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Association between vitamin D level in rheumatoid arthritis in males and females

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ABSTRACT

Background and Aims: Rheumatoid Arthritis is an autoimmune disease of unknown aetiology. The worldwide prevalence of rheumatoid arthritis is estimated to vary between 0.5 to 1.5% with geographic variation. The rationale behind relating vitamin D and RA is based on two facts. The first one is that there is evidence indicating that patients with RA have low levels of vitamin D. The second one is that the presence of vitamin D and VDR in macrophages, chondrocytes and synovial cells in the joints of these patients has also been demonstrated. The present study was designed to study the vitamin D status/ level in rheumatoid arthritis in males and females.

Materials and Methods: The study was carried on 100 subjects chosen randomly with 75 females and 25 males in age group of 16 – 65 years. Their demographic data was collected. Vitamin D level, rheumatoid factor assay and ESR were analyzed.

Result: Higher level of disease activity as measured by DAS 28 score was associated with vitamin D deficiency. Females reported higher values for ESR, DAS 28 score and lower levels of vitamin D level as compared to males.

Conclusion: Vitamin D deficiency was positively associated with increase in DAS 28 score and rheumatoid arthritis (RA). Female sex had more preponderance for RA development. Rheumatoid factor had no gender preponderance.

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1. Introduction

Rheumatoid Arthritis (RA) is a chronic autoimmune inflammatory systemic disease that predominantly affects the synovial joints, causing significant morbidity and shortened life expectancy.¹ It is a chronic inflammatory systemic disease which has variable effects.² It can progress to become severe and disabling in a short period of time.³ It is the most common encountered connective tissue disease.⁴ The condition also has widespread extra-articular manifestations including vasculitis, inflammation in the heart, lungs and peripheral neuropathy. The

disease confers an increased risk of many other diseases including cardiovascular diseases, pulmonary dysfunction, renal disorders and intestinal pathologies, along with a significantly increased risk of premature death.⁵

Vitamin D is essential for bone mineral metabolism and is obtained from either dietary sources or sun exposure. Dietary sources fulfil only 20% of the body's daily requirement of vitamin D while synthesis in the skin after sun exposure is most important for maintenance of adequate levels in body.⁶ Vitamin D deficiency may increase the risk for the development of rheumatoid arthritis.⁷ Recently the role of vitamin D deficiency in the pathogenesis of rheumatoid arthritis as well as relationship between vitamin

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D deficiency and activity of RA has been widely studied.⁸

Is vitamin D level related to rheumatoid arthritis?. Is there any difference in males and females for the parameters studied?. The present study was done to determine the vitamin D levels/status in patients with rheumatoid arthritis in males and females.

2. Materials and Methods

2.1. Ethics, consent and approval

Ethical clearance was obtained from the Institutional Ethics Committee (IEC) of GMC Jammu, J&K, India vide registration number Cat B/C 436/ IEC/ 2018/ 665. The subjects were briefed about the study and informed written consent for participation in the study was taken.

2.2. Sampling

The present study was performed on 100 subjects in age group of 16 - 65 years chosen randomly with no gender bias. Out of 100 subjects who visited OPD, 75 were females and 25 males. A minimum sample size of 88 subjects was calculated on the basis of previous study. Prevalence of vitamin D (deficiency and insufficiency) in RA patients was 90% with 7% relative precision with constants $\alpha = 0.05$ and $\beta = 0.2$ using Open Epi software. However, for better results, 100 subjects were chosen.

Rheumatoid arthritis patients who met the American College for Rheumatology (ACR/EULAR 2010)⁹ criteria were included in the study. The patients older than 65 years, other connective tissue diseases (SLE, osteoarthritis), diabetes, malignancy, CKD with GFR 40ml/min/1.73m², celiac disease, malabsorption, IBD, pregnancy, lactation, long term usage of tubercular medication, fungal medications, those on hormone replacement therapy, vitamin D supplementation before experiment and had documented cardiac disease were excluded.

2.3. Study design

The subjects who visited OPD were selected for the study. Rheumatoid arthritis positive patients were selected as subjects. Brief history was taken and demographic parameters like age, sex, duration of disease were recorded. Their vitamin D level, rheumatoid factor assay and ESR were analyzed.

2.4. Study tool

Method of Estimation of vitamin D [25(OH) D3] - 3ml of venous blood of patients of RA was obtained in the morning. Serum 25(OH) D3 level was determined by electro-chemiluminescence (E-CLIA Method) by using ADVIA Centaur Kit.¹⁰

Definition of vitamin D status in relation to 25(OH) D3 levels by US endocrine society.

S.No.	Vitamin D status	Levels
1	Deficiency	<20ng/ml
2	Insufficiency	21-29ng/ml
3	Sufficiency	>30ng/ml
4	Toxicity	>150ng/ml

1mcg=40IU; 0.025mcg=1U

Rheumatoid factor assay was done by qualitative slide agglutination method and ESR analysis was done by Westergren's method.¹¹

2.5. Statistical analysis

For computing the results, student t test was used to analyse the difference in males and females. Association was found between various parameters using chi square test. Karl Pearson coefficient was found between vitamin D and DAS 28. The results were computed as significant at $p < 0.05$ level (*), more significant at $p < 0.01$ level (**) and highly significant at $p < 0.001$ level (***).

3. Result

Out of 100 subjects, there were 75 female and 25 male subjects. Demographic profile, ESR, vitamin D level of subjects was analysed between males and females. [Table 1]

Association was carried out between disease activity [DAS 28] and vitamin D level in males and females as depicted in Tables 2 and 3.

Association was also found in males and females for rheumatoid factor (RF) and EULAR scores. [Tables 4 and 5]

4. Discussion

In rheumatoid arthritis, body's immune system attacks its own tissues including joints. In severe cases, it may attack internal organs. Vitamin D is responsible for increasing the intestinal absorption of calcium, magnesium and phosphate. It has significant role in calcium homeostasis and metabolism. In the present study, role of vitamin D was found to be positively associated with rheumatoid arthritis.

In the present study, female sex dominated the study group with 75% as compared to male sex (25%) with female to male ratio of 3:1. The mean age of females was 44.58 ± 12.77 and for males was 47.88 ± 11.74 . Most of RA patients were in the age group of 41-60 years (54%) followed by 21-40 years (32%). This was consistent with previous studies which also showed the female predominance in rheumatoid arthritis.¹² A study on 40 patients of rheumatoid arthritis had 6 male and 34 female subjects with most patients in age group 41-55 years.¹³

Female subjects exhibited higher mean values for ESR, DAS 28 score while vitamin D level was lower in females compared to males though it was non-significant. Previous studies have shown that ESR values are higher

Table 1: Gender-wise distribution of variables associated with vitamin D level in RA

S.No.	Parameters	Females [n=75]			Males [n = 25]			P value
		Minimum	Maximum	Mean \pm SD	Minimum	Maximum	Mean \pm SD	
1	Age	18.00	67.00	44.58 \pm 12.77	20.00	65.00	47.88 \pm 11.74	0.258
2	ESR	8.00	100.00	46.44 \pm 27.20	8.00	102.00	39.56 \pm 25.59	0.269
3	EULAR	6.00	8.00	6.48 \pm 0.64	6.00	7.00	6.20 \pm 0.40	0.044*
4	DAS 28	1.60	7.40	3.76 \pm 1.61	1.20	6.80	3.40 \pm 1.54	0.342
5	VIT- D	4.20	67.64	18.57 \pm 8.99	9.06	36.50	22.44 \pm 8.14	0.059
6	Duration	0.60	96.00	5.82 \pm 10.92	1.20	12.00	4.60 \pm 2.62	0.582

ESR is in mm/hr, Duration is in years

Table 2: Association between DAS 28 and Vitamin D levels

S.No.	DAS 28	Vitamin D level			Total	Significance	
		< 20	21 - 29	>30		χ^2 -value	p-value
1	<2.6	17	8	9	34	12.77*	0.0052**
	2.6 – 3.2	3	7	1	11		
	3.3 – 5.1	17	10	2	29		
	\geq 5.1	22	4	0	26		
	Total	59	29	12	100		

Correlation coefficient between vitamin D and DAS 28 was found to be - 0.35 that was significant at $p < 0.001$ level.

Table 3: Association between DAS 28 and vitamin D level in females andmales

S.No.	DAS 28	Vitamin D	Gender	N	Mean \pm SD	Significance			
						t-value	p-value		
1	< 2.6	< 20	Females	16	13.72 \pm 3.81	-0.105	0.917		
			Males	1	14.14 \pm 0.00				
		21 – 29	Females	4	26.14 \pm 2.65	1.479	0.190		
			Males	4	23.74 \pm 1.86				
		>30	Females	5	38.84 \pm 16.12	0.535	0.609		
			Males	4	34.45 \pm 1.44				
		2	2.6 – 3.2	< 20	Females	2	16.86 \pm 3.10	-0.194	0.866
					Males	2	17.63 \pm 4.65		
				21 – 29	Females	5	25.17 \pm 1.93	0.474	0.660
					Males	1	24.16 \pm 0.00		
>30	Females			1	36.00 \pm 0.00				
	Males			0					
3	3.3 – 5.1			< 20	Females	17	13.96 \pm 4.85	-0.404	0.695
					Males	4	14.62 \pm 2.27		
				21 – 29	Females	6	23.94 \pm 1.96	-1.619	0.156
					Males	2	26.37 \pm 0.97		
		>30	Females	0					
			Males	2	31.74 \pm 0.84				
		4	>5.1	< 20	Females	17	14.66 \pm 3.82	2.021	0.059
					Males	2	9.06 \pm 0.00		
				21 – 29	Females	2	24.50 \pm 0.70	1.720	0.184
					Males	3	20.63 \pm 2.97		
>30	Females			0					
	Males			0					

Table 4: Association for rheumatoid factor in females and males

RF	Females		Males		Total		Significance	
	Frequency	%	Frequency	%	Frequency	%	χ^2 -value	p-value
Positive	64	85.3	23	92	87	87	0.2653*	0.303
Negative	11	14.7	2	8	13	13		
Total	75	100	25	100	100	100		

RF is rheumatoid factor

Table 5: Association for EULAR scores in females and males

EULAR	Females		Males		Total		Significance	
	Frequency	%	Frequency	%	Frequency	%	χ^2 -value	p-value
=6	45	60	20	80	65			
>6	30	40	5	20	35		3.297	0.035*
Total	75	100	25	100	100	100		

in females compared to males¹⁴ with rheumatoid arthritis patients reporting abnormal ESR values.¹⁵ Previous studies have reported disease activity associated with rheumatoid arthritis to be worse in women than in men.¹⁶ Studies have shown that vitamin D levels are lower in female sex compared to males.¹⁷

In the present study, there was positive association between development of rheumatoid arthritis and vitamin D level. There are studies which suggest correlation between vitamin D deficiency and several autoimmune disorders, including SLE, inflammatory bowel disease, multiple sclerosis, insulin-dependent diabetes mellitus, and RA.¹⁸ Another study found that 90% of RA patients were either vitamin D deficient or insufficient which is consistent with our study. Patients with high disease activity had significantly low vitamin D levels on comparison with the patients with low or moderate disease activity. Vitamin D had significant negative correlation with DAS 28 score.¹⁹

A study on cohort of 44 patients of rheumatoid arthritis concluded that vitamin D levels were low in RA patients as compared to controls and levels of 25(OH) D3 were found to be negatively correlated to the DAS 28 score which is consistent with our study.²⁰ Another study found that vitamin D levels in 116 Rheumatoid Arthritis patients were significantly low in maximum patients. Vitamin D levels were deficient in 63.8% patients and insufficient in 22.4% patients.²¹

In the present study, non significant results were found for rheumatoid factor in males and females. Studies have shown rheumatoid factor to be equally prevalent among genders.²²

5. Limitation of Study

The level of vitamin D varies with exposure to sunlight and hence occupation. Patients of rheumatoid arthritis and exposure to sunlight probably have decrease disease activity as supported by the fact that RA patients are generally advised to have sunlight exposure. A separate study is required to study the effect of occupation on rheumatoid arthritis and vitamin D level. However, study gave us an important insight into fact that vitamin D levels are low in patients of RA.

6. Conclusion

Vitamin D was significantly low in rheumatoid arthritis patients concluding that vitamin D levels had negative

association with the disease activity as measured by DAS 28 score. The values of factors associated with development of RA were more in females than males. Female sex had more preponderance for development of RA. RF had no gender preponderance.

7. Acknowledgment

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8. Conflict of Interest

None.

9. Source of Funding

None.

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