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ESTIMATION OF VITAMIN D LEVELS IN RHEUMATOID ARTHRITIS (RA) PATIENTS AND ITS CORRELATION WITH THE DISEASE ACTIVITY

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ABSTRACT

Aims and Objectives: The study was conducted to estimate the levels of Serum 25-hydroxyvitamin D [25(OH) D] in rheumatoid arthritis (RA) patients, to compare these levels with age and sex matched control subjects and to see the correlation of 25-hydroxyvitamin D [25(OH) D] with RA disease severity. To see correlation of dry eye with RA disease severity. **Materials and Methods:** This was a hospital based prospective case control study was conducted at Sher-I-Kashmir Institute Of Medical Sciences (SKIMS), Soura over a period of two years. 75 RA patients diagnosed as per 2010 ACR-EULAR criteria were taken up for study and 75 healthy age and sex matched control subjects were taken from general population. The disease severity in the RA patients was assessed by DAS 28 ESR SCORE. Components of DAS 28 score were erythrocyte sedimentation rate (ESR), swollen and tender joint count (both 0-28) and patient assessed global score (0-100, where 0- excellent, 100- very poor). DAS-28 score > 5.1 defined high disease activity, DAS-28 score >3.2 but ≤ 5.1 - moderate disease activity , DAS-28 score >2.6 but ≤ 3.2 defined low disease activity and DAS -28 score ≤ 2.6 defined as remission. RA patients were evaluated for dry eye disease. **Results:** Our study found that 112 (74.66%) subjects among the study population had vitamin D levels either in the insufficient or deficient range but there was statistically no significant difference between the vitamin D levels among the cases of RA and the controls(p=0.676). However, among RA cases having high disease activity(DAS 28 >5.1), 35 of the 36 patients (97.2%) had vitamin D levels either in insufficient or deficient range, which on comparison with those in remission or having low or moderate disease activity showed that the patients with high disease activity had significantly lower vitamin D levels, p value =0.002.The mean ± SD of vitamin D levels in the high disease activity group was 14.10 ±7.36,which in comparison to those in remission or with low or moderate disease activity was significantly lower, p < 0.001. There was significant negative correlation between disease activity measured by DAS-28 score in RA patients and serum 25(OH) vitamin D level, Pearsons Correlation coefficient, r = - 0.4217 (p=0.0002). Dry eye was diagnosed in 33(44%) RA patients. Mean DAS28 in patients with dry eye was 5.00±1.3 and in RA patients without dry eye was 3.5±1.4, p-value <0.0001 which is statistically significant. **Conclusion:** These results point to the immuno-modulatory role of vitamin D in RA and hence the therapeutic role of maintaining vitamin D sufficiency in RA patients to get better outcomes in terms of disease severity. Our study showed a positive correlation between RA disease severity and Dry eye disease.

KEYWORDS

RA, 25(OH) vitamin D, DAS 28, Dry Eye.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology marked by a symmetric, peripheral polyarthritis1. Symmetric swelling of multiple joints with tenderness and pain is characteristic.2,3 It is a systemic disease and hence results in a variety of extra articular manifestations4 like constitutional symptoms as weight loss, fever, fatigue, malaise, depression. Subcutaneous nodules occur in 30-40% of the patients. Secondary sjogren syndrome occurs in 10% of the patients manifesting as keratoconjunctivitis sicca (dry eyes) or xerostomia (dry mouth). Ocular involvement in the form of episcleritis and scleritis can occur.

RA affects approximately 0.5-1% of the adult population worldwide.5,6 The incidence of RA increases between 25 and 55 years of age after which it plateaus until the age of 75 and then decreases.5,6 It is more common in women than men, female: male ratio is 3:17.

Genetic factors contribute to occurrence of RA as well as to its severity. Most of this risk is associated with allelic variation in the HLA-DRB1 gene which encodes the MHC II β-chain molecule. The largest genetic association with RA outside the HLA region lies within the protein tyrosine phosphatase non-receptor 22 (PTPN22) gene.[8,9]

The clinical diagnosis of RA is largely based on signs and symptoms of a chronic inflammatory arthritis, with laboratory and radiographic results providing important supplemental information. The 2010 ACR-EULAR criteria (2010 Rheumatoid Arthritis Classification Criteria: An American College of Rheumatology/European League against Rheumatism Collaborative Initiative) require a score of ≥ 6/10 for definite diagnosis of RA.[10]

It has been suggested that some genetic and environmental risk factors interact to increase the risk of RA.11 One potential environmental factor for RA that has been studied extensively in the past decade is vitamin D.11 These epidemiological observations have been supported by in vitro studies in which the active form of vitamin D 1,25-dihydroxyvitamin D (1,25(OH)2D) has been found to have potent anti-proliferative, antibacterial and anti-inflammatory properties.12 As 25(OH)D is the major form of vitamin D in circulation and the principal determinant of patient vitamin D 'status', 25(OH)D deficiency has been suggested to lead to impaired immune system related synthesis of 1,25(OH)2D and consequential suboptimal antibacterial and anti-inflammatory immune responses.13 Consistent with this hypothesis, some epidemiological studies have reported an inverse association between serum 25(OH)D concentrations and RA disease activity and severity.14 Nevertheless, the effect of vitamin D in RA causality and progression is still undefined.

Keeping the immunomodulatory role of Vitamin D in mind we undertook this study with an aim to estimate the levels of 25(OH) vitamin D in RA patients, compare them with healthy controls and to examine the correlation between vitamin D status and RA disease severity and its relation with dry eye disease.

AIM OF THE STUDY

This study was conducted to estimate the levels of Serum 25-hydroxyvitamin D [25(OH) D] in rheumatoid arthritis (RA) patients and to compare these levels with age and sex matched control subjects. To see the correlation of 25-hydroxyvitamin D [25(OH) D] with RA disease severity.

To see corelation of dry eye with RA disease severity.

MATERIALS AND METHODS

This was a hospital based prospective case control study, conducted at Sher-I-Kashmir Institute Of Medical Sciences (SKIMS) from 2017 to 2018. 75 RA patients diagnosed as per 2010 ACR-EULAR criteria10 were taken up for study from the Rheumatology unit of General Medicine department SKIMS and the Department of General medicine, SKIMS MC bemina .75 healthy age and sex matched control

subjects were taken from general population. The disease severity in the RA patients was assessed by DAS 28 ESR SCORE.15 Components of DAS 28 score were erythrocyte sedimentation rate (ESR), swollen and tender joint count (both 0-28) and patient assessed global score (0-100, where 0- excellent, 100- very poor). DAS-28 score > 5.1 defined high disease activity, DAS-28 score >3.2 but ≤ 5.1 - moderate disease activity , DAS-28 score >2.6 but ≤3.2 defined low disease activity and DAS -28 score ≤ 2.6 defined as remission.37 Rheumatoid Arthritis patients were examined by an ophthalmologist for the presence of dry eye disease and to see its relation with RA disease severity. Dry eye was diagnosed by Schirmer test and TBUT.

Inclusion Criteria

All the patients attending the medicine OPD (SKIMS & SKIMS MC) were carefully examined. Patients with clinical, biochemical and serological findings consistent with the diagnosis of RA as per 2010 ACR- EULAR criteria were included in this study, after obtaining a written informed consent. The controls were recruited from the general population after their consent for participation in the study.

Exclusion Criteria

Patients having other rheumatological diseases like SLE etc; malabsorption syndromes like celiac disease etc. chronic renal failure, chronic liver disease or any other systemic illness as well as hypercalcemia of any origin like hyperparathyroidism were excluded from the study. Patients who had received or currently receiving medications like systemic steroids, bisphosphonates, vitamin D, phenytoin, phenobarbitone, anti-tubercular drugs, anti-fungal drugs, immune-suppressants, calcium supplements, hormonal replacement therapy or had a history of taking Vitamin D supplements in last two years were also excluded from the study.

RESULTS

The study included a total of 150 subjects of which 75 were cases of rheumatoid arthritis(RA) fulfilling the EULAR 2010 criteria and 75 were the control subjects taken from the general population. The mean age ±SD in RA group was 45.2±8.93 and in the control group was 44.7±9.25. There was no significant difference among both the groups with regards to age (p=0.999).

There were 25 (16.7%) males and 125 (83.3%) females in the study population. Out of 25 males 12 were RA patients and 13 were controls while as out of 125 females 63 were RA patients and 62 were controls. There was no significant difference among both the groups with regards to sex (p=0.827). CRP was positive in 56 (74.7%) of RA patients and negative in 19 (25.3%) patients, while it was positive in 2(2.6%) negative in 73 (97.3%) of the controls, P <0.001 which was significant.

Among the RA patients ESR was > 30 in 36 (48.0%), 21-30 in 13 (17.3%),11-20 in 13(17.3%) and 0-10 in 13(17.3%), while as it was 0-10 in 75(100%) of the controls, P <0.001 which was significant.

Among the RA group RF was high positive in 35(46.7%), low positive in 40(53.3%) and negative in 0(0%) of the patients while as it was negative in 75(100%) of the controls, P <0.001 which was significant. Among the RA group anti CCP was high positive in 43(57.3%), low positive in 31(41.3%) and negative in 1(1.3%) of the patients while as it was negative in 75(100%) of the controls, P <0.001 which was significant. Table 1.

Table 1: Demographic Characteristics And Comorbidities

	RA	CONTROLS	p-value
Number	75	75	
Mean age ± SD (years)	45.2±8.93	44.7±9.25	>0.999
Sex Male Female	 12(16.0)% 63(84%)	 13(17.3%) 62(82.7%)	0.827
CRP Positive Negative	 56(74.7%) 19(25.3%)	 2(2.6%) 73(97.3%)	<0.001
RF Negative Low Positive High Positive	 0(0.0%) 40(53.3%) 35(46.7%)	 75(100%) 0(0.0%) 0(0.0%)	<0.001
Anti CCP Negative Low Positive High Positive	 1(1.3%) 31(41.3%) 43(57.3%)	 75(100%) 0(0.0%) 0(0.0%)	<0.001
Mean Vitamin D ± SD	26.55±32.01	24.66±22.74	0.676

Disease Activity (das 28)

Among the RA patients DAS 28 score in 14 patients (18.7%) was <2.6, in 4(5.3%) patients 2.6-3.2, in 21(28.0%) patients 3.3-5.1 and in 36(48.0%) patients > 5.1,while as in the control group it was <2.6 in 75(100%) of the controls, P <0.001 which was significant. Table 2.

Mean Vitamin D Levels In Different Disease Activity Groups:

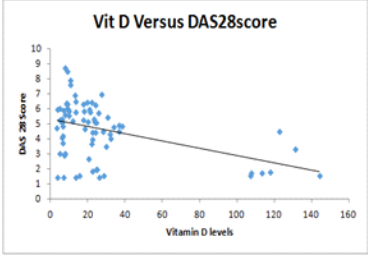
The mean ± SD, vitamin D levels in the patients having DAS 28< 2.6(remission) was 54.12 ±50.75,in patients having DAS 28- 2.6-3.2(low disease activity) was 10.16 ±6.97,in those with DAS 28 -3.3-5.1(moderate disease activity) was 32.65 ±33.35 and in those with DAS 28 >5.1(high disease activity) was 14.10 ±7.36. P <0.001 which was statistically significant. Table 2.

Table 2. Mean Vitamin D Levels In Different Disease Activity Groups

DAS 28	N	Mean±SD	p-value
<2.6	14(18.7%)	54.12±50.75	<0.001
2.6-3.2	4(5.3%)	10.16±6.97	
3.3-5.1	21(28%)	32.66±33.35	
>5.1	36(48%)	14.11±7.36	

Correlation Between Disease Activity (das 28) And Vitamin D Levels:

There was significant negative correlation between disease activity measured by DAS-28 score in RA and serum 25(OH) vitamin D level, Pearsons Correlation coefficient, r = -0.4217 (p=0.0002).



Association Of Dry Eye With Disease Severity

Out of 75 RA patients 33(44%) were diagnosed with dry eye. Out of these 33 patients Schirmer test was found 5-10 mm in 20(60.6%) of patients and <5 mm in 13(43.33%) patients. TBUT was 5-10 s in 18(54.54%) patients and <5 s in 15(45.45%). Mean DAS 28 in patients with and without dry eye was 5.00±1.3 and 3.5±1.4 respectively, showing a statistically significant difference. Table 3.

Table 3. Dry Eye And Disease Activity

Ocular Tests	N(%) Total 33	Mean DAS 28
Schirmer test 5-10 mm <5 mm	 20(60.6%) 13(43.33%)	With Dry Eye 5.00±1.3 Without Dry Eye 3.5±1.4 p-value <0.0001
TBUT 5-10 s <5s	 18(54.54%) 15(45.45%	

DISCUSSION

Rheumatoid arthritis (RA) is a progressive inflammatory disease characterized by inflammation of the synovium that leads to the destruction of joint, bone and cartilage. Genetic factors are known to contribute to the risk of RA.16-19 Additionally, a range of environmental factors that include tobacco smoking,20 alcohol intake21,22 and dietary factors23 have also been shown to contribute to the risk of RA. One potential environmental factor for RA that has been studied extensively in the past decade is vitamin D.24 This focus is due, in part, to the accumulating evidence suggesting that a worldwide deficiency in vitamin D might be linked with common health problems in humans.[25]

Our study was a case control study conducted on a study population of

150 subjects, among them 75 were RA cases diagnosed as per 2010 ACR EULAR criteria and 75 were age and sex matched controls. The mean age ± SD in RA group was 45.2 ±8.93 and in the control group was 44.7 ± 9.25. There was no significant difference among both the groups with regards to age(p=0.999) .There were 25 (16.7%) males and 125 (83.3%) females in the study population, out of 25 males 12 were RA patients and 13 were controls while as out of 125 females 63 were RA patients and 62 were controls. Again, there was no significant difference among both the groups with regards to sex(p=0.827).

All the patients assigned to the RA group 75(100%) were fulfilling EULAR 2010 criteria of ≥6/10. The disease severity in the RA patients was assessed by DAS 28(ESR) SCORE.37 Among the RA patients DAS 28 score in 14 patients (18.7%) was <2.6(remission),in 4(5.3%) patients 2.6-3.2(low disease activity), in 21(28.0%) patients 3.3-5.1(moderate disease activity) and in 36(48.0%) patients > 5.1(high disease activity). Estimation of serum 25-hydroxyvitamin D [25(OH) D] levels was done by chemiluminiscence method.

The mean±SD vitamin D levels in the RA group was 26.55±32.01 (insufficient) and in the control group was 24.66±22.74 (insufficient) , with a statistically insignificant P value of 0.676. Thus our results showed that vitamin D levels of RA patients were not significantly different from healthy controls, although the mean levels were insufficient in both the groups. These results were in accordance with the studies done by Rossini M et al26 and Turhanoğlu AD et al27. In their study Turhanoğlu AD et al27 found that the mean of the 25-OH vitamin D levels of the patients with RA was not different than that of controls (P = 0.936).

Further, the disease activity in RA patients DAS 28 ESR was compared with the Vitamin D levels among the different disease activity groups. The mean ± SD vitamin D levels in the patients having DAS 28< 2.6(remission) was 54.12 ±50.75, in patients having DAS 28- 2.6-3.2(low disease activity) was 10.16 ±6.97, in those with DAS 28 -3.3-5.1(moderate disease activity) was 32.65 ±33.35 and in those with DAS 28 >5.1(high disease activity) was 14.10 ±7.36. Comparison of the mean vitamin D levels (±SD) in the different disease activity groups again showed that patients with high disease activity had significantly lower vitamin D levels in comparison to patients in remission or with low or moderate disease activity, p value <0.001. There was significant negative correlation between disease activity measured by DAS-28 score in RA and serum 25(OH) vitamin D level, Pearsons Correlation coefficient, r = - 0.4217 (p=0.0002). Similar results have been found by numerous other studies like Sharma R et al28 in their study have found that vitamin D levels in high disease activity group was significantly low compared to vitamin D level in patients with low and moderate disease activity (p<0.001) and vitamin D level had significant negative correlation with DAS28 score (r=-0.604, p<0.001.

In our study out of 75 RA patients 33(44%) were diagnosed with dry eye. Out of these 33 patients Schirmer test was found 5-10 mm in 20(60.6%) of patients and <5 mm in 13(43.33%) patients. TBUT was 5-10 s in 18(54.54%) patients and <5 s in 15(45.45%). Mean DAS 28 in patients with and without dry eye was 5.00±1.3 and 3.5±1.4 respectively, showing a statistically significant difference. Thus showing that dry eye symptoms are related to disease severity. These results are consistent with a study done by jasmine wong yumori et al.29

CONCLUSION

To conclude, our study found that there was statically no significant difference between levels of vitamin D in the two groups but there was significant negative correlation between disease activity measured by DAS-28 score in RA patients and serum 25(OH) vitamin D level. These results point to the immuno-modulatory role of vitamin D in RA and hence the therapeutic role of maintaining vitamin D sufficiency in RA patients to get better outcomes in terms of disease severity. It was also seen that dry eye disease symptoms were directly related to disease severity.

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