International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 1231-1239 www.ijprajournal.com ISSN: 2249-7781

A Cross-sectional study for the correlation of Vitamin D level and severity of Early Rheumatoid Arthritis

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Submitted: 04-04-2024 Accepted: 14-04-2024

ABSTRACT
Background:Rheumatoid Arthritis (RA) is a chronic inflammatory multisystemic disorder that can cause significant deformity and disability. Vitamin D has a role in Th1-medicated autoimmune diseases like RA. Also, some observational studies have concluded that Vitamin D supplementation reducesthe severity of RA.
Aims:To find out any correlation betweenVitamin D levels and severity of Early RA.
Settings and Design: Cross-sectional single-centre observational study.
Methods and Material: This was an observational study. All patients with Early RA were screened and evaluated as per protocol. No extra tests were done.
Statistical Analysis used:Pearson's Chi-Square test for Independence of Attributes/ Fisher's Exact Test was used to find the association between the categorical variables as appropriate.
Results and Conclusion: We found that all patients of Early RA had moderate to severe disease activity without any relation with their Vitamin D level ($p > 0.05$)

I. INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic inflammatory multisystemic disorder that can cause significant deformity and disability. Clinical presentation has both musculoskeletal and systemic features [1]. Early Rheumatoid Arthritis is defined when the patient diagnosed with Rheumatoid Arthritis has a disease onset of less than 12 months [2]. According to the 1987 ARA classification criteria for Rheumatoid Arthritis demonstrated 91-94% sensitivity and 89% specificity for Rheumatoid Arthritis diagnosis [3]. However, the criteria usually detected Rheumatoid Arthritis in later stages and predicted more erosive disease [4]. According to the 2010 ACR/EULAR criteria, patients who have at least 1 joint of clinical synovitisshould be tested for Rheumatoid Arthritis.ACR/EULAR classification system is a score-based algorithm for diagnosis of Rheumatoid Arthritis [5].If patients already have erosive changes characteristic of Rheumatoid Arthritis, diagnosis of Rheumatoid Arthritis is done even if there are non-contributory tests [6]. Despite all the clinical and laboratory evaluations, sometimes the diagnosis of Rheumatoid Arthritis in the early stages is difficult. For that purpose, MRI and ultrasound enable early diagnosis, follow-up, treatment, and post-inflammatory joint damage assessment. MRI additionally shows bone marrow inflammation and axial spine involvement [7].Identification of Early Rheumatoid Arthritis at the beginning of treatment can affect the disease course, prevent the development of joint erosions, or retard the progression of the erosive disease [8], and can affect disease outcome even to a remission state [9]. Early treatment also slows down the development and progression of the complications of Rheumatoid Arthritis [10].

The immune cells express vitamin D receptors (VDR) and produce 1,25(OH)2D, which is the biologically active metabolite of vitamin D3. The tissue level of 1,25(OH)2D and its immunomodulatory activity is dependent on serum 25(OH)D concentration and on cytokines that are produced by the immune cells. A low level of serum 25(OH)D decreases the 1,25(OH)2D synthesis and leads to decreased function of autocrine and paracrine systems [11]. Vitamin D shifts the adaptive immune system from Th17 and Th1 cells towards Th2 cells and regulatory T cells. The presence of vitamin D deficiency impairs physiological activities in directing Th1 toward Th2-driven conditions and results in cytokine production toward Th17 cells. Since imbalance in Th1/ Th17 cells and hyperfunctioning of Th17 cells are both characteristics of Rheumatoid Arthritis. Thus, vitamin D deficiency by increased

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 1231-1239 www.ijprajournal.com ISSN: 2249-7781

production of cytokines may perpetuate the inflammatory process to chronic inflammation [12]. The normal level of Vitamin D is between 30 and 50 ng/ml. Several methods have been routinely used in the quantification of Vitamin D which are competitive protein-binding assays, radioimmunoassay, chemiluminescence immunoassays, liquid chromatography with UV detection, and liquid chromatography-mass spectrometry or tandem mass spectrometry [13].

II. REVIEW OF LITERATURE

Scott et al [14]have performed a study that has shown 50% of the risk for the development of Rheumatoid Arthritis is attributable to genetic factors. Smoking is the main environmental risk. Hence, for the development of Rheumatoid Arthritis patients need to have both genetic and environmental risks.

Malaviya et al [15] have performed another study among the Indian population which showed a Rheumatoid Arthritis prevalence of 0.75%. The prevalence of Rheumatoid Arthritis in India is similar to that reported in developed countries. Hence, we can refer to studies of European, North African, and West Asian populations to compare them with the Indian population.

Goemaere et al [16] have performed a study that hasshown that the median age of onset of symptoms of Rheumatoid Arthritis is 45 years in women and 50 years in male. The female to male ratio of all patients was 2.3; with increasing age, the female to male ratio decreased from 3.7 before 30 years of age to 1 after the 6th decade of life, with a peak at the age of 40-44 years. Hence, there can be an effect of age-related changes in sex hormone levels on the pathogenesis of Rheumatoid Arthritis.

Furuta et al [17] performed another study to compare the clinical features of patients with Early Rheumatoid Arthritis and Established Rheumatoid Arthritis (disease duration of more than 3 years). It was concluded there are no significant differences in frequencies of morning stiffness, rheumatoid nodules, elevation of ESR, positivity of CRP, and RA factor. However, after treatment marked improvement and remission were more in the Early Rheumatoid Arthritis group thanthe Established Rheumatoid Arthritis group. Hence, early initiation of treatment leads to better outcomes and control of the disease.

Grassi et al [18] have performed a study that has shown that Rheumatoid Arthritis can affect any joint but has more predilection to affect small joints of the hand causing pain, early morning stiffness, and motion restriction.

Figus et al [19] have conducted a study on the extra-articular manifestations of Rheumatoid Arthritis. Cardiovascular (CV) disease is the most common cause of death in patients with Rheumatoid Arthritis, followed by respiratory disease. To minimize morbidity and mortality, physicians must manage Rheumatoid Arthritis disease activity (treat-to-target) and monitor risk factors and concomitant conditions.

Singh et al [20] have performed a study among the Indian population which has shown the DAS28 score to be a good clinical indicator to assess the severity of Rheumatoid Arthritis. Hence, our selection of choose DAS 28 score to assess the severity of Early Rheumatoid Arthritis is justified.

England et al [21] have performed a study on the role of ESR with Rheumatoid Arthritis and Pope et al [22] have performed another role on the role of CRP with RA. Both studies have shown that an increase of ESR and CRP in patients with Rheumatoid Arthritis has an increased risk of cardiovascular disease, metabolic syndrome, diabetes, and pulmonary diseases via various mechanisms. Hence, patients with high ESR and CRP should be monitored closely as they are at a higher risk of developing systemic complications.

Aletaha et al [23] and Mimori [24] have performed studies regarding the role of RA factor and Anti CCP on Rheumatoid Arthritis. They have shown that the positivity of RA factor and Anti CCP both serve as serologic markers for early diagnosis and prognostic indicators of joint destruction in patients of Rheumatoid Arthritis. Hence, patients with positive RA factor and Anti CCP will have early and more severe joint destruction and require early and aggressive treatment.

Lin et al [25] recently performed a study regarding the availability of drugs for the treatment of Rheumatoid Arthritis. The available DMARDs are subdivided into (1) conventional synthetic DMARDs, (2) targeted synthetic DMARDs, and (3) biological DMARDs. While DMARDs have repeatedly demonstrated the potential to greatly improve disease symptoms and prevent disease progression in Rheumatoid Arthritis patients, they are associated with considerable side effects and high financial costs. Non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids can also be used [26]. Forestier et al [27] have shown **a**erobic activities, dynamic muscular

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 1231-1239 www.ijprajournal.com ISSN: 2249-7781

reinforcement, and therapeutic patient education are valuable in non-drug management.

There have been multiple studies that have been done to correlate the Vitamin D level with the severity of Rheumatoid Arthritis.

Zakeri et al [28],Song et al [29],Kostoglou-Athanassiou et al [30], Rossini et al [31], Welsh et al [32], Kerr et al [33] have found that patients of Rheumatoid Arthritis with higher disease activity have increased prevalence of Vitamin D deficiency.Mouterde et al [34] conducted a study on patients of Early Rheumatoid Arthritis and measured their serum Vitamin D at baseline who were included in the ESPOIR cohort which concluded that Vitamin D deficiency was associated with more active and severe disease of Early Rheumatoid Arthritis at baseline.Meena et al [35] have performed a study among the Indian population which has concluded that Vitamin D deficiency is related to increased severity of Rheumatoid Arthritis.

Hence, all these studies indicate that Vitamin D deficiency could be related to increased severity of Early Rheumatoid Arthritis.

Some studies have shown different outcomes:

Craig et al [36], Baker et al [37], and Braun-Moscovici et al [38] have conducted studies that did not find any relationship between Vitamin D level and the severity of Rheumatoid Arthritis.Harrison et al [39] conducted a study on the Birmingham Early Inflammatory Arthritis Cohort which concluded that there was no clear association between Vitamin D level with severity of Early Rheumatoid Arthritis.

Hence, some studies indicate that Vitamin D deficiency could not be related to increased severity of Early Rheumatoid Arthritis.

There is no uniformity among the studies done after a thorough review of existing literature.

Selvarajan et al [40] conducted a systematic review from a total of 2998 articles which concluded that Vitamin D deficiency is prevalent in healthy Indian individuals irrespective of their exposure to sunlight. Hence, a normal adult Indian could have Vitamin D deficiency.

Guan et al [41] conducted a systematic review and meta-analysis from databases which concluded that with Vitamin D supplementation there is an improvement inthe severity of Rheumatoid Arthritis. Hence, Vitamin D supplementation may help in reducing the severity of Early Rheumatoid Arthritis but the confounding effect of DMARDs is not considered.

Gaps in Literature

After careful study of the available literature about this field of study, the following gaps could be identified for which the topic is taken up for study.

1. The number of studies on the correlation between Vitamin D levels and Early Rheumatoid Arthritis severity is very few among the Indian population.
2. Most of the studies have been done on the deficiency of Vitamin D and Rheumatoid Arthritis severity, but the correlation with Early Rheumatoid Arthritis is not studied widely. There is also variability of results among these studies for the correlation of Vitamin D level and Rheumatoid Arthritis severity, hence it necessitates further studies. Including all the degrees of Rheumatoid Arthritis stages will reduce the sensitivity of the study.

Primary Objective

Estimation of Vitamin D levels among the patients of Early Rheumatoid Arthritis with varying severity and to find any possible correlation between Vitamin D levels and Early Rheumatoid Arthritis severity.

III. MATERIAL AND METHODS

Materials of study

1. Study Site

In-patient and Out-patient departments of Apollo Multispecialty Hospitals, Kolkata.

2. Study Design

A cross-sectional observational study.

3. Study Interventions

No specific intervention except follow-up of reports on an Outpatient basis and telephonic calls.

4. Study Duration

1-year duration from January 2021 to January 2022.

5. Study Population

All male and female patients with Early Rheumatoid Arthritis.

6. Sample Size

The number of patients recruited in the study was63.

The formula used to calculate the sample size was as follows,

$$n = \frac{z^2 pq}{d^2}$$

where n = sample size

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Volume 9, Issue 2 Mar-Apr 2024, pp: 1231-1239 www.ijprajournal.com ISSN: 2249-7781

z = the standard normal deviate, which is 1.96 at 95% confidence interval
p = prevalence in the population of the factor under study
Here we take p = .65% = 0.0065 (from previous study)
q = 1-p = 0.9935
d = Absolute precision

Hence, using the formula $=\frac{z^2pq}{d^2}$ = $\frac{(1.96)^2*0.0065*0.9935}{d^2(0.0004)}$, we getn > 62
Hence, we took at least 63 patients in our study.

(a) Inclusion Criteria
All male and female patients in both In-patient and Outpatient departments with Early Rheumatoid Arthritis.
(b) Exclusion Criteria
(i) Patients with osteoarthritis, gout, psoriatic arthritis, systemic lupus erythematosus, or any other inflammatory arthritis were excluded.
(ii) Patients on Vitamin D supplementation were excluded.

7. Clinical and Laboratory Investigations
All patients at both In-patient and Outpatient departments with Early Rheumatoid Arthritis wereinterviewed regarding personal details of the age of onset of symptoms, duration of symptoms, pattern and progression of joint involvement, presence of swelling severity of pain in the joints, and drug history. The laboratory investigations included complete blood counts, serum creatinine, ESR, CRP, uric acid, Rheumatoid Factor, Anti CCP, and Vitamin D (measured via chemiluminescence immunoassay estimating 25(OH) Vitamin D level). X-rays of the hand, elbow joint, shoulder joint, knee joint, and foot were done. All the investigations done in the study were according to the normal basic work-up for any patient of Early Rheumatoid Arthritis, no special investigation was done.

Method of Measurement
Disease activity score of 28 joints according to the guidelines of the American College of Rheumatology.
Calculation of the DAS28 score was done by following measures:
1. Counting the number of swollen joints (out of 28)
2. Counting the number of tender joints (out of 28)
3. Taking blood to measure the erythrocyte sedimentation rate (ESR)
4. Asking the patient to make a "global assessment of health" (indicated by marking on a 10-point line between very good and very bad).

These results were incorporated into a mathematical formula to produce the overall disease activity score,
DAS28 = 0.56√(28TJC) + 0.28√(28SJC) + 0.70 Ln (ESR) + 0.014VAS
(Here TJC = Tender joint count, SJC = Swollen joint count, Ln = log, VAS = Visual analog scale)
Disease severity was assessed according to the value of the DAS28 score as follows,
- Remission: DAS28 ≤2.6
- Low disease activity: 2.6 <DAS28 ≤3.2
- Moderate disease Activity: 3.2 <DAS28 ≤5.1
- High disease Activity: DAS28 >5.1

The 28 joints that are included in the DAS28 score are- proximal interphalangeal joints, metacarpophalangeal joints, wrist joints, elbow joints, shoulder joints, and knee jointson both sides.

Statistical Methods
Collected data wasanalyzed by the following statistical method:
Continuous variables were expressed as Mean ± Standard Deviation or Median (Min–Max) and categorical variables were expressed as the Number of patients and percentage of patients.
Pearson's Chi-Square test for Independence of Attributes/ Fisher's Exact Test was used to find the association between the categorical variables as appropriate.
To find the association between two continuous variables we used Pearson's correlation coefficient or Spearman's correlation coefficient as appropriate (if required).
The p-value of <0.05 was considered statistically significant.

Ethical Considerations
An application was made to the institutional ethics committee to allow data to be collected from individual patients. The data was collected anonymously from the hospital database and was processed anonymously.
The collected data included anonymous interviews of the patient regarding personal details

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 1231-1239 www.ijprajournal.com ISSN: 2249-7781

of age of onset of symptoms, duration of symptoms, pattern, and progression of joint involvement, presence of swelling and severity of pain in the joints, and drug history. The laboratory investigations included complete blood counts, serum creatinine, ESR, CRP, uric acid, Rheumatoid Factor, Anti CCP, and Vitamin D (measured via chemiluminescence immunoassay estimating 25(OH) Vitamin D level). X-rays of the hand, elbow joint, shoulder joint, knee joint, and foot were done. All the investigations done in the study were according to the normal basic work-up for any patient to establish the diagnosis of Early Rheumatoid Arthritis and to prognosticate.

Patients were not subjected to any other special investigations or procedures as a part of the study which was mentioned as a part and parcel of the informed consent provided to the patient.

IV. RESULTS

From the study, it was found that out of a total of 63 patients, 21 patients (33.33%) were from the 41-50 years of age group with a mean age of 47.9206 years.

81% percent of patients (51) were female and 19% of patients (12) were male with a ratio of 4.25.

6 patients (9.52%) presented between 0 to 3 months of disease onset, 28 patients (44.44%) presented to the clinic between 4 to 6 months of disease onset, 22 patients (34.92%) presented between 7 to 9 months of disease onset and 7 patients (11.11%) presented between 10 to 12 months of disease onset.

The minimum number of tender joints was 4 and the maximum was 16 with a median of 8joints. The minimum number of swollen joints was 0 and the maximum was 14 with a median of 5 joints. The pain described by the patient in the visual analog scale was a minimum of 2 points and a maximum of 10 points with a median of 6.

ESR was found to be raised in 57 patients (90.48%) and normal in 6 patients (9.52%). CRP was found to be raised in 49 patients (77.78%) and normal in 14 patients (22.22%).

RA Factor and Anti CCP were positive in 47 patients (74.6%) and negative in 16 patients (25.4%).

DAS28 score showed 17 patients (26.98%) in the moderate disease activity group and 46 patients (73.02%) in the high disease activity group with a median score of 5.4.It had a positive correlation with the inflammatory marker of ESR.

33 patients (52.39%) had Vitamin D deficiency, 23 patients (36.5%) had Vitamin D insufficiency and 7 patients (11.11%) had normal Vitamin D levels with a median of 19 ng/ml.

After proper analysis of the collected data, we matched the components of the DAS 28 score with Vitamin D levels and arrived to the conclusion of there is no significant correlation between DAS 28 score with Vitamin D levels as the p-value was more than 0.05 for all of them.

V. DISCUSSION

The onset of Rheumatoid Arthritis is related to menopause and hormonal changes as described by Wong et al [42].

The sex ratio of patients was slightly higher than the previously documented ratio of 3 as described by Favalli et al [43].

As per a study by Gomes et al [44] in Brazil, the mean duration of disease of rheumatoid arthritis diagnosis was 28 months with diagnoses up to 3 and 12 months at 27.7% and 64.8%, respectively. Hence, the proportion of patients with Very Early Rheumatoid Arthritis i.e. disease duration of 0 to 3 months in our study was significantly lower than the previously documented data.

Significant joint involvement associated with uncontrolled pain was present in most of the patients at presentation.

Both ESR and CRP were found higher as compared to a previous study by Wolfe [45]. Hence, our study population is probably at a higher risk of developing multisystemic involvement and complications.

RA factor and Anti CCP both are predictors for progressive and erosive joint disease. So, we can predict that most of the patients we interviewed will probably have significant diseases if not treated adequately.

DAS 28 score was found to be 6 at presentation in Rheumatoid Arthritis patients done in South India by Kumar et al [46]. DAS 28 score indicates that most of the patients during presentation had high disease activity.

Vitamin D levels were lower than the observed Vitamin D levels in Rheumatoid Arthritis patients by Caen et al [47]. It has been previously discussed that the healthy Indian population is usually Vitamin D deficient. Hence, our finding of lower Vitamin D levels could be unrelated to Early Rheumatoid Arthritis.

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 1231-1239 www.ijprajournal.com ISSN: 2249-7781

Hence, there was no correlation found between the severity of early RA and Vitamin D levels in our study.

VI. CONCLUSION

Through this study, it was observed that most of the patients were female, and they had symptoms onset at peri-menopausal age with moderate to high disease activity. All patients were interviewed on their first visit to the clinic, naïve to any treatment- hence can be attributed to having moderate to high disease activity during the interview. Although most of the patients interviewed had sub-optimal Vitamin D levels, it has been elaborated in the review of literature that in the Indian population there is insufficiency/ deficiency of Vitamin D even in healthy individuals. We matched the number of tender joints, the number of swollen joints, the pain described by the patient in the visual analog scale, ESR, and DAS 28 score with Vitamin D levels and concluded that there was no correlation betweenthe number of tender joints, number of swollen joints, pain described by the patient in visual analog scale, ESR and DAS 28 score with Vitamin D levels.

Conflict of Interest
None
Funding
None
Ethical Clearance
IEC Ref: IEC/DNB/2020/11/25; Received on 30/11/2020.

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