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Dear Dr. Dibyendu Mukherjee, Dr. Suman Naiya,
Dr. Suvajit Chakraborty, Dr. Rahul D. Chakrabarty,
Dr. Sucharita Patra,

We have reached a decision regarding your submission to International Journal of Advances in Medicine, "Adherence to methotrexate therapy among
rheumatoid arthritis patients in Eastern India".

Our decision is to: Accept

Your article will be published in Volume 7, Issue 6 of International Journal of Advances in Medicine, in June 2020. You will receive proofs of your article in due course.

I would like to remind that you could send your future manuscripts to International Journal of Advances in Medicine.

Sincerely,

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**Original Research Article**

# Prescription audit of rheumatoid arthritis patients treated at primary and secondary care level, before reaching a tertiary care centre hospital in Eastern India

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## ABSTRACT

**Background:** To analyse the usage pattern of pharmacological agents in the treatment of rheumatoid arthritis in Eastern India at a community level before reaching a specialized rheumatology clinic.
**Methods:** Total 200 patients earlier diagnosed to be RA on treatment were selected and their demographic details, duration of treatment, agents prescribed, adverse drug reactions (ADRs) were analysed.
**Results:** At the end of the study analysis, we observed that HCQ (24.4%) and Sulphasalazine (20.9%) were the commonest disease modifying anti-rheumatoid drug (csDMARD) used, followed by Methotrexate (16.9%). Dual combination csDMARD (33.1%) was preferred. Biological therapy was a rarity (0.5%). Steroids (21.0%) and NSAIDs (22.5%) was commonly used. Complementary and Alternative Medicines (CAM) (44.0%) was used often. Polypharmacy was the trend. Not all patients diagnosed as RA met the 2010 ACR/EULAR classification criteria of RA.
**Conclusions:** In 15% patients, the diagnosis of RA was inappropriate according to the recent classification criteria. csDMARD was preferred either as monotherapy or combination therapy. Use of steroids and NSAID was a common practice. ADR were mild in severity.

**Keywords:** Prescription audit, Rheumatoid arthritis

## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic illness in which immunologically mediated inflammation of synovia-lined joints can result in marked disruption of joint structure and function.[1] It involves flares and remissions, flares being characterised by pain.[2] Uncontrolled RA is associated with joint deformity and significant health care related expenses.[3] The prevalence of RA in adult population in India is approximately 0.75%.[4]

Lack of adequate manpower and training facilities, staggering costs of therapy and unique problems like burden of infectious diseases, challenges adequate management of rheumatic diseases in this country.[5] In India, like many other developing countries, the diagnosis and management of most RA patients are primarily done by family physicians, orthopaedic specialists and practitioners of alternative medicines.



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This prescription audit was undertaken to assess the demographic profile of RA in this part of the country, the current treatment pattern of RA in the community as rendered by primary and/or secondary physicians and other practitioners of alternative medicine and also to assess whether the diagnosis of RA are in accordance to the 2010 ACR/EULAR classification criteria.[13]

The current standard therapy for RA is disease-modifying anti rheumatic drugs (DMARD) therapy along with anti-inflammatory therapy using non-steroidal anti-inflammatory drugs (NSAIDs).[6] The 2012 American College of Rheumatology guidelines for the treatment of RA advocates early initiation and aggressive use of DMARDs in patients with RA.[7] The use of csDMARDs and other drugs for RA are associated with a number of adverse drug reactions (ADRs). Of major concern, is the cost of therapy of such chronic diseases like RA. Newer agents like biological disease-modifying anti rheumatic drugs that provide rapid relief of symptoms of pain and disability in RA have been approved. However, such therapies have prohibitive costs that curtails widespread usage, and hence affects treatment outcomes.[8]

Complementary and alternative medicine (CAM) is frequently used by patients with RA both in western countries as well as in developing countries such as India.[9] In addition, the ADRs and drug-drug interactions with CAM and the mainstream medicines remain largely unknown.[9] The ADR associated with these regimes, as reflected in the prescriptions studied, were also taken into consideration.

## METHODS

The prescription audit was conducted in the rheumatology clinic at KPC Medical College and Hospital for a period of 6 months from April 2019 to October 2019, after approval from the Institute's Ethical Committee.

Diagnosed RA patients attending the rheumatology clinic for the first time were enrolled. Participation was voluntary. A total of 200 patients were enrolled in the audit as per the inclusion criteria after taking written and verbal consent.

### *Inclusion criteria*

- Diagnosed adult patients of RA of either sexes
- Treated for at least 6 months by primary and secondary care givers and carrying all their prescriptions
- Never before treated by specialist in rheumatology practice
- Willing to participate in the audit after giving written consent

### *Exclusion criteria*

- Patients having associated psychiatric ailments
- Patients requiring hospitalisation in last 6 months
- Patients having diabetes as a comorbidity
- Pregnancy
- Children below the age of 14 years

### *Study design*

Following details were recorded from each prescription: (1) patient's demographic profile, (2) details about the disease, (3) concomitant illnesses, (4) treatment details, (5) ADR as documented in the prescriptions

To study the prescription pattern, following prescribing indicators were used: (1) average number of drugs per encounter; (2) percentage of drugs with injectables prescribed; (3) percentage (%) of drugs prescribed from the WHO list of Essential Medicines, 2019.[10] Leflunomide, though not in the WHO list of Essential medicine, was taken into consideration as it is a standard csDMARD used in RA.

ADRs, as recorded in the prescriptions were noted using the Central Drugs Standard Control Organisation ADR performa.[11] Causality assessment for the ADRs was performed as per the WHO Collaborating Centre for International Drug Monitoring assessment Uppsala Monitoring Centre (WHO-UMC) Scale.[12,13]

ADRs were graded as mild, moderate, severe, and severe life-threatening as follows: (1) Mild - transient or mild discomfort; no limitation in activity; no medical intervention/therapy required. (2) Moderate - limitation in physical activity; some assistance may be needed for normal activity; no or minimal medical intervention/therapy required. (3) Severe - marked limitation in physical activity; some assistance usually required; medical intervention/therapy required, hospitalisation possible. (4) Severe life-threatening - extreme limitation in physical activity; significant assistance required; significant medical intervention/therapy required, hospitalisation necessary. The usage of CAM was assessed. Patients were asked about the type and duration of CAM usage as this is usually not recorded in the prescription.

## RESULTS

A total of 200 previously diagnosed RA patients with their previous medical documents, meeting the inclusion and exclusion criterion, were included in the audit. Of them, 161 (80.5%) patients were females and 39 (19.5%) were males. The mean age of the female and male subjects was 31.7 and 46.5 years respectively (Table 1).



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**Table 1: Demographic details.**

| No of patients (n) | 200 |
|---|---|
| Male | n= 39 (19.5%) |
| Female | n=161 (80.5%) |
| Mean age male (Yrs) [n=39] | 46.5 |
| Mean age female (Yrs) [n=161] | 31.7 |

The median time interval from the diagnosis to the first contact with a specialist rheumatology clinic was found to be 5.11 years and 4.89 years in case of male and female subset respectively (Table 2).

**Table 2: Median time interval before attending a specialist clinic.**

| Male RA (n=39) | 5.11 yrs |
|---|---|
| Female RA (n=161) | 4.89 yrs |

**Table 3: Diagnosis meeting ACR/EULAF criteria.**

| Diagnosed before reaching rheumatology clinic | Diagnosis revised on reaching rheumatology clinic |
|---|---|
| Male (n=39) | n=28 (71.8%) |
| Female (n=161) | n=142 (87.6%) |

**Table 4: Analysis of prescriptions as per drugs prescribed.**

| | Male (n=39) | Female (n=161) |
|---|---|---|
| Average number of drugs prescribed for arthritis | 4.8 (±2.18) | 6.3 (±2.03) |
| Prescriptions containing injectables | 3 (7.7%) | 7 (4.3%) |
| Prescriptions containing Steroids | 11 (28%) | 31 (19.3%) |
| Prescriptions containing csDMARDs | 26 (66.7%) | 146 (90.7%) |
| Prescriptions containing NSAIDs | 14 (35.9%) | 31 (19.3%) |
| Prescriptions containing CAMs (other than Calcium) | 19 (48.7%) | 69 (42.8%) |
| Prescriptions containing bDMARDs (oral/injectables) | 0 (0.0%) | 1 (0.6%) |

**Table 5: Analysis of prescriptions as per starting of csDMARD.**

| | Male (n=39) | Female (n=161) |
|---|---|---|
| Prescriptions where csDMARD started by family physician | 11 (28.2%) | 79 (49.1%) |
| Prescriptions where csDMARD started by orthopedic specialist | 12 (30.7%) | 52 (32.3.1%) |
| Prescriptions where csDMARD started by RMP | 3 (7.7%) | 15 (9.3%) |

**Table 6: Disease-modifying anti rheumatic drugs (csDMARD) in prescriptions.**

| Monotherapy with csDMARDs | Number (% of individual drug amongst total csDMRDs use) |
|---|---|
| HCQ | 42 (24.4%) |
| Sulphasalazine | 36 (20.9%) |
| MTX | 29 (16.9%) |
| Leflunomide | 0 (0.0%) |
| **Dual Combination csDMARDs** | |
| MTX with HCQ | 18 (10.5%) |
| HCQ with Sulphasalazine | 17(9.9%) |
| MTX with Leflunomide | 3 (1.7%) |
| HCQ with Sulphasalazine | 19 (11.0%) |
| HCQ with Leflunomide | 1 (0.5%) |
| Sulphasalazine with Leflunomide | 0 (0.0%) |
| Triple or more Combination csDMARDs | 7 (4.0%) |

Of the 200 pre diagnosed RA patients included in the study only 71.8% males and 87.6% females fulfilled the diagnostic criteria of RA according to 2010 ACR/EULAR classification criteria (Table 3). The average number of drugs per prescription was 4.8 in males and 6.3 in females. Of all the drugs prescribed,



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csDMARDs, the mainstay of treatment in RA was 90.7% in females to 66.7% in males. NSAID was prescribed in 35.9% in males and 19.3% in females. Steroids was used in 28% of males and 19.3% of females. CAMs was prescribed in 48.7% and 42.9% of males and females in this study analysis. Oral biologics was prescribed only in 1 female patient. Injectable medication was given to 7.7% and 4.3% of male and female patients respectively. (Table 4).

The csDMARDs prescribed were started by Family physicians in 28.2% of males and 49.1% of females and by Orthopaedic specialist in 30.7% and 32.3% of males and females respectively. In only 7-9% of the patients these csDMARDs were started by Registered Medical Practitioners (RMPs) (Table 5).

**Table 7: Various combination therapy.**

| Various combination therapy | |
|---|---|
| csDMARD combination only | 25 |
| csDMARD + NSAID | 31 |
| csDMARD + steroid | 17 |
| csDMARD + NSAID + steroid | 28 |
| csDMARD + CAM | 24 |
| csDMARD + CAM + NSAID | 25 |
| csDMARD + CAM + NSAID + steroid | 4 |
| CAM + NSAID | 26 |
| CAM + steroid | 9 |
| NSAID + steroid | 16 |

In 62.2% of the patients csDMARD was started as a monotherapy (HCQ being the commonest with 24.4%, followed by Sulphasalazine (20.9%) and Methotrexate (16.9%). In 33.1% patients dual csDMARDs were given and 4% received triple combination of csDMARDs (Table 6). Leflunomide, though a recommended csDMARD, was not started as csDMARDs were used with and without other agents like steroids, NSAIDs or CAMs (Table 7).

**Table 8: Complementary and alternative medicine used by study patients.**

| System of medicine | No. of patient (%) | ADR |
|---|---|---|
| Ayurveda | 41 (20.5%) | Not known |
| Homeopathy | 37 (17.5%) | Not known |
| Unani | 6 (3.0%) | Not known |
| Combination | 4 (2.0%) | Not known |

In our study, we found CAMs was used in 88 patients in combination with csDMARD, steroids or NSAID (Table 6). Of the CAM users found in the study, 20.5% used Ayurveda, 17.5% used Homeopathy, 3% Unani and 2% combination (Table 8).

Adverse drug reactions (ADR) were noted in some patients with the commonest being nausea and vomiting in 22%. Mucositis, drug rash, bone marrow suppression though rare was found in 3%, 2.5% and 4.5% of cases respectively (Table 9). These were from the prescriptions during the first visit. None of the ADR were severe enough necessitating hospitalisation. In the audited prescription the offending drugs were discontinued in most cases. The casualty assessment as was done according to the WHO-UCM casualty assessment scale showed the ADR to be "Probable" in 3 patients, "Possible" in 11 patients and "Unlikely" in rest cases.

**Table 9: Adverse drug reactions and their incidence.**

| ADR | Incidence |
|---|---|
| Nausea, vomiting | 44 (22%) |
| Epigastric pain | 31 (15.5%) |
| Headache | 8 (4.0%) |
| Constipation | 9 (4.5%) |
| Diarrhoea | 11 (5.5%) |
| Deranged liver functions | 29 (14.9%) |
| Oral ulcer, mucositis | 6 (3.0%) |
| Skin rashes | 5 (2.5%) |
| Bone marrow suppression (minor or major) | 9 (4.5%) |

## DISCUSSION

The findings of the prescription audit conducted in our Tertiary Care Hospital, Kolkata, provide an insight into the primary and secondary level care rendered to RA patients in the community before being evaluated by specialist in a tertiary care rheumatology clinic. The demographic profile, prescription trend, and ADRs were also studied. Majority of the patients were middle aged females. RA is one of the many chronic inflammatory diseases that predominate in females.[3] The prevalence is about 2.5 times higher in females than males.[3] Our study also showed a considerable female predominance of RA (80.5%). Another study conducted by Mittal et al. in India reported more than 80% of the RA patients to be females, which is in agreement with our study.[14] The average number of drugs per prescription was found to be 4.8 in male and 6.3 in female, which is more than the WHO recommendations.[14] It has been recommended that the number of drugs prescribed per prescription should be two and that justification for prescribing more than two drugs would be required because of the increased risk of drug interactions.[15]

Of the pre-diagnosed cases of RA in our study group, only 71.8% of males and 87.6% of females fulfilled the diagnostic criteria of RA according to the "2010 American College of Rheumatology/European League Against Rheumatism Classification Criteria for RA" at



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the time of initial presentation.[16] Earlier the 1987 ACR criteria for diagnosis of RA was followed, which was more stringent compared to the newer 2010 ACR/EULAR criteria.[17] This clearly shows that RA is over diagnosed in our cohort, though patient memory bias during the questonaire / interview based recall needs consideration.

In our audit HCQ (24.4%) was the commonest csDMARD used in the community followed by Sulphasalazine (20.9%), instead of methotrexate (16.9%) which is the csDMARD of the choice according to ACR and EULAR recommendations. ACR 2008 Task Force Panel (TFP) recommended Methotrexate as the first-line treatment in patients with active RA, unless contraindicated or not tolerated.[18] Leflunomide may be used as an alternative to methotrexate, although gastrointestinal adverse effects are more common. Sulfasalazine or hydroxychloroquine is recommended as monotherapy in patients with low disease activity or without poor prognostic features (e.g., seronegative, nonerosive RA).[19] These recommendations were often not followed in the prescriptions by the primary and secondary level caregivers.

Approximately 7% patients were on combination csDMARDs with 3 drugs and 33.6% on dual csDMRDs using permutation and combinations of MTX, sulfasalazine, and hydroxychloroquine. Various meta-analysis and recommendations shows that combination therapy with two or more csDMARDs is more effective than monotherapy, however, adverse effects may also be greater.[20] Yet in this study cohort monotherapy with csDMARD (62.2%) was widely used compared to combination csDMARDs.

In another Indian study by Sukhpreet et al it was found that combination of two csDMARDs was commonly prescribed and the study by Shini et al reported that majority of the patients were on single csDMARD.[21,22]

The variation in number of csDMARDs prescribed might be due to the varied severity of disease encountered in different communities. Leflunomide, though a recommended csDMARD after MTX, was not generally used in the study group patients.

The reason behind the underusage might be because of its ADR profile and lack of proper knowledge regarding the subsequent routine monitoring parameters at the primary and secondary care level. csDMARD was prescribed in 45% of cases by primary family physicians and 32% by orthopaedic specialists, compared to only 9% by RMPs, though csDMARDs/bDMARDs are the mainstay of treatment in RA patients according to all recommendations.[18] Delay in treat-to-target therapy with DMARDs in RA only increases joint destructions, mortality and long term mobility.[18]

Use of steroids (28%: 19.3%::M:F) and NSAID (35.9% : 19.3% :: M:F) was reported in these patients prior to attending the tertiary rheumatology clinic. Ideally, NSAIDs and corticosteroids are used only for short-term management.[23] Long term used of steroids and NSAID only increases the side-effects associated with these agents.[18,6,7] Usually with judicious use of csDMARDs the usage of NSAIDs and steroids can be minimised.[6]

Calcium and Vitamin D3 supplements and PPI were also present in a significant number of prescriptions. Though they are not as a part of the regular recommendations of ACR or EULAR guidelines, these agents were probably given to prevent ADRs such as epigastric pain or to manage steroid-associated osteoporosis. Folic acid was co-prescribed to prevent methotrexate associated toxicity.

ADRs were reported from a significant number of patients. However, majority of the ADRs were mild in nature and did not require any significant intervention. Overall the use of too many drugs in a prescription only leads to increased chance of drug-to-drug interaction, loss of efficacy, leading to non-compliance from the patient perspective.[16]

Biological agents (anti-TNF, anti-CD20, anti-T-cells, etc) approved for treatment of RA were neither prescribed nor administered to our study group of patients before they attended the tertiary rheumatology clinic.

Only one patient received oral JAK inhibitor Tofacitinib. The reason might be because of the high cost of biological therapy and lack of expertise regarding the use of these newer molecules by the treating physicians at the primary and secondary care level.

The usage of CAM was relatively low in the study population. However, no ADRs were recorded from the use of these agents as per the data obtained from screening the prescriptions. Nevertheless no one can be certain of their contribution to drug-to-drug interactions with the csDMRDs and other drugs used resulting in consequent ADRs.

The recent recommendations and guidelines for treatment on rheumatological diseases needs widespread circulation amongst the primary and secondary care givers and only then the RA patients in the community will be benefited at large.

## CONCLUSION

In this cohort of pre-diagnosed RA patients, not all fulfilled the classification criteria of RA. According to



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our prescription audit, significantly higher number of drugs per prescription was used. Treatment of RA was found to be primarily based on csDMARDs, though not prescribed to all patients of RA, ignoring the present recommendation. The concomitant use of multiple csDMARDs was prescribed, though monotherapy with csDMARD was more frequently used. MTX, the mostly recommended drug for RA, was not used in most patients. Use of steroids and NSAID though recommended only for short term use, was used on long term basis in our cohort of RA patients. ADRs reported were generally mild in nature. CAM usage was relatively low in the study population. Usage of biological agents for the treatment of RA was negligible.

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Original Article

# Effect of 1,25 dihydroxy vitamin D3 supplementation on pain relief in early rheumatoid arthritis

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## Abstract

**Background:** To assess effect of 1,25 dihydroxy vitamin D3 supplementation on pain relief in early rheumatoid arthritis (RA). **Materials and Methods:** An open-labeled randomized trial was conducted comparing 60,000 IU 1,25 dihydroxy vitamin D3 + calcium (1000 mg/day) combination [Group A] versus calcium (1000 mg/day) only [Group B], as supplement to existing treatment regimen in early RA. Primary outcome included (i) minimum time required for onset of pain relief (Tm) assessed through patients' visual analog scale (VAS); (ii) % change in VAS score from onset of pain relief to end of 8 weeks. Secondary outcome included change in disease activity score (DAS-28). **Results:** At the end of 8-weeks, Group A reported 50% higher median pain relief scores (80% vs. 30%; $P < 0.001$) and DAS-28 scores ($2.9 \pm 0.6$ vs. $3.1 \pm 0.4$; $P = 0.012$) compared to Group B; however, Tm remained comparable ($19 \pm 2$ vs. $20 \pm 2$ days; $P = 0.419$). Occurrence of hypovitaminosis-D was lower (23.3%) compared to Indian prevalence rates and was a risk factor for developing active disease (Odds Ratio (OR) = 7.52 [95% Confidence Interval (CI) 2.67–21.16], $P < 0.0001$). Vitamin D deficiency was significantly ($P < 0.001$) more common in female gender, active disease, and shorter mean disease duration. Vitamin D levels were inversely correlated to disease activity as assessed by DAS-28 ($r = -0.604$; $P < 0.001$). **Conclusions:** Vitamin-D deficiency is a risk factor for developing active disease in RA. Weekly supplementation of 60,000 IU of 1,25 dihydroxy vitamin D3 in early RA results in greater pain relief. The number needed to treat for this additional pain relief was 2. **Identifier:** CTRI/2018/01/011532 (www.ctri.nic.in).

**Keywords:** 1,25 dihydroxy vitamin D3, early rheumatoid arthritis, pain relief, visual analogue scale

## Introduction

Rheumatoid arthritis (RA) is an autoimmune, inflammatory disease of unknown etiology.[1] It involves flares and remissions, flares being characterized by pain.[2] Both T-cell and B-cell lymphocytes have been implicated in such disease pathogenesis;[3,4] however, preliminary data suggest that RA associated diffuse musculoskeletal pain could be linked to vitamin D deficiency.[5]

Vitamin D is synthesized in the skin by the action of ultraviolet irradiation.[6] It has extraskeletal effects and immunomodulatory actions.[7-9] It decreases the production of inflammatory mediators like Interferon-Y (IFN-Y), Interleukin-2 (IL-2) and Interleukin-5 (IL-5) in Helper-T cells (Th-1) cells and increases the production of Interleukin-4 (IL-4) by Th-2 cells resulting in immunosuppressive action. Several studies have indicated the status of vitamin D deficiency as a risk factor in RA.[10-14] Vitamin D deficiency is also implicated in autoimmune conditions, such as diabetes mellitus type-1, multiple sclerosis, etc.[11]

The current standard therapy for RA is disease-modifying antirheumatic drug (DMARD) therapy along with anti-inflammatory therapy using non-steroidal anti-inflammatory drugs (NSAIDs).[15] Since symptomatic pain relief is a strong determinant of treatment compliance, several new biological agents that provide rapid relief of symptoms of pain and disability in RA have been approved.

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## Results

Figure 1 depicts the study progress. There were no drop-outs and complete data from all subjects was available for analysis. No major adverse events were recorded. In most cases, events like gastrointestinal upset, dermal rashes (e.g., with methotrexate therapy) were therapeutically managed with satisfactory outcomes.

Baseline demographic characteristics of study population have been described in Table 1. Both groups had well-matched baseline and demographic characteristics. Female representation was higher in both groups. Group A (vitamin D3 + calcium) reported significantly better scores in TJC, VAS, and DAS-28, Table 1. Improvement in disease activity for group B remained nonsignificant.

Occurrence of hypovitaminosis-D was lower (23.3%) compared to Indian prevalence rates and was found to be a risk factor for developing active disease (OR = 7.52 [95% CI 2.67–21.16], $P < 0.0001$). Normal reference level of 25-hydroxy vitamin D was taken as 20 ng/mL, which marks the threshold below which parathyroid hormone (PTH) rises to compensate for the deficiency.

Table 2 depicts comparative outcome assessment between two treatment groups. At the end of 8-weeks, Group A reported 50% higher median pain relief scores (80% vs. 30%; $P < 0.001$) and DAS-28 scores (2.9 ± 0.6 vs. 3.1 ± 0.4; $P = 0.012$) compared to Group B; however, Tm remained comparable (19 ± 2 vs. 20 ± 2 days; $P = 0.419$). Number needed to treat (NNT) to achieve the additional 50% pain relief at the end of 8 weeks was 2 (NNT = 100/50% = 2).

Table 3 depicts association analysis between subject characteristics and vitamin D status (normal versus low). Subjects with low vitamin D levels (23.3%) had significantly lower values (14.17 ± 3.27 ng/mL). Majority (94.3%) cases with low vitamin D levels were females with a mean age of 40.7 ± 12.8 years. Mean Body mass-index (BMI) was comparable in both groups. History of smoking was positive in nearly 13% cases in both groups.

With regard to disease status, mean DAS score at baseline in subjects with low vitamin D levels was significantly higher at 3.6 ± 0.01. Assuming DAS-28 >3.2 in case of active disease, 74.28% ($n = 26$) cases were diagnosed having active disease compared to 29.62% ($n = 24$) cases with normal vitamin D levels. Mean disease duration in vitamin D deficient population was significantly lower (4.7 ± 0.9 months).

Put together, vitamin D levels were lower in the setting of female gender ($P < 0.001$), higher disease activity ($P < 0.001$) and shorter mean disease duration ($P < 0.001$). The vitamin D levels were inversely correlated with disease activity assessed by DAS-28 ($r = -0.604$; $P < 0.001$).

## Discussion

Preliminary data indicate that vitamin D deficiency is associated with clinical activity in RA. Hence, quantification of serum 25 (OH) vitamin D, consequently, vitamin D supplementation could possibly alleviate some symptoms in RA. Such findings should be an area of concern for primary care physicians. Being first point of contact in healthcare, they must include testing for patient vitamin D status in the

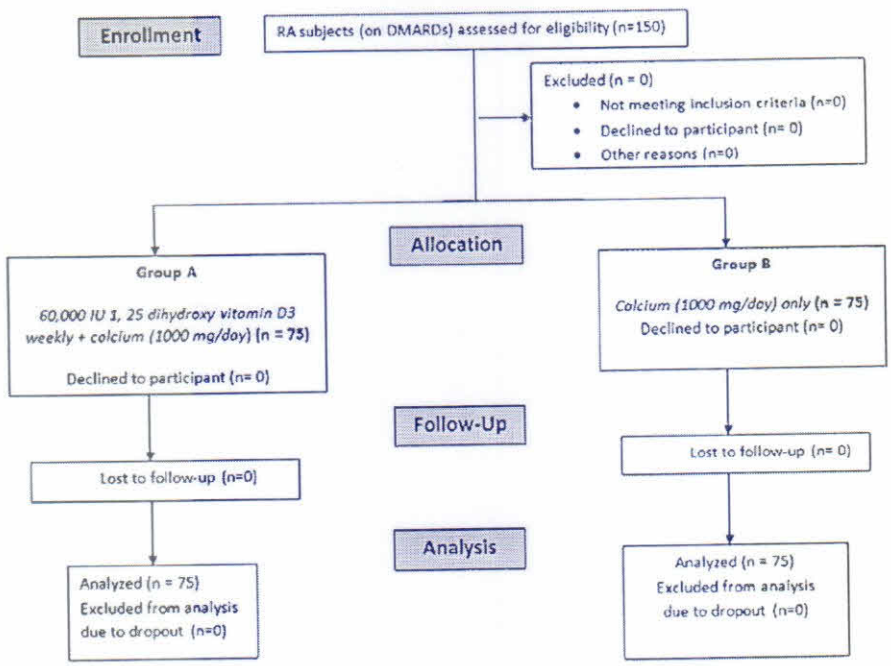


**Figure 1:** Adapted *CONSORT* flow-diagram showing study outline



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However, such therapies have prohibitive costs that curtails widespread usage, and hence treatment outcomes.[16]

Of late, many clinicians recommend 1,25 dihydroxy vitamin D3 supplementation along with calcium supplementation in RA, mainly due to its positive role in RA-associated osteoporosis and suppression of autoimmunity. In fact murine models have shown that experimental arthritis can be prevented by administration of 1,25 dihydroxy vitamin D3.[17] However, preliminary clinical data on role of supplementation of 1,25 dihydroxy vitamin D3 in early RA is inconclusive.[12,18] To this effect, the current study was designed to assess the effect of 1,25 dihydroxy vitamin D3 supplementation on pain relief in the setting of early RA.

## Materials and Methods

### Ethics

The study was conducted in accordance with the Helsinki II declaration and protocol was approved by the institutional ethics committee (IEC) at KPC Medical College and Hospital, Jadavpur, Kolkata, India (KPCMCH/IEC/829). It was registered under *www.ctri.nic.in* (REF/2018/01/017016). Written informed consent was obtained from all participants.

### Sample population

Treatment-naïve early RA (duration <2 years) subjects attending rheumatology clinic at KPC Medical College and Hospital from June 2016 to June 2017 were enrolled. Participation was voluntary.

Exclusion criteria included (i) patients who had been on steroids during the past year; (ii) known to have disorders of calcium metabolism, such as malabsorption, hyperparathyroidism, chronic renal failure, renal tubular acidosis or pancreatitis; (iii) known allergy to DMARDs, 1,25 dihydroxy vitamin D3 or calcium supplements; (iv) patients unlikely for follow-up during study period; (v) patients unable to afford triple DMARD therapy; (vi) patients suspected to have vasculitis; (vii) patients unable to mark the pain scale; (viii) calcium intake >2 g/day; (viii) Paget's disease; (ix) hyperthyroidism; (x) pregnancy; (xi) women 45–55 years old or within 5 years of menopause. Subjects currently on osteoporosis medication, estrogen, or a spine or hip T-score $\leq -3.0$ were also excluded.

### Sample size

A pilot questionnaire survey was conducted to estimate minimum time required for onset of pain relief (Tm). A total of 25 patients with RA who were initiated on 1, 25 dihydroxy vitamin D3 therapy within the past 6 months were surveyed in the clinic. The survey data indicated that most patients had varying amounts of pain relief scores ranging from 20% to 70%. Median [interquartile range (IQR)] Tm was 44 days (15–180 days).

Calculation of sample size was based on the data obtained from initial study. A difference of $\pm$ 14 days was anticipated for early pain relief in patients receiving vitamin D3 and calcium. Alpha error was kept at 5% and the power of the study was placed at 80%. The calculated sample size was 68 in each arm. A 10% drop-out rate was estimated; hence, 75 patients were included in each study arm. Subjects enrolled in the initial survey were excluded.

### Study design

The study was designed as 8-week, parallel, open-label, randomized trial. After initial protocol review by IEC, clinical screening was done for subject recruitment. Tender joint count (TJC), swollen joint count (SJC), biochemical, and relevant radiological investigations were undertaken. Disease activity markers like erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) were assessed and disease activity score (DAS-28) score was calculated.

Eligible patients ($n$ = 150) were then randomized using on-site computer-generated block randomization schedule in blocks of 4. Subjects were subsequently allocated in either of the following two groups (i) Group A ($n$ = 75) receiving 1, 25 Vitamin D3 60,000 IU once weekly along with calcium carbonate (1000 mg/day); (ii) Group B receiving only calcium carbonate (1000 mg/day). Both groups were well-matched for baseline and demographic characteristics. Subjects were also asked to apply sunscreen (with Sun Protection Factor 65) for entire study period to adjust for confounding factors.

### Outcome assessment

Primary outcome included (i) the minimum time (days) required for onset of pain relief (Tm); (ii) % change in visual analog scale (VAS)[19] score from onset of pain relief to end of 8-weeks. Secondary outcome included change in DAS-28.

Subjects had to mark pain as the percentage of pain on the VAS on recruitment and thereafter, every week for 8-week duration. Provision of sending VAS scores electronically to investigators was made to minimize loss to follow-up. The pain scale was standardized to 100% pain at study initiation. Secondary outcomes included changes in DAS-28 score.

## Data Management and Analysis

### Statistical analysis

An intention-to-treat protocol was followed. Subgroup comparisons were done with Student's independent sample $t$ test for numerical data. Repeated measure Analysis of Variance (rANOVA) with *post hoc* Dunnet test was done for intragroup analysis. Chi-square test with Yates correction was used for categorical variables. Pearson's correlation was used to assess any relation between DAS-28 scores and vitamin D levels. A $P$ value <0.05 was considered statistically significant for all measurements. All analyses were done using *GraphPad package* (2015 GraphPad Software, Inc, CA).



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outcome in RA, of which vitamin D deficiency is probably both a causation and a sign.

Our study depicts that additional pain relief as clinical benefit in early RA could be achieved by supplementing existing DMARD therapy with 1, 25 dihydroxy vitamin D3 at 60,000 IU/week (8,571 IU/day). Similar findings have been reported in two previous unblinded studies.[18,20] However, many studies have indicated the contrary, for instance, a previous open-label study[21] had demonstrated no additional clinical benefit in RA, while a double-blind, placebo-controlled study ($n = 117$)[22] detected no change in RA-related pain scores following 12-weeks of vitamin D supplementation.

Clinically and statistically significant NNT measure of 2 denotes that one needs to treat only two RA patients with 60,000 IU/week of vitamin D for 8 weeks, to give additional 50% pain relief over and above the benefit achieved by standard DMARD regimen. In many ways, economical evaluation of long-term therapy costs of DMARD or biological agents may justify such supplementations.

Interestingly, time to onset of pain relief was comparable in both groups and not affected by vitamin D therapy. The delayed appearance of effect of 1,25 dihydroxy vitamin D3 could be a potential reason of the initial time lag to initial pain relief. The difference in VAS scores substantiates such finding, since the difference in VAS scores was comparable at baseline unlike by the end of 8 weeks, where group A reported higher pain relief scores.

The normal requirement of 1,25 dihydroxy vitamin D3 in normal adults is 200 IU/day,[23] but some studies have used doses as high as 50,000 IU/day in vitamin D-deficient patients without causing any dose-related toxicity.[24] In the current study, a higher dose of 60,000 IU/day was associated with higher pain relief. No serious adverse event was recorded either. However, whether using higher doses of vitamin D3 in short-term setting can result in better outcomes is an area of intense exploration.

Prevalence of vitamin deficiency at 23.33% in the current study is lower in comparison to data from Indian population.[25] The study data also found a strong inverse correlation between 25 hydroxy vitamin D levels and RA disease activity, despite conflicting preliminary data.[26-29] However, recent studies among RA patients from India corroborate our findings, for instance in studies conducted by Sharma *et al.*[30] ($n = 80$), Meena *et al.*[31] ($n = 50$), and Borukar *et al.*[32] ($n = 42$), it was found that serum vitamin D levels were inversely correlated with DAS-28 scores.

With regard to vitamin D status and disease activity, our study data indicated that vitamin D levels were lower in subpopulation with shorter mean disease duration. This trend is consistent with previous data depicting lower serum value of 25(OH) vitamin D in early RA in comparison with the patients experiencing established disease.[33] Moreover, this indicates that in the setting of a strong inverse correlation between serum vitamin D level and DAS-28 score, vitamin D deficiency can trigger and initiate disease sequelae in autoimmune conditions like RA.

### Limitations

Despite having significant study findings, the key limitations which precluded the study included limited sample size, lack of placebo-control, and double-blinding. A single-dose arm rather than multiple-dose arm of 1,25 (OH) vitamin D3 was used as the study was designed to be a pilot study.

Hypovitaminosis-D was categorized according to Institute of Medicine[34] criteria of vitamin D repletion as 25(OH) vitamin D levels ≥20 ng/mL. Since most subjects (approximately 82%) had 25(OH) vitamin D levels >20 ng/mL at randomization, null findings in Group B (calcium only) might reflect vitamin D adequacy among many. Moreover, the fact that we studied vitamin D3 rather than vitamin D2 may implicate potential bias since vitamin D3 has a longer half-life, which might have prevented nadir levels during initial weeks, since insignificant changes in pain scores.

## Conclusion

Vitamin-D deficiency is a risk factor for developing active disease in RA. Weekly supplementation of 60,000 IU of 1,25 dihydroxy vitamin D3 in early RA results in greater pain relief. The number needed to treat for this additional pain relief was 2.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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**Table 1: Baseline characteristics of 150 study subjects with rheumatoid arthritis**

| Variables | Group A (*n*=75) [Vitamin D3 + Calcium] | Group B (*n*=75) [Calcium] | *P* |
|---|---|---|---|
| Age (years) | | | |
| Range | 18-64 | 18-67 | 0.456 |
| Mean age±SD | 36.7±10.9 | 38.8±13.5 | |
| Median (IQR) | 36 (29-44) | 39 (29-53) | |
| Gender, *n* (%) | | | |
| Male | 10 (13.3) | 15 (20) | 0.27 |
| Female | 65 (86.6) | 60 (80) | |
| BMI (kg/m$^2$), mean±SD | 25.2±4.8 | 26.7±5.6 | 0.08 |
| Current or past smoker | 11 (14.6) | 9 (12) | 0.63 |
| Disease duration (months), mean±SD | 7.2±4.2 | 7.6±3.8 | 0.54 |
| Disease activity, *n* (%) | | | |
| High | 3 (4) | 2 (2.6) | > 0.99 |
| Moderate | 66 (88) | 68 (90.6) | |
| Low | 6 (8) | 5 (6.6) | |
| Remission | 0 (0) | 0 (0) | |
| Disease status | | | |
| TJC (Range) | 0-1 | 0-2 | 0.10 |
| SJC (Range) | 0-3 | 0-3 | 0.13 |
| ESR (mm/1st hr); mean±SD | 26±6.3 | 27.9±8 | 0.85 |
| CRP (mg/dL); mean±SD | 5.7±2.2 | 5.2±1.8 | 0.22 |
| VAS score; mean±SD | 74.2±9.6 | 73.9±9.9 | 0.85 |
| DAS-28 score; mean±SD | 3.5±0.4 | 3.9±2.8 | 0.44 |
| Comorbidities | | | |
| Hypertension | 30 (40) | 25 (33) | 0.95 |
| Type 2 diabetes | 15 (20) | 20 (27) | |
| Dyslipidemia | 3 (4) | 2 (3) | |
| Lung disease | 3 (4) | 5 (7) | |
| Renal disease | 2 (3) | 3 (4) | |
| Anemia and hematological abnormality | 2 (3) | 2 (3) | |
| Ulcer and stomach disease | 19 (25) | 16 (21) | |
| Infectious disease | 1 (1) | 2 (3) | |

Group A: 60,000 IU 1, 25 dihydroxy vitamin D3 weekly + calcium (1000 mg/day); Group B: calcium (1000 mg/day), as supplement to existing DMARD regimen. SD: Standard deviation; IQR: Inter-quartile range; CRP: C-reactive protein; DAS-28: Disease activity score using 28-joints; ESR: Erythrocyte sedimentation rate; VAS: Visual analogue scale. Disease activity was assessed according to the value of DAS28 score as follows: Remission: DAS28 ≤2.6, Low disease activity: 2.6 <DAS28 ≤3.2, Moderate disease Activity: 3.2 <DAS-28 ≤5.1, High disease Activity: DAS28 >5.1

**Table 2: Comparison between study arms in relation to primary outcome measures**

| Variable | Group A [Vitamin D3 + Calcium] | Group B [Calcium] | *P* |
|---|---|---|---|
| Time required for onset of pain relief (days), mean±SD | 19±2 | 20±2 | 0.419 |
| % Reduction in VAS score at the end of 8 weeks (range) | 80 (0-100) | 30 (0-100) | <0.001** |
| DAS-28 score at the end of 8 weeks | 2.9±0.6 | 3.1±0.4 | 0.012* |

Group A: 60,000 IU 1, 25 dihydroxy vitamin D3 weekly+calcium (1000 mg/day); Group B: calcium (1000 mg/day), as supplement to existing DMARD regimen. VAS: Visual Analogue Scale. *$P$≤0.05, **$P$≤0.001, statistically significant

**Table 3: Association analysis between subject characteristics and vitamin D status**

| Variables | Vitamin D normal[a] (*n*=115) | Vitamin D deficiency[b] (*n*=35) | *P* |
|---|---|---|---|
| Age (years), mean±SD | 36.8±9.43 | 40.7±12.8 | 0.160 |
| Female sex, *n* (%) | 65 (56.7) | 33 (94.3) | <0.001** |
| Smoking current/past, *n* (%) | 15 (13) | 5 (14.2) | 0.849 |
| BMI (kg/m$^2$), mean±SD | 26.9±5.2 | 26.4±5.7 | 0.854 |
| Vitamin D level (ng/mL), mean±SD | 32.73±4.88 | 14.17±3.27 | <0.001** |
| Disease duration (months), mean±SD | 8.2±1.7 | 4.7±0.9 | < 0.001** |
| Active disease, *n* (%) | 24 (29.62) | 26 (74.28) | <0.001** |
| DAS-28 score, mean±SD [range] | 3.3±0.06 [0-8.2] | 3.6±0.01 [1.1-7.3] | <0.001** |

[a]Vitamin D ≥20 ng/mL; [b]Vitamin D <20 ng/mL; SD: Standard deviation; IQR: Interquartile range; CRP: C-reactive protein; DAS-28: Disease activity score using 28-joints; ESR: Erythrocyte sedimentation rate; VAS: Visual analog scale. **$P$≤0.001, statistically significant

yearly physicals. Moreover, since vitamin D deficiency may be seen as part of unhealthy habits such as poor nutrition, alcohol abuse, smoking, lack of physical exercise, etc., there must be due regard to health education of patients. Social economic factors may be part of the deficiency as well, and the sum total of all these factors leads to a poorer disease



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# Demographic profile of Acute Pancreatitis in Eastern India: A Single Centre Experience

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## ABSTRACT

**Background:** Little is known about the etiological risk factors of acute pancreatitis (AP) in Eastern India. **Aims and Objective:** The aim of this study is to assess current trends in the etiology of AP in Eastern India. **Materials and Methods:** A retrospective study with cross-sectional design was undertaken. It was based on patient records admit between January 2014 and January 2017 with physician-assigned diagnoses of AP at KPC Medical College & Hospital, Kolkata (n = 234). Multivariate analyses were done to identify risk factors, and distribution was compared on the basis gender. Groups were selected on the basis of a working diagnosis. A stratified comparison was done in 3 commonest etiology groups identified: 'alcohol', 'non-alcohol' and 'idiopathic'. **Results:** The commonest etiologies were attributed to alcohol (29.4%), idiopathic cause (20.5%), and obstructive cause (14.5%). Prevalence of AP was higher with alcoholism in men (37% vs. 10.8%; $p<00.1$), however, idiopathic cause (12.3% vs. 37.8%), duct obstruction (1.2% vs. 43.2%), obesity (6.1% vs. 24.3%), and hypertriglyceridemia (6.1% vs. 14.8%) were higher among females ($p< 0.001$ for all comparisons). Compared to non-alcoholics, patients with idiopathic AP were more likely to be overweight ($p = 0.019$) and have T2 DM ($p = 0.021$). Impact assessment of T2 DM status further revealed that the risk of AP was even greater with obesity (Odds Ratio [OR] 1.37; 95% Confidence Interval [CI] 0.57 – 3.26; $p = 0.047$) and smoking (OR 1.72; 95% CI 1.0 – 2.97; $p = 0.049$). Eighteen cases (7.7%) of 'severe' AP were identified, mostly due to: trauma in 6 (2.5%), idiopathic in 6 (2.5%), gallstones in 4 (1.7%), and alcoholism in 2 (0.8%). **Conclusion:** Alcohol intake is the predominant etiological risk factor for acute pancreatitis in Eastern India. Gender and type 2 diabetes mellitus are important contributory determinants.

**Key words:** Acute pancreatitis, Risk factors, Diabetes Mellitus, Retrospective study, Cross-sectional study

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## BACKGROUND

Acute Pancreatitis (AP) is an inflammatory process due to autodigestion of the gland by pancreatic digestive enzymes, leading to impairment of function or any morphologic changes.[1] It can recurr intermittently, contributing to ongoing insult, referred to as 'Chronic Pancreatitis' (CP).[2] Severe AP (SAP) develops in about 25% of patients with AP. The average mortality rate in SAP approaches 2–10%.[3]

The incidence of AP is much higher in USA, Finland, and Scotland (49.3, 46.6 and 41.9 per 100,000 populations, respectively).[4] In 2009, it led to approximately 275,000 hospitalizations per year in the US.[5] Hospitalization rates due to AP are found to increase progressively with age.[6] For people aged 35-75 years, the rates double for males and quadruple for females.[7] Blacks are 3 times more risk of developing AP to whites.[8] However, little is known about the reasons for such racial disparity.

Conditions that can predispose to development of AP include: alcoholism, gallstones, abdominal surgery, certain medication re-exposures (didanosine, asparaginase, azathioprine, valproic acid, pentavalentantimonials,

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