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Exploring the Link Between Vitamin D Deficiency and Pain in Rheumatoid Arthritis: A Correlative Study

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ABSTRACT

Rheumatoid arthritis (RA) is an autoimmune disorder characterized by joint pain, stiffness, swelling, impaired joint function, and elevated levels of acute-phase reactants. Pain is a significant source of discomfort for RA patients. Vitamin D, known for its immunomodulatory effects, has shown potential efficacy in RA management, indicating its possible therapeutic benefits for these patients. This study aimed to assess the efficacy of vitamin D in mitigating the inflammatory response and subsequently alleviating pain in RA patients. The study involved 123 RA patients attending our tertiary care center. Participants were divided into two groups: one received vitamin D supplementation, while the other was given a placebo. Disease activity and Visual Analog Scale (VAS) scores were recorded at baseline and at 1-month and 3-month follow-ups. At baseline, vitamin D levels were inversely correlated with disease activity. In the vitamin D group, the mean VAS score did not decrease significantly from baseline at 3-month follow-up. Similarly, in the placebo group, the mean VAS score did not decrease significantly from baseline at 3-month follow-up. Vitamin D supplementation did not result in a statistically significant improvement in VAS scores, indicating the need for further research to evaluate the role of vitamin D in RA treatment.

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Key Words
Rheumatoid arthritis, vitamin D, pain, visual analog scale

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INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune condition characterized by pain, stiffness, swelling, joint dysfunction and elevated acute-phase reactants. It markedly diminishes individuals' quality of life, productivity and utilization of healthcare services. Pain is the most distressing symptom for RA patients[1-3], aggravating disability, psychological discomfort, and sleep disturbances. Notably, pain can contribute more significantly to functional impairment than structural joint damage[4-6]. Females are more frequently affected than males, with peak prevalence occurring between the ages of 50 and 60. Standard treatments for RA include Disease-Modifying Antirheumatic Drugs (DMARDs), Non-Steroidal Anti-Inflammatory Drugs, and Glucocorticoids. Contemporary therapies, such as biological agents, focus on mitigating inflammation rather than curing the disease, thereby enhancing both short-term and long-term treatment outcomes.

Vitamin D receptors (VDRs) are present in peripheral mononuclear blood cells, substantiating its immunomodulatory effects. Vitamin D reduces the activity of antigen-presenting cells, inhibits T-cell proliferation and decreases the production of T helper cell-1 cytokines such as IL-2, interferon-gamma, and tumor necrosis factor-alpha[7,8]. A deficiency in Vitamin D is linked to various connective tissue diseases, including systemic lupus erythematosus and RA[9-11].

The immunomodulatory properties of Vitamin D may be particularly beneficial for RA patients, suggesting a potential therapeutic role for Vitamin D in this population[12]. VDRs have been identified in several cell types, including macrophages, chondrocytes and synoviocytes within the synovial membrane where cartilage degradation occurs. Vitamin D deficiency is notably prevalent among RA patients[13,14]. Beyond its hormonal functions, Vitamin D has multiple properties such as immune system modulation, anti-inflammatory effects and antiproliferative actions, which can be harnessed in treating connective tissue disorders and arthropathies like RA[15]. This has prompted us to investigate the relationship between pain in RA and Vitamin D, as well as the therapeutic potential of Vitamin D in managing RA.

MATERIALS AND METHODS

This prospective, comparative study was conducted in a tertiary care center. A sample size of 120 was determined to be adequate, providing a 95% confidence interval and a 10% margin of error.

Participants aged 18-75 years with a diagnosis of RA based on the 2019 American Academy of Family Physicians criteria were included. Individuals with chronic conditions, including malnutrition, liver diseases and kidney diseases, were excluded from the study. Participants taking medications such as anticonvulsants, diuretics and thyroxin, which affect serum calcium and Vitamin D levels, were also excluded. Additionally, those with endocrine disorders, such as hyperparathyroidism, hyperthyroidism and diabetes mellitus, were not considered. Subjects who had taken Vitamin D, either orally or via injection, within the past six months were excluded. Finally, individuals younger than 18 or older than 75 years of age were not eligible for participation.

Eligible subjects were recruited from the Outpatient Department. Participants were randomly divided into two groups using an odd-even system. Group I, consisting of 60 RA patients, received Vitamin D supplementation (60,000 IU weekly) along with DMARDs. Group II, also consisting of 60 RA patients, received a placebo in addition to DMARDs.

Demographic information (name, age, sex, address, occupation), age at symptom onset, illness course, joint involvement patterns, joint swelling and discomfort and medication history were recorded. Disease severity was assessed using the Disease Activity Score of 28 joints (DAS28) as per American College of Rheumatology guidelines. VAS scores were recorded at baseline and at 1-month and 3-month follow-ups. VAS scores were then compared between the Vitamin D supplemented group and the placebo group.

Data were entered into an MS Excel spreadsheet and analyzed using SPSS version 20. Frequencies and percentages were used to describe ordinal or nominal data. Means, standard deviations and ranges were used to describe continuous data. The Student t-test was used to compare the two groups, with a $P<0.05$ considered statistically significant.

RESULTS AND DISCUSSIONS

Table 1 presents the age and gender distribution of the study population. The mean age of participants in Group I was 52.24±11.36 years, with a gender distribution of 16.67% males and 83.33% females. Group II had a slightly younger mean age of 48.87±9.95 years, with a gender distribution of 18.33% males and 81.67% females. Each group consisted of 60 participants.

Table 2 provides data on serum vitamin D levels and Visual Analog Scale (VAS) scores at presentation and follow-up for Group I. Participants in the remission category had a mean vitamin D level of 34.09 ng/ml and demonstrated significant improvement in pain scores, with VAS scores decreasing from 2 at day 0 to 1 at 3 months. In the low vitamin D category, individuals had a mean level of 31.16 ng/ml and experienced a slight reduction in pain scores from 1.76 at day 0-1.40 at 3 months. Those in the moderate vitamin D category had a mean level of 22.04 ng/ml and showed a gradual decrease in VAS scores from

Table 1: Age and Gender distribution of study population

Group	Age	Male		Female		Total	
	Mean ± SD	n	%	n	%	n	%
Group I	52.24 ± 11.36	10	16.67	50	83.33	60	100
Group II	48.87 ± 9.95	11	18.33	49	81.67	60	100

Table 2: Vitamin D levels and VAS scores at presentation and follow up in Group I

Category	n	S. Vitamin D (ng/ml)	VAS score (day 0)	VAS score (1 month)	VAS score (3 months)
Remission	1	34.09 ± 0	2 ± 0	2 ± 0	1 ± 0
Low	4	31.16 ± 1	1.76 ± 1.15	1.76 ± 1.15	1.40 ± 0.58
Moderate	26	22.04 ± 2	2.24 ± 1.2	2.05 ± 0.92	1.84 ± 0.83
High	29	17.41 ± 8	4.56 ± 1.43	3.69 ± 1.12	2.76 ± 1.1

Table 3: Vitamin D levels and VAS scores at presentation and follow up in Group II

Category	n	S. Vitamin D (ng/ml)	VAS score (day 0)	VAS score (1 month)	VAS score (3 months)
Remission	2	28.57 ± 1.67	2.38 ± 0.71	1.90 ± 0	0.95 ± 0
Low	4	31.24 ± 3.59	3.24 ± 0.5	2.37 ± 0.5	2.05 ± 2
Moderate	20	24.15 ± 2.83	4.09 ± 1.89	3.15 ± 1.42	2.13 ± 2.13±0
High	22	16.30 ± 2.77	4.62 ± 1.75	3.80 ± 1.41	3.20 ± 3.20±1

2.24 at day 0-1.84 at 3 months. Participants with high vitamin D levels, with a mean of 17.41 ng/ml, had the highest initial VAS scores of 4.56, which decreased to 2.76 at 3 months.

Table 3 shows similar data for Group II. Individuals in the remission category had a mean vitamin D level of 28.57 ng/ml and reported a decrease in VAS scores from 2.38 at day 0-0.95 at 3 months. The low vitamin D category had a mean level of 31.24 ng/ml, with VAS scores decreasing from 3.24 at day 0-2.05 at 3 months. For those in the moderate vitamin D category, the mean serum level was 24.15 ng/ml, with initial VAS scores of 4.09 reducing to 2.13 over 3 months. In the high vitamin D category, the mean serum level was 16.30 ng/ml, with VAS scores decreasing from 4.62 at day 0 to 3.20 at 3 months.

Overall, the data suggest a correlation between higher vitamin D levels and lower pain scores across both groups, with improvements observed over the follow-up period. Group I exhibited a more pronounced reduction in pain scores compared to Group II, however it was not statistically significant ($P>0.05$).

Chronic synovitis, systemic inflammation, and autoantibody production are characteristic features of RA[16]. The development of RA is influenced by both genetic and environmental factors[17,18]. Patients with RA often use various medications, including steroids, which can impact Vitamin D metabolism. Monitoring Vitamin D levels is crucial for effective pain management in RA patients. Although Vitamin D's lipid-soluble properties have been well documented[19], recent research has revealed its extensive role in modulating the immune system[20] and its potential link to RA pathogenesis[21].

Lee and Bae's meta-analysis reported an inverse correlation between Vitamin D levels and RA disease activity, a finding consistent with our study, which also identified a negative correlation between disease activity and serum Vitamin D levels[22]. Prior research has highlighted the anti-inflammatory properties of active Vitamin D, suggesting its potential as a therapeutic biomarker for monitoring RA progression and treatment efficacy[23]. In our study, RA patients receiving concurrent Vitamin D supplementation showed improved Visual Analog Scale (VAS) scores, reduced disease activity (as measured by DAS 28) and decreased total joint count and swollen joint count. However, the improvement in VAS scores was not statistically significant compared to the study by Guan *et al.,* which reported a significant reduction in VAS scores with Vitamin D doses >50,000 IU over >12 weeks. Some experimental studies have demonstrated Vitamin D's analgesic effects in RA patients[24], though Salesi and Farajzadegan found no association between serum Vitamin D levels and markers like ESR, VAS, swollen joints count, or tender joints count, despite improvements in these parameters with Vitamin D administration[25]. In our study, although both groups experienced VAS score improvements, the difference was not statistically significant. This lack of significant effect may be attributed to the small sample size and the relatively short duration (3 months) of Vitamin D supplementation in our study. Previous research has indicated that higher doses of Vitamin D (100,000 IU) and longer supplementation durations (6 months to 1 year) can lead to statistically significant improvements in VAS scores compared to placebo groups[26].

The strengths of our study include its placebo-controlled, double-blinded design and its demonstration of the inverse relationship between serum Vitamin D levels and RA disease activity, highlighting the prevalence of low Vitamin D levels among RA patients. However, the study is limited by its small sample size and single-center design and longer follow-up is necessary. Future research should involve larger sample sizes and higher doses of Vitamin D over extended periods.

CONCLUSION

In comparison to the control group, the subjects who were administered Vitamin D supplementation

did not exhibit a statistically significant improvement in their Visual Analog Scale (VAS) scores, which are commonly used to quantify pain intensity. This lack of significant change suggests that Vitamin D supplementation may not effectively alleviate pain symptoms as measured by the VAS in the studied population. Consequently, this finding underscores the necessity for further rigorous research to explore the potential therapeutic effects of Vitamin D in pain management, taking into consideration variables such as dosage, duration of supplementation, baseline Vitamin D levels and the specific characteristics of the study population. This additional research is critical to ascertain whether there might be subgroups of patients who could benefit from Vitamin D supplementation or if alternative therapeutic strategies should be considered.

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