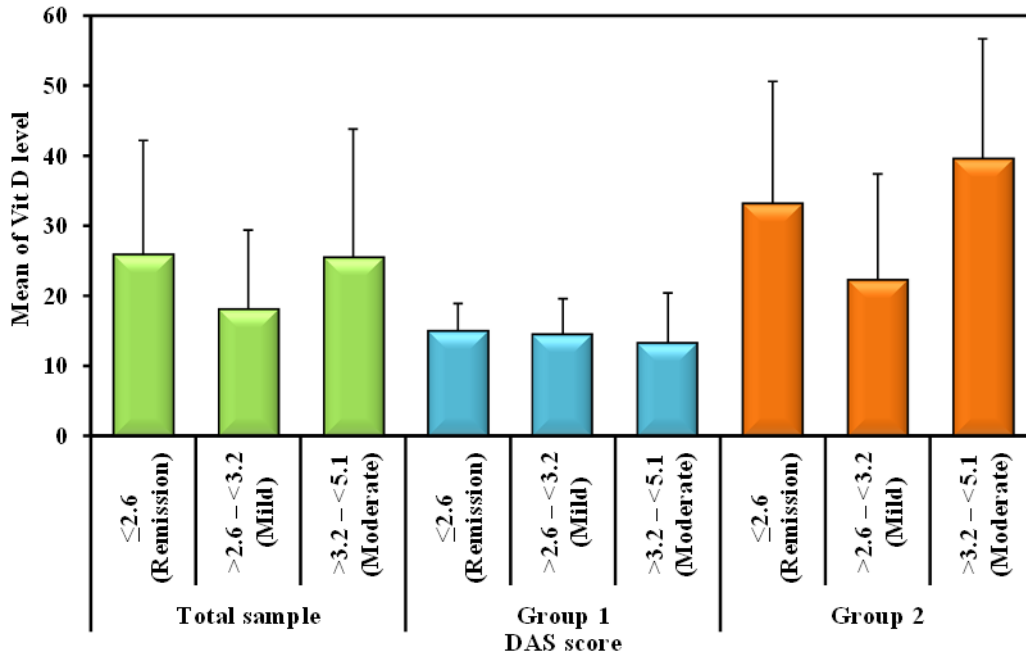


Fig. 8: Relation between vitamin D level and DAS score in each group and total sample.

Discussion:

RA is an autoimmune rheumatic disorder which not only has articular manifestations, but also, extra-articular ones that can represent the most serious illness outcomes during the patient's long-life duration.⁽¹⁴⁾

Depression and, generally, mood changes are coincident extra-articular assaults affecting high percentage of chronically ill patients including rheumatic disease, where it represents about 14-48% of total RA patients.⁽¹⁵⁾

Whether or not vitamin D level is impacting the RA disease activity or the disease severity, it is well established by many studies that vitamin D deficiency is linked to psychological health and wellbeing in normal population. The relation between the vitamin D level and mood changes disorders is

growing with many trials for therapeutic efficacy of vitamin D on the mental health.⁽¹⁶⁾

In many studies there were differences in vitamin D level as regards age and sex, extreme age and females in childbearing period were found to have the lowest level of vitamin D which could be explained by the social life, education and the multiple pregnancies and giving birth.⁽¹⁷⁾ While our study showed no significance as regards age or sex in both groups. Nevertheless, the vitamin D level was surprisingly lower in males than females which agree with another study showing the same findings.⁽¹⁸⁾

Significant result was found in having more depression and mood changes in males than females which disagreed with researchers

who found that females are twice more prone to develop depression than males.⁽¹⁹⁾

Besides, there was no significant difference between the two groups for the duration of illness, the laboratory indicators, or the disease activity score. While the DAS score was higher in group 1 than group 2 which can explain the effect of vitamin D deficiency on the RA outcome expression indicated by the higher DAS score in the group with low vitamin D. These findings agreed with another research which showed that vitamin D supplementation in RA active patients might improve the disease activity and severity.⁽²⁰⁾

On the other hand, the correlation of vitamin D level with the laboratory results showed significance only with anti-CCP. Coincident findings with others who claimed the connection between the immune response parameters and vitamin D role and those who found positive relation with the anti-CCP as well.^(21 and 22)

The link between the vitamin D deficiency in RA patients in both groups found that there was high significance between low vitamin D and the psychological parameters in the form of total Beck scale and most of the mood change variables (except for the sleep disturbance)⁽²³⁾. While the group which had normal vitamin D showed better psychological performance and impact. Many authors and studies established the same findings in normal population on one side and autoimmune disorders, including RA patients, on the other side.^(24 and 26)

In the same context, the low vitamin D correlated significantly with sadness, irritability, dissatisfaction, and fatigability variables denoting that the vitamin D is correlated with the mood changes and psychological wellbeing. This agrees with other studies which linked depression, anxiety, and suicidal attempts with the vitamin D level changes. The status would be higher incidence if associated with chronic illness as RA.⁽²⁷⁾

Interestingly, we did not find significant correlation between the vitamin D level and sleep disturbance or the discouragement about future parameters of patients in both groups which disagrees with others who found that sleep pattern is affected in patients who have low vitamin D level.^(2 and ,29)

The relation between degrees of disease activity outcome was not established to have significance with low vitamin D rather than the disease course itself. When the vitamin D level correlated with the DAS score in group 1 who has low vitamin D, negative correlation was encountered but with no significance. In agreement with other study found the same but did not prove the significant relation claiming that no correlation between serum vitamin D level and disease activity or functional ability.⁽³⁰⁾ Other authors found that the relation of vitamin D level and vitamin D insufficiency correlates inversely with RA activity suggesting that the vitamin D level is associated with susceptibility to RA activity.⁽³¹⁾

Significant relation between the depression Beck scale and disease activity was exhibited

in our study in total sample patients denoting that disease activity correlated with the psychological expression in RA patients in general regardless the vitamin D level.⁽³²⁾

Conclusion:

Our study concluded that vitamin D correlates with the psychological outcome and mood changes in RA patients, while the relation with the disease activity was not proven and might need wide scale meta-analysis study in different country. More therapeutic trials are recommended to study the effect of vitamin D supplementation on the mood changes in rheumatic diseases and on psychiatric wellbeing in general.

List of abbreviations:

RA: rheumatoid arthritis; Vit. D: Vitamin D.; G1: Group 1.; G2: Group 2; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; DAS: disease activity index; ESR: erythrocyte sedimentation rate; RF: rheumatoid factor; Anti-CCP: Anti-citrullinated cyclic peptides; DMARDs: Disease modifying anti rheumatic drugs.

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