

A study to find correlation of Vitamin D level with Disease Activity Measured by DAS 28 Score In Rheumatoid Arthritis Patients

Dr. Dharam.P.Bansal¹, Dr. Pradeep Kumar sharma², Dr.Venus Sharma³,
Dr. Arpit Pareek⁴, Dr.Piyush⁵

¹(Professor Department of medicine/Mahatma Gandhi Medical College & Hospital, Jaipur, Rajasthan)

^{2,4,5}(PG Resident Department of medicine/ Mahatma Gandhi Medical College & Hospital, Jaipur, Rajasthan)

³(Senior Resident Department of Anaesthesia/ S.M.S. Medical College & Hospital, Jaipur , Rajasthan)

Corresponding Author: Dr.Pradeep kumar sharma

Abstract: Introduction: Rheumatoid arthritis is an immune-mediated disease, mainly driven by Th1 cells. Prevalence of RA is approximately 0.8% of population (range 0.13-1.2%). Overall prevalence of RA is three times higher in women than in men Vitamin D may have a role in Rheumatoid arthritis because it suppresses Th1 cells which are a part of adaptive immunity. Data obtained from animal models show that the VDR ligand along with other factors may control the development of RA⁵. Due to possible role of vitamin D in development of RA and its severity, we conducted this study to find out correlation between rheumatoid arthritis disease activity and serum Vitamin D level. **Material and methods:** Hospital based case control type of analytical study of 80 cases of Rheumatoid arthritis and 80 controls studied based on detailed history, examination, blood investigations, DAS 28 score. **Results:** In our study there was significant negative correlation between disease activity measured by DAS-28 in RA and serum 25(OH) Vitamin D level ($p < 0.05$) **Conclusion:** The result of our study showed that In Rheumatoid arthritis, disease activity measured by DAS-28 is inversely related to Vitamin D level. So timely vitamin d supplementation to patients can reduce inflammatory burden.

Keywords: American college of Rheumatology (ACR), Rheumatoid arthritis, DAS-28 score, Autoimmune

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I. Introduction

Vitamin D is a fat soluble secosteroid in which one of the rings has been broken by ultraviolet B sunlight. Cutaneous exposure to ultraviolet B photons (290–315 nm) results in the photolytic conversion of 7-dehydrocholesterol to previtamin-D3 followed by thermal isomerization to vitamin D3. Two-step activation process occurs subsequently with hepatic hydroxylation to form 25(OH)D and further, chiefly renal hydroxylation, to form 1,25 dihydroxyvitamin D [1,25(OH)2D].

De novo synthesis in the skin is main source of vitamin D. Synthesis of vit D in the body is dependent on multiple factors like latitude, atmospheric pollution, clothing, skin pigmentation and duration and time of exposure to sunlight. 1 billion people worldwide has been estimated to have Vitamin D deficiency or insufficiency¹. Vitamin D deficiency is very common in India in all the age groups and both sexes across the country²⁻⁴.

Vitamin D is not truly a vitamin at all, but a steroid hormone that can act through receptors found on cells in multiple organ systems, including the immune system⁵. In recent studies discovery of the vitamin D receptor (VDR) in the cells of the immune system and several of these cells produce the vitamin D hormone suggested that it could have immunoregulatory properties. However, vitamin D insufficiency is emerging as a clinical problem of global proportions and epidemiology has linked vitamin D status with autoimmune disease susceptibility and severity. Therefore, 1,25-dihydroxyvitamin D3 [1,25(OH)2D3] the biologically active metabolite of Vitamin D3, not only regulates bone and calcium metabolism but also exerts immunomodulation via the nuclear VDR expressed in antigen-presenting cells and activated T/B cells⁸.

In particular, this regulation is mediated through interference with nuclear transcription factors such as NF-AT and NF- κ B or by direct interaction with vitamin D responsive elements in the promoter regions of cytokine genes.

The mechanisms of vitamin D immunomodulation Dendritic cells (DCs) are primary targets for the immunomodulatory activity of 1,25(OH)2D3, as indicated by inhibited DC differentiation and maturation, leading to down-regulated expression of costimulatory molecules (CD40, CD80 and CD86), MHC-II and decreased production of IL-12.

Rheumatoid arthritis is an immune-mediated disease, mainly driven by Th1 cells. Vitamin D may have a role in Rheumatoid arthritis because it suppresses Th1 cells which are a part of adaptive immunity. Data obtained from animal models show that the VDR ligand along with other factors may control the development of RA⁶ More recently, it was investigated if serum vitamin D metabolites may be inversely associated with current disease activity, severity and functional disability in patients with early RA⁷.

A recent study evaluated the association of dietary and supplemental vitamin D intake with RA incidence Greater intake of vitamin D was inversely associated with risk of RA⁸. These immunomodulatory and anti-inflammatory activities might be particularly efficient in RA patients and support a therapeutic role of 1,25 (OH)2D3 in such a disease.

Due to possible role of vitamin D in development of RA and its severity, we conducted this study to find out correlation between rheumatoid arthritis disease activity and serum Vitamin D level.

II. Aims And Objective

To find out correlation between Rheumatoid arthritis disease activity and Vitamin D levels.

III. Material And Methods

It is a hospital based case control study conducted during Jan 2017 to Jan 2018. Considering prevalence of R.A. to be .8% and 2% absolute error ,sample size comes out to be 80. So 80 patients of Rheumatoid arthritis diagnosed according to 1987 revised criteria of the American College of Rheumatology (ACR), who attended the medicine IPD and OPD of MGMC HOSPITAL Jaipur were included in the study after considering all inclusion and exclusion criteria.

First of all informed consent was taken from all the eligible patients and Institute Ethics Committee approval was obtained before start of study. Information about the subject's sociodemographic data which included sex, age, education, occupation, address was taken. A complete history including complaints, history of present illness, past history, family history, personal history and drug history were also noted. 80 Control subjects were selected from general population who were age and sex matched and free from any systemic illness. Data were collected by using performa meeting the objectives of study. Purpose of study was explained to patients. Detailed h/o, clinical examination ,blood investigations ,vitamin d level, DAS 28 score was calculated. Statistical analysis was done by using Microsoft Office Excel. Mean and standard deviation will be calculated .Appropriate statistical test will be applied to find significant association. Statistical significance was defined at a level of 5% ($p < 0.05$).

Inclusion criteria: All Patients fulfilling ACR criteria of Rheumatoid arthritis.

Exclusion Criteria:

1. Chronic Renal failure
2. Systemic Lupus Erythematosus
3. Diabetes Mellitus
4. Osteoarthritis
5. Mixed connective tissue disorders
6. Patient on enzyme inducer drugs. Eg Eg: Phenytoin, Barbiturates, Rifampicin.

IV. Observation And Result

Table1: Age and sex wise distribution of study participants (cases and controls)

AGE GROUP	MALE		FEMALE		TOTAL	
	NO.	%	NO.	%	NO.	%
<25	3	13.04	11	8.03	14	8.75
25-34	1	4.35	39	28.47	40	25.00
35-44	4	17.39	31	22.63	35	21.88
45-54	9	39.13	35	25.55	44	27.50
55-65	5	21.74	20	14.60	25	15.63
>65	1	4.35	1	0.73	2	1.25
TOTAL	23	100.00	137	100.00	160	100.00

CHI-SQUARE = 9.422 WITH 5 DEGREES OF FREEDOM ; P = 0.100

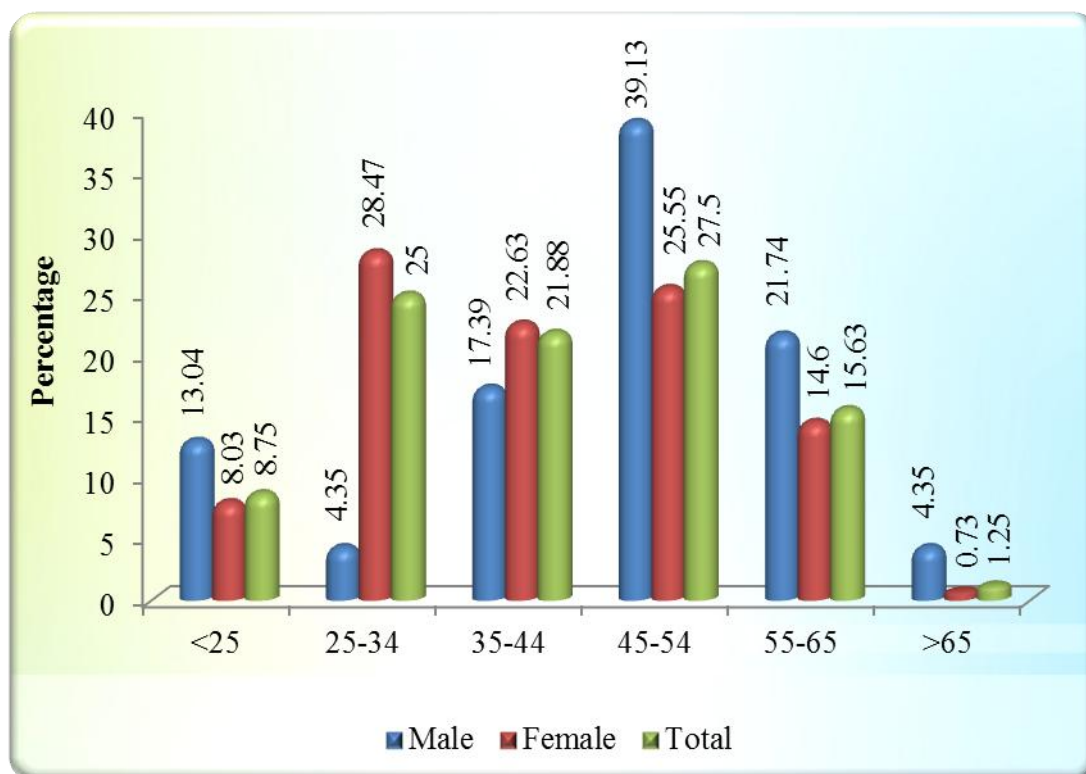


Figure 1: Distribution of Study Participants According to Age & Sex

Table 1 shows the age and sex wise distribution of study participants which include both case of RA and controls. Out of 160 participants 23 were males (14.4%) and 137 were females (85.6%). In the age group < 25 year; there were 3 (13.04%) males and 11 (8.03%) females. In between 25-34 years, there was 1 (4.35%) male and 39 (28.47%) females. In between 35-44 years, there were 4 (17.39%) males and 31 (22.63%) females. In between 45-54 years, there were 9 (39.13%) males and 35 (25.55%) females. In between 55-65 years, there were 5 (21.71%) males and 20 (14.60%) females. In age group > 65 years, there was 1 (4.35%) male and 1 (0.73%) female. Maximum number of participants was in age group 45-54 years. Maximum numbers of females were in age group 25-34 years and maximum numbers of males were in the 45-54 year age group. Females outnumbered male in each age group except in the age group >65 years in which number of male and female were equal. CHI-SQUARE Test (9.422 with 5 degrees of freedom) used and results shows that there was comparable distribution of male and females in different age group in all study participants.

Table 2: Age wise distribution of study participants (cases and controls)

AGE GROUP	CASE		CONTROL		TOTAL	
	NO.	%	NO.	%	NO.	%
<25	7	8.75	7	8.75	14	8.75
25-34	20	25.00	20	25.00	40	25.00
35-44	18	22.50	17	21.25	35	21.88
45-54	21	26.25	23	28.75	44	27.50
55-65	13	16.25	12	15.00	25	15.63
> 65	1	1.25	1	1.25	2	1.25
TOTAL	80	100.00	80	100.00	160	100.00

CHI-SQUARE = 0.159 WITH 5 DEGREES OF FREEDOM; P = 1.000

Table 2 show the age wise distribution of cases and control subjects. In age group < 25 years cases were 7 (8.75%) and controls were 7 (8.75%). In between 25-34 year cases were 20 (25%) and controls were 20 (25%). In between 35-44 years cases were 18 (22.50%) and controls were 17(21.25%). In between 45-54 year age group cases were 21 (26.25%) and controls were 23 (28.75%). In between 55-64 year age group cases were 13 (16.25%) and controls were 12 (15%). In the age group >65 years cases were 1 (1.25%) and controls were 1(1.25%). Maximum number of case and control were in the age group 45-54 year age group. Chi square (0.159 with 5 degrees of freedom) test results shows that cases and controls were age matched (p > 0.05).

Table 3: Sex wise distribution of cases and control subjects

SEX	CASE		CONTROL		TOTAL	
	NO.	%	NO.	%	NO.	%
MALE	11	13.75	12	15.00	23	14.38
FEMALE	69	86.25	68	85.00	137	85.63
TOTAL	80	100.00	80	100.00	160	100.00

CHI-SQUARE = 0.000 WITH 1 DEGREE OF FREEDOM; P = 1.000

Table 3 shows sex wise distribution of cases and control subjects. Out of 80 cases 11 (13.75 %) were males and 69 (86.25%) were females. Out of 80 controls 12 (15%) were male and 68 (85%) were females. Chi square (0.000 with 1 degree of freedom) test results shows that cases and controls were sex matched (p >0.05).

Table 4: Distribution of cases and controls according to RF

RF	CASE		CONTROL	
	NO.	%	NO.	%
POSITIVE	62	77.50	4	5.00
NEGATIVE	18	22.50	76	95.00
TOTAL	80	100	80	100

Table 4 shows distribution of cases and controls according to Rheumatoid factor. Out of 80 cases, 62 (77.50%) were Rheumatoid factor positive and 18 (22.50%) were Rheumatoid factor negative. Out of 80 controls, 4 (5%) were Rheumatoid factor positive and 76(95.00%) were Rheumatoid factor negative.

Table 5: Comparison of Vitamin D level with respect to ESR in cases of RA

ESR	N	MEAN	STD. DEVIATION	MINI-MUM	MAXI-MUM	ANOVA		TUKEY HSD
						F	SIG.	
<20	22	18.81	9.19	6.5	42.81	5.85	0.004	3
20-50	36	20.03	11.90	3.65	48.91			3
>50	22	10.95	7.48	2.28	26.7			1.2
TOTAL	80	17.20	10.74	2.28	48.91			

Table 5 shows comparison of mean serum 25(OH) Vitamin D level with respect to ESR. There were three group of patients Group A (ESR <20 mm/hr), group B(ESR 20-50 mm/hr), Group C (ESR > 50 mm/hr). There were 22 patients in group A. Mean 25(OH) vitamin D level in the group was 18.81 ng/ml with standard deviation 9.19. Minimum level of 25(OH) vitamin D in the group was 6.5 ng/ml while maximum was 42.81 ng/ml. There were 36 patient in group B. Mean 25(OH) vitamin D level in the group was 20.03 ng/ml with standard deviation 11.90. Minimum level of vitamin D in the group was 3.65 ng/ml while maximum was 48.91 ng/ml. There were 22 patients in group C. mean 25(OH) Vitamin D level in the group was 10.95 ng/ml with standard deviation 7.48. Minimum level of Vitamin D in the group was 2.28 ng/ml while maximum was 26.7 ng/ml. Mean 25(OH) Vitamin D of all patients of RA was 17.202 ng/ml with standard deviation 10.743. Minimum level of 25(OH) Vitamin D was 2.28ng/ml while maximum was 48.91 ng/ml.

ANOVA test was used and results showed that there is statistically significant difference between mean serum 25(OH) vitamin D level in patients of RA with relation to ESR.

Post Hoc tuckey HSD test was done which showed that 25(OH) Vitamin D level in patients with high ESR (>50 mm/hr) was significantly low than those with ESR <20 mm/hr and ESR 20-50 mm/hr.

Table 6: Distribution of cases according to Disease activity score (DAS-28 score)

DAS-28 SCORE	CASE	
	NO.	%
<3.2	17	21.25
3.2-5.1	32	40.00
> 5.1	31	38.75
TOTAL	80	100.00

Table 6 shows distribution of cases according to DAS-28 score. Out of 80 cases, 17 (21.25%) had low disease activity with DAS-28 score less than 3.2. Moderate disease activity (DAS-28 score 3.2 - 5.1) was present in 32 (40%) cases. 31(38.75%) cases had High disease activity with DAS-28 score more than 5.1.

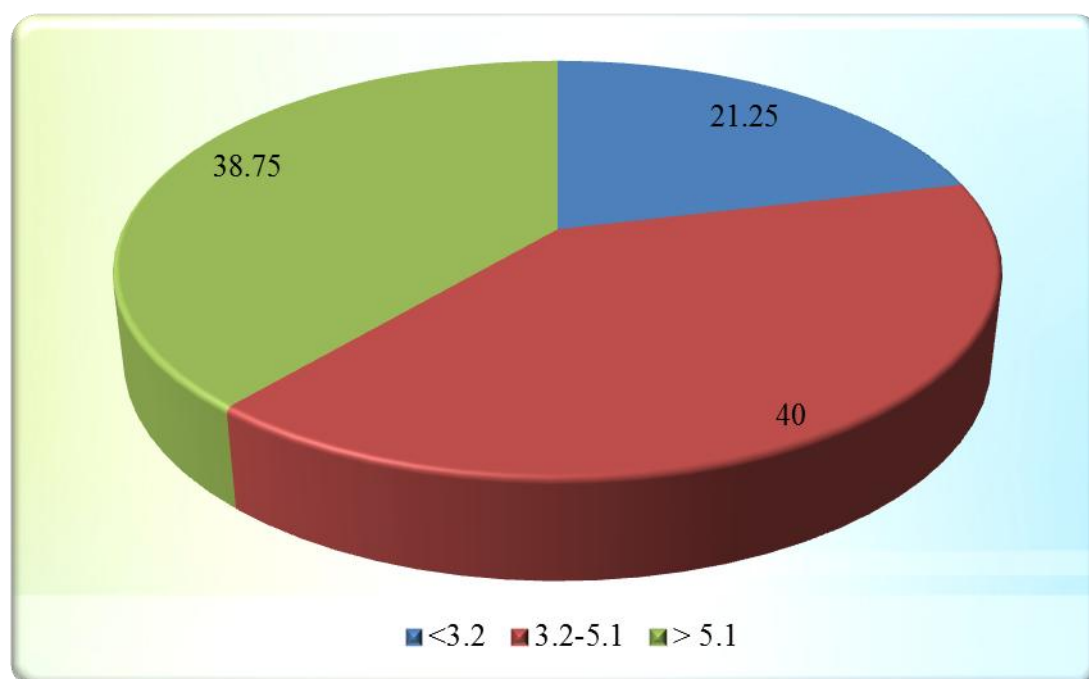


Figure 2: Distribution of Cases According To Disease Activity (N=80)

Table 7: Comparison of mean serum 25(OH) Vitamin D level with respect to disease activity

ACTIVITY	N	MEAN	STD. DEVIATION	MINI-MUM	MAXI-MUM	ANOVA		TUKEY HSD
						F	SIG	
LOW	17	24.7082	9.68477	11.52	48.60	26.317	.000	3
MODERATE	32	21.3581	10.01712	10.50	48.91			3
HIGH	31	8.7945	5.17736	2.28	26.48			1,2
TOTAL	80	17.2016	10.74288	2.28	48.91			

Table 7 shows Comparison of mean serum 25(OH) Vitamin D level with respect to disease activity in patients of Rheumatoid arthritis. There were 17 (21.25%) cases in low disease activity group (DAS 28 score <math>< 3.2</math>) and the mean serum 25(OH) Vitamin D levels were 24.7082 ng/ml with standard deviation of 9.6847. Minimum level of 25(OH) Vitamin D in this group was 11.52 ng/ml while maximum was 48.60 ng/ml.

There were 32 (40.00%) cases in moderate disease activity group (DAS 28 score 3.2 - 5.1) and the mean serum 25(OH) Vitamin D levels were 21.3581 ng/ml with standard deviation 10.0171. Minimum level of 25 (OH) Vitamin D in this group was 10.50 ng/ml while maximum was 48.91 ng/ml.

There were 31 (38.75 %) cases in high disease activity group (DAS>5.1) and the mean serum 25(OH) Vitamin D level was 8.7945 ng/ml with standard deviation 5.1773. Minimum level of 25 (OH) Vitamin D in this group was 2.28 ng/ml while maximum was 26.48 ng/ml.

Mean 25(OH) Vitamin D of all cases were 17.2016 ng/ml with standard deviation 10.7428. Minimum levels of 25(OH) Vitamin D was 2.28 ng/ml while maximum was 48.91 ng/ml.

ANOVA test was applied with p value 0.000 which was statistically significant. Post hoc Turkey HSD test was done which showed that 25(OH) Vitamin D levels in patients with high disease activity was significantly low than those with low and moderate disease activity.

Table 8: Correlation of serum 25 (OH) Vitamin D levels with respect to disease activity

ACTIVITY	N	PEARSON CORRELATION	'P' VALUE
LOW	17	.041	.877
MODERATE	32	-.159	.385
HIGH	31	-.219	.237
TOTAL	80	-.604**	.000

** . CORRELATION IS SIGNIFICANT AT THE 0.01 LEVEL (2-TAILED).

Table 8 shows Correlation of serum 25 (OH) Vitamin D levels with respect to disease activity. Among all 80 cases of RA Pearson correlation coefficient was -0.604 with p value 0.0000 which was statistically highly significant. Patients of RA with low disease activity (DAS-28 score <math>< 3.2</math>) had Pearson correlation coefficient

0.041 with p-value 0.877 which was statistically not significant. Cases in moderate disease activity (DAS-28 score 3.2-5.1) had Pearson Correlation Coefficient -0.159 with p value 0.385 which was statistically not significant. Cases in high disease activity (DAS-28 > 5.1) had Pearson correlation Coefficient -0.219 with p value 0.237 which was statistically not significant. There is negative correlation between serum Vitamin D level and DAS 28 score. Correlation coefficient -0.604 and correlation is statistically significant ($p < 0.05$).

V. Discussion

Vitamin D deficiency is very common in India in all the age groups and both sexes across the country²⁻⁴ Vitamin D is a fat soluble vitamin which in addition to its role in calcium homeostasis has a plethora of effects including immunomodulation, pleiotropic effects, modulating propensity to infection and blood pressure regulation. Vitamin D can be ingested orally or can be formed endogenously in cutaneous tissue following exposure to ultraviolet B light.

Rheumatoid arthritis is an immune dependent disease, mainly driven by Th1 cells. The characteristic features associated with disease are erosive arthritis and joint destruction, which lead to morbidity and increased mortality. Although the etiology of RA remains a mystery, a variety of studies suggest that a blend of environmental and genetic factors are responsible. Vitamin D may have a role in Rheumatoid arthritis because it suppresses Th1 cells which are a part of adaptive immunity. Data obtained from animal models show that the VDR ligand along with other factors may control the development of RA⁶. Low Vitamin D level has been implicated as a risk factor in development of Rheumatoid arthritis⁸ and recent studies has linked low Vitamin D levels with increased disease activity in Rheumatoid arthritis^{7,8,9-11}.

The present study was conducted on 80 patients of Rheumatoid arthritis (RA) and 80 healthy control subjects. Cases were taken from patients of RHEUMATOID ARTHRITIS MGMC, Jaipur and controls were taken from general population. Patients gave their informed consent and the local ethical committee approved the protocol. These patients underwent complete clinical assessment, disease activity by DAS 28 score and investigations including Hemoglobin, Total leucocyte count, Platelet count, ESR, serum calcium, serum phosphorus, serum creatinine, Rheumatoid factor, CRP and 25(OH) Vitamin D levels.

The results are as follows:

Age and Sex wise distribution

Mean age of 80 patients of Rheumatoid arthritis (RA) was 40.97 ± 12.52 years. Age range was 18-74 years. Maximum number of cases 21(26.25%) were in 45-54 year age group. Mean age of 80 Controls was 42.63 ± 12.66 years. Age range was 16-68 years. Maximum number of control 23 (28.75%) were in 45-54 year age group.

Mean age in a study done by Turhanoglu et al¹ was 46.27 ± 11.87 years in patient with Rheumatoid arthritis and 44.83 ± 10.60 years in healthy controls. Student unpaired t test was used which showed p value 0.405 which is statistically not significant which means cases and control were age matched.

In our study out of 80 patients of RA, 69 (86.25%) were females and only 11(13.75%) cases were males. Female to male ratio was 6.2:1. In a study done by Rossini et al² 85% were females and female to male ratio was 5.6:1. Silman³ in his study concluded that prevalence of Rheumatoid arthritis is approximately three times greater in women than in men. Among 80 control subjects, 12 (15.06%) were males and 68(85.00%) were females. Chi square test (0.000 with 1 degree of freedom) was used and results showed that cases and controls were sex matched ($p > 0.05$).

ESR distribution among case and controls

In our study, the mean ESR of 80 patients of RA was 40.96 ± 27.14 mm/hr. ESR range in patients of RA was 10-120 with minimum ESR 10 mm/hr and maximum ESR 120 mm/hr. The mean ESR of 80 control subjects was 19.06 ± 5.06 mm/hr. ESR range in control was 10 -28 with minimum ESR was 10 mm/hr and maximum ESR was 28 mm /hr. Student unpaired t test was used and the results showed that there is significant difference between mean ESR of cases and controls ($p < 0.05$). These results can be explained by the presence of high ESR in Rheumatoid arthritis patients due to chronic persistent inflammation.

Comparison and correlation between 25(OH) vitamin level and serum ESR in patients of RA

In our study we had three groups based on serum ESR of RA patients. Group A had serum ESR <20 mm/hr, Group B had serum ESR 20-50 mm/hr and Group C had serum ESR >50 mm/hr. Out of 80 patient 22 (27.5%) were in group A with mean serum level of 25(OH) Vitamin D was 18.81 ± 9.19 ng/ml. Range of 25(OH) Vitamin D in this group was 6.5-42.81 ng/ml. Out of 80 patients 36(45%) were in group B with mean serum level of 25(OH) Vitamin D was 20.03 ± 11.90 ng/ml. Range of 25(OH) in this group was 3.65-48.91 ng/ml. Out of 80 patients 22 (27.5%) were in group C with mean serum level of 25(OH) vitamin D was 10.95 ± 7.48 ng/ml. Range of serum 25(OH) Vitamin D in this group was 2.28 – 26.7 ng/ml. ANOVA test (Analysis of variance

test) was used and results showed that there is significant difference in mean serum 25(OH) Vitamin D level with relation to serum ESR ($p < 0.05$) in patients of RA. In our study there was negative correlation between serum ESR and 25(OH) Vitamin D level (Pearson correlation coefficient -0.247) which was statistically significant ($p < 0.05$). These results indicate that as the ESR rises, which is a marker of increased inflammatory burden in RA, Vitamin D levels falls.

DAS -28 score and comparison with 25(OH) Vitamin D level

In our study we had three group of disease activity. DAS-28 score > 5.1 indicate high disease activity. DAS-28 score $3.2-5.1$ indicate moderate disease activity and DAS-28 score < 3.2 indicate low disease activity. Out of 80 patients of RA, 17 (21.25%) were in low disease activity with mean serum 25(OH) Vitamin D was 24.70 ± 9.68 ng/ml. Range of 25(OH) Vitamin D in low disease activity group was $11.52-48.60$ ng/ml. Out of 80 patients 32 (40%) were in moderate disease activity group with mean serum 25(OH) Vitamin D levels 21.35 ± 10 ng/ml. range of Vitamin D in moderate disease activity group was $10.50-48.91$ ng/ml. Out of 80 patients, 31 (38.75%) were in high disease activity group with mean serum 25(OH) Vitamin D levels 8.79 ± 5.17 ng/ml. range of Vitamin D in high disease activity group was $2.28-48.91$ ng/ml.

ANOVA test (Analysis of variance test) was used and results showed that mean 25(OH) Vitamin D levels were significantly low with respect to disease activity (ANOVA $p < 0.05$) (Table 9). Post hoc Tuckey HSD test revealed that 25(OH) Vitamin D level in patients with high disease activity were significantly low than those with low and moderate disease activity. These results showed that Vitamin D deficiency is more common among patients with high disease activity while Vitamin D insufficiency is more common among patients with low and moderate disease activity. These results are in accordance to the previous studies done by Turhanoglu et al (2009) which showed that Vitamin D deficiency is more severe in patients with high disease activity by DAS-28 score. These results are also in accordance to the study done by Rossini et al (2010).

Kerr GS et al studied prevalence of Vitamin D insufficiency/ deficiency in RA and association with disease activity and severity¹³. They concluded 25-OH-D deficiency, but not insufficiency, was independently associated with higher tender joint counts and highly sensitive C-reactive protein levels.

Haque UJ et al studied relationships among Vitamin D, disease activity, pain and disability in RA¹⁴. They concluded that Vitamin D deficiency was common in RA. In patients with moderate to high disease activity, vitamin D deficiency was associated with higher DAS scores, pain and disability. In 2007 Patel et al reported an inverse association between disease activity and vitamin D metabolite concentrations in patients with early polyarthritis⁷. At baseline, there was an inverse relationship between 25(OH) D levels and the tender joint count, DAS28 score and Health Assessment Questionnaire (HAQ) score. They demonstrated reduction in RA disease activity with 1,25(OH)2D supplementation¹²

DAS -28 score and correlation with 25(OH) vitamin D

Among all 80 patients of RA there was negative correlation between disease activity and 25(OH) Vitamin D level (Pearson correlation coefficient -0.604) which was statistically significant ($p < 0.05$). These results indicate that 25(OH) Vitamin D levels have significant negative correlation with DAS-28 score among all patients of RA. These results are in accordance to the previous studies done by Turhanoglu et al (2009) which showed that Vitamin D levels were significantly negatively correlated with DAS-28 (Correlation coefficient -0.431 , $p = 0.000$).

In our study cases of RA who had low disease activity (DAS-28 < 3.2) did not have statistically significant correlation with 25(OH) Vitamin D levels (Pearson correlation coefficient 0.04 , p value > 0.05). Those patients of RA who had moderate disease activity (DAS-28 score $3.2-5.1$) also did not have statistically significant correlation with Vitamin D levels (Pearson correlation coefficient -0.159 , p value > 0.05). Similarly RA patients with high disease activity (DAS 28 score > 5.1) did not have statistically significant correlation with 25(OH) vitamin D levels (Pearson correlation coefficient -0.219 , p value > 0.05).

VI. Conclusion

- Vitamin D levels are reduced as the inflammatory burden increases in Rheumatoid arthritis.
- In Rheumatoid arthritis, disease activity measured by DAS-28 is inversely related to Vitamin D level.
- In further studies, larger study groups can be taken to evaluate the effects of vitamin d supplementation on rheumatoid arthritis patients.

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