Original Article

DOI: 10.7860/JCDR/2022/58232.16837

Efficacy of Vitamin D Supplementation among Newly Diagnosed Cases of Rheumatoid Arthritis Proposed to be Managed by Methotrexate Monotherapy: A Randomised Controlled Study

Orthopaedics Section

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ABSTRACT

Introduction: Methotrexate (MTX) has been the main drug that has been used worldwide for the treatment of Rheumatoid Arthritis (RA) either as a monotherapy or in combination with other Disease Modifying Antirheumatic Drugs (DMARD). Vitamin D deficiency has been shown to play an important role in the pathogenesis and progression of RA and its supplementation could have a promising role in management of RA.

Aim: To evaluate the efficacy of vitamin D supplementation among newly diagnosed of RA cases scheduled for MTX monotherapy.

Materials and Methods: This randomised controlled study was done at Era's Lucknow Medical College and Hospital, Lucknow, India from January 2016 to December 2017. A total of 100 newly diagnosed patients of RA were randomised to two groups: group A (n=50) received MTX monotherapy supplemented with 400 IU 25 Hydroxy [25(OH)] vitamin D twice a day (case group) whereas group B (n=50) received MTX monotherapy with placebo. Serum 25-Hydroxy vitamin D [S.25(OH)], American College of Rheumatology (ACR) score, Erythrocyte Sedimentation Rate (ESR) and Serum C-Reactive Protein (S.CRP) were assessed at enrollment, three months and six months. Data was analysed using Statistical Package for Social Sciences software (SPSS) version 21.0 software. Chi-square and Independent sample t-test were used to compare the data.

Results: Overall majority of patients were females 57% and 43% were males with mean age 40.98±8.83 years (range 26-60 years). At baseline, mean vitamin D levels were 22.94±12.41 and 25.54±12.79 ng/mL in groups A and B, respectively (p-value >0.305). Mean ACR scores at baseline, three months and six months were 7.06±0.77, 5.16±1.11 and 4.42±0.93, respectively in group A and 7.02±0.74, 5.78±0.98 and 5.11±1.11, respectively in group B. At final follow-up, mean reduction in ACR scores and S. CRP levels was significantly higher in group A as compared to that in group B (p-value <0.001). Simultaneously, there was a significantly higher increase in vitamin D levels in group A as compared to that in group B (p-value <0.001).

Conclusion: Vitamin D supplementation helped to potentiate the efficacy of MTX monotherapy in RA. Vitamin D deficiency causes diffuse musculoskeletal pain and its supplementation is needed for osteoporosis prevention.

Keywords: American college of rheumatology score, C-reactive protein, Erythrocyte sedimentation rate

INTRODUCTION

Rheumatoid arthritis (RA) is a common, chronic, inflammatory, autoimmune disease of unknown aetiology. Population studies show its prevalence at a point of time to be close to 0.56% [1]. The disease affects the synovium and progresses from inflammatory changes to cartilage and bone destruction [2]. It may subsequently end up causing systemic inflammation that may affect multiple organ systems too [3]. It is responsible for decline in the quality of life of patients, affects their work opportunities and carries a huge economic burden too [4]. MTX is one of the most common and most extensively used treatment modality for treatment of RA for more than three decades. Low-dose, weekly MTX (10 to 25 mg/wk.) is used as monotherapy or in combination with other drugs has a superior efficacy profile as defined in placebo controlled trials and comparable efficacy to other drugs including anti-TNF therapy [5].

Vitamin D deficiency has been shown to be correlated with the appearance of autoimmune diseases, such as diabetes mellitus type 1 and multiple sclerosis [6]. It has been shown that vitamin D, apart from regulating calcium and phosphorous metabolism, also plays an important role in regulation of immune and anti-inflammatory activities [7,8]. Role of vitamin D deficiency in pathogenesis, progression and severity of RA has also been potentiated in some studies [9-13]. Encouraged by this relationship, several workers have evaluated the role of vitamin D supplementation with MTX therapy in management of RA particularly newly diagnosed RA in both human as well as animal studies [14-16]. However, these studies produced equivocal results without providing any conclusive result. Hence, the present study was conducted to assess the role of vitamin D supplementation in patients of RA managed by MTX monotherapy. The null hypothesis being that 'Vitamin D supplementation has no effect on RA patients on MTX monotherapy'.

MATERIALS AND METHODS

This prospective randomised controlled study was carried out at Era's Medical College and Hospital, Lucknow, India for a period of two years from January 2016 to December 2017 after obtaining approval from Institutional Ethics Committee (No. ELMC/EC/2016/08). Informed consent was obtained from all the patients.

Inclusion criteria: Confirmed adult cases (aged 18-60 years) of newly diagnosed (within six months of diagnosis) RA (ACR Score >6/10) were included.

Exclusion criteria: Patients with conditions like hypercalcemia, hypercalciuria, calcium intake >2 g/day, nephrolithiasis, creatinine >2.0 mg/dL, Paget's disease, hyperthyroidism, pregnancy, and women of 45-55 years old or within five years of menopause and

those who were on osteoporosis medication, oestrogen or cases with spine or hip T-score <-3.0 were excluded.

Sample size calculation: It was based on a projected 10% mean difference in disease regression (in terms of CRP levels) with a pooled standard deviation (SD) of 15% between two study groups [17]. Sample size projections were done at 95% confidence and 80% power. The calculated sample size was 37 in each group and finally 50 number, was considered for each group.

Study Procedure

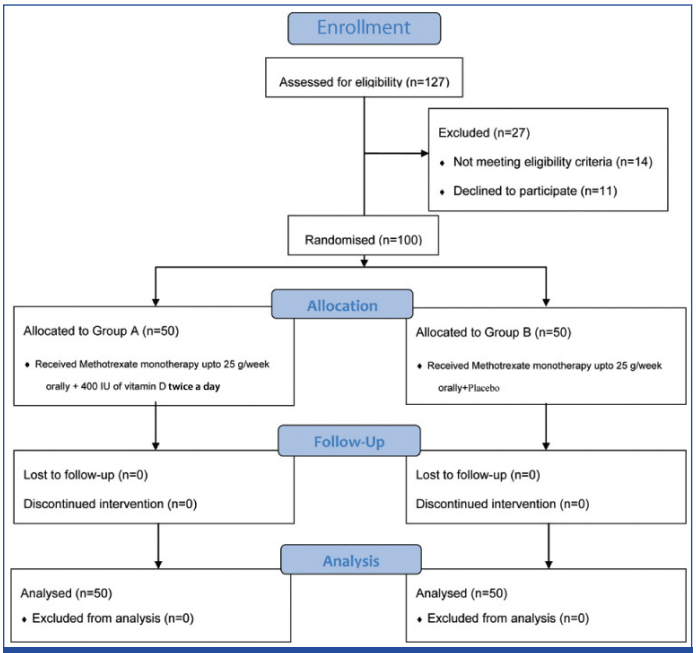
Demographic details (age and sex) of patients fulfilling the inclusion criteria were noted. Medical history was obtained and Dual Energy X-Ray Absorptiometry (DEXA) scan was performed for assessment of osteoporosis status [18]. Detailed history along with present and past history of fractures was taken and thorough examination was done. The patients were then assessed for eligibility and were asked for their willingness to participate in the study.

A total of 127 patients were screened for eligibility, 14 failed to meet the eligibility criteria, 11 declined to participate and two were excluded owing to other reasons (inability to come for follow-up). Finally, a total of 100 patients were included in the study and were randomised to one of the following two groups using computerised random number tables:

Group A (Cases group) (n=50): In this group, apart from usual treatment of MTX monotherapy upto 25 g/week orally upto six months, additionally the patients were given 400 IU of vitamin D twice a day for six months.

Group B (Placebo group) (n=50): In this group, apart from usual treatment of MTX monotherapy upto 25 g/week orally upto six months, additionally the patients were given colour and weight matched placebo.

At enrollment (baseline), routine haematological and biochemical assessments [Haemoglobin (Hb), Total Leucocyte Count (TLC), liver function and renal function]) were performed. Assessment according to ACR criteria and serum 25(OH) vitamin D assessment was done at enrollment (baseline), three months (mid-term assessment) and six months (final assessment) respectively [19]. All the patients completed the follow-up [Table/Fig-1]. At each follow-up, vitamin D assessments were done and all those patients achieving vitamin D levels >60 ng/mL at any time, were advised to stop the supplementation.



[Table/Fig-1]: CONSORT (Consolidated Standards of Reporting Trials) flow diagram.

STATISTICAL ANALYSIS

Data was analysed using SPSS version 21.0. Proportional data was compared using Chi-square test, whereas mean differences were compared using Student t-test. A p-value <0.001 was considered as statistically significant.

RESULTS

Age of patients ranged from 26 to 60 years. Mean age of group A was 41.46±8.89 years as compared to 41.94±9.01 years in group B. Overall majority of patients were females 57% and 43% were males. Proportion of females was slightly higher in group A (62%) as compared to that in group B (52%). Mean duration of illness was 3.38±1.19 months in group A and 3.18±1.25 months in group B. There was no statistically significant difference between the two groups with respect to age, sex and duration of illness (p-value >0.05). Mean haemoglobin levels were 10.96±1.61 and 10.76±1.78 g/dL, respectively in groups A and B while mean TLC levels were 6.77±1.70 and 7.12±1.95 thousands/mm^3, resepctively in group A and B. Statistically, there was no significant difference between two groups with respect to Hb levels and TLC (p-value >0.05). All the patients had blood sugar, liver function and renal function tests within normal range and there was no statistically significant difference between two groups with respect to any of these parameters (p-value >0.05) [Table/Fig-2].

Values in Mean±SD			
Parameters	**Group A (n=50)**	**Group B (n=50)**	**Statistical values**
Age (in years) (Mean±SD) (Range)	41.46±8.89 (26-60)	41.94±9.01 (29-58)	t=0.538; p=0.592
Male:Female	19:31	24:26	χ^2=1.020; p=0.313
Duration of illness (Mean±SD) (months)	3.38±1.19	3.18±1.25	t=0.822; p=0.413
Hb (g/dL)	10.96±1.61	10.76±1.78	t=0.590; p=0.557
TLC (×10^3)/cumm	6.77±1.70	7.12±1.95	t=-0.951; p=0.344
RBS (mg/dL)	110.40±31.41	111.62±26.28	t=-0.211; p=0.834
S.Bil. (mg/dL)	0.65±0.23	0.68±0.27	t=-0.551; p=0.583
SGPT (IU/L)	44.82±2.42	45.38±2.50	t=-1.138; p=0.258
SGOT (IU/L)	45.82±2.57	45.28±2.14	t=1.142; p=0.256
S.Creatinine (mg/dL)	0.67±0.14	0.70±0.13	t=-0.948; p=0.346
B.Urea (mg/dL)	28.74±5.52	29.64±5.44	t=-0.821; p=0.414

[Table/Fig-2]: Baseline Demographic, clinical and biochemical profile of patients in two study groups.
HB: Hearmoglobin; TLC: Total leucocyte count; RBS: Random blood sugar; S.Bil: Serum bilirubin; SGPT: Alanine transaminase; SGOT: Serum glutamic oxaloacetic transaminase; S.:Serum; B.: Blood

At baseline, mean ACR scores ranged from 6 to 9. Mean ACR scores were 7.06±0.77 and 7.02±0.74 in groups A and B respectively. Mean serum CRP, ESR and 25(OH) vitamin D levels were 7.91±1.28 mg/L, 27.30±6.05 mm/hr and 22.94±12.41 ng/mL respectively in group A and 7.55±1.81 mg/dL, 28.16±9.14 mm/hr and 25.54±12.79 ng/mL respectively in group B. Statistically, there was no significant difference between two groups with respect to any of these parameters (p-value >0.05) [Table/Fig-3]. At three and six months, patients in group A had significantly lower mean ACR, S. CRP and ESR levels as compared to that in group B (p-value <0.05) and significantly higher mean Serum 25(OH) vitamin D levels as compared to that in group B (p-value <0.001) [Table/Fig-3]. At final follow-up mean ACR, serum CRP, ESR and 25(OH) vitamin D levels were 4.42±0.93, 5.85±1.41 mg/L, 17.72±2.83 mm/hr and 38.60±10.75 ng/mL, respectively in group A and 5.14±1.11, 7.34±1.41 mg/L, 19.76±4.72 mm/hr and 24.80±12.36 ng/mL respectively in group B. Statistically, there was a highly significant difference (p-value <0.001) between two groups with respect to change in all these parameters [Table/Fig-3].

On final evaluation, mean reduction in ACR, S.CRP and ESR levels were higher in group A as compared to that in group B. The

Values in Mean±SD				
	Parameters	Group A (n=50)	Group B (n=50)	Statistical values
A. Baseline				
1.	ACR score (range)	7.06±0.77 (6-9)	7.02±0.74 (6-9)	t=0.265; p=0.792
2.	S.CRP (mg/L)	7.91±1.28	7.55±1.81	t=1.133; p=0.260
3.	ESR (mm/hr)	27.30±6.05	28.16±9.14	t=-0.555; p=0.260
4.	25(OH) vitamin D (ng/mL) (range)	22.94±12.41 (6-47)	25.54±12.79 (7-48)	t=1.032; p=0.305
B. Mid-term follow-up (three months)				
1.	ACR score (range)	5.16±1.11 (3-7)	5.78±0.98 (3-8)	t=-2.693; p=0.004
2.	S. CRP (mg/L)	6.59±1.59	7.65±1.84	t=-3.088; p=0.003
3.	ESR (mm/hr)	20.12±4.07	22.16±5.76	t=-2.047; p=0.043
4.	25(OH) vitamin D (ng/mL)	37.06±11.43	25.36±12.66	t=4.851; p<0.001
C. Final follow-up (six months)				
1.	ACR score (range)	4.42±0.93 (3-7)	5.14±1.11 (3-8)	t=-3.525; p=0.001
2.	S. CRP (mg/L)	5.85±1.41	7.34±1.41	t=5.275; p<0.001
3.	ESR (mm/hr)	17.72±2.83	19.76±4.72	t=2.620; p=0.010
4.	25(OH) vitamin D (ng/mL)	38.60±10.75	24.80±12.36	t=5.955; p<0.001

[Table/Fig-3]: Comparison of study variables (ACR score, 25(OH) vitamin D, ESR and CRP levels) between two study groups at baseline and different follow-up intervals.

difference between two groups was also significant statistically for change in ACR and S.CRP levels (p-value <0.05). With respect to 25(OH) vitamin D levels, in group A, there was an increase in mean levels (15.66±7.79 ng/mL) whereas in group B, there was a decrease in mean levels (-0.74±3.40 ng/mL). Statistically, this difference was significant (p<0.001) [Table/Fig-4].

Values in Mean±SD			
Parameters	Group A (n=50)	Group B (n=50)	Statistical
ACR score	-2.64±1.31	-1.88±1.02	t=3.24; p=0.002
S.CRP (mg/L)	-2.12±1.88	-0.17±2.40	t=4.52; p<0.001
ESR (mm/hr)	-9.58±5.73	-7.96±7.84	t=-1.18; p=0.241
25(OH) Vit D (ng/mL)	15.66±7.79	-0.74±3.40	t=13.63; p<0.001

[Table/Fig-4]: Comparison of overall change in different study variables at final follow-up between two study groups.

DISCUSSION

The rheumatoid arthritis is a painful autoimmune disorder characterised by flares and remissions. Vitamin D is involved in bone and calcium metabolism and its deficiency is known to be associated with diffuse musculoskeletal pain. The prevalence of vitamin D deficiency has been found to be high in patients of RA and its deficiency has been linked to disease severity, as well [20].

In the present study, both the groups showed reduction in disease activity in terms of reduction in ACR score, S.CRP and ESR levels, however, this reduction was faster and significantly higher in group A as compared to group B, thus, vitamin D supplementation potentiated the therapeutic effect of MTX monotherapy. The patients included in the present study were newly diagnosed cases of RA and were treatment naïve. The return of normal levels of vitamin D in the supplemented group influenced the disease activity, positively in terms of relatively lesser CRP levels, reduced ESR and low ACR scores. The role of vitamin D levels and disease activity in terms of ESR and CRP levels was also reported by Kostoglou-Athanassiou I et al., who found that lower vitamin D levels were significantly correlated with higher CRP and ESR values [20]. The findings of present study also showed that patients in group A has higher vitamin D levels as compared to group B, who had significantly lower CRP and ESR values as well as ACR scores. Chandrashekara S and Patted A too in their study similar to current study showed that supplementation of vitamin D helps to provide a significant improvement in disease activity within a short duration [21]. In a study of Gopinath K and Danda D, vitamin D supplementation helps in achieving significantly higher reduction in pain scores as compared to non supplemented group thus showing the effect of vitamin D supplementation on disease activity [22]. In the present study, though it did not include pain as an outcome variable as it may be subjective in nature, however, other more objective parameters also endorsed the trends as observed in literature.

The findings of the present study are in agreement with the observations of Salesi M and Farajzadegan Z which showed a better treatment outcome in vitamin D supplemented group as compared to placebo group, however, they did not find it to be significant statistically (p-value >0.05) [14]. It is difficult to ascertain the exact reason for this difference, however, some of the possible reasons for this difference could be the fact that in present study all the patients were naïve to treatment whereas in their study, the patients were on MTX therapy for >24 weeks prior to initiation of study. Another reason could be difference in profile of patients, which was unexplained in their study whereas in present study, the patients were relatively younger and dominantly females [14]. Difference in method of outcome measurement could be another reason for this difference, as authors observed the outcome in terms of CRP levels, ESR and ACR scores, whereas they evaluated the outcome in terms of change in Disease Activity Score-28 (DAS28) scores. Although similar to present study, they also observed a significant increase in vitamin D levels in supplemented group as compared to non supplemented group, however, they were not able to substantiate transformation of increased vitamin D levels to change in disease activity. A positive role of vitamin D on RA by increasing the dietary intake of vitamin D has also been documented in another study [23].

The findings of present study, rejects the null hypothesis, as it showed that vitamin D supplementation to MTX among newly diagnosed RA cases helps to normalise the vitamin D levels and also have a significant impact on reducing the disease activity.

Limitation(s)

One of the limitations of present study, was that it was limited only till six months and during that period almost all the patients in supplemented arm had achieved vitamin D levels within normal range. In view of achievement of normalcy in all the patients, whether the vitamin D supplementation is to be still continued is a question to be answered. Moreover, till the end of study, the trend of having better disease activity profile continued to sustain in vitamin D supplemented group.

CONCLUSION(S)

The present study had achieved the aim of finding the role of vitamin D supplementation in RA patients on MTX monotherapy as evident from significantly lower CRP and ESR values, as well as ACR scores. Hence, further studies are recommended to be conducted for a longer duration in order to assess the optimum time, till when supplementation should be continued.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jun 18, 2022
- Manual Googling: Jul 28, 2022
- iThenticate Software: Aug 02, 2022 (15%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jun 04, 2022**
Date of Peer Review: **Jul 10, 2022**
Date of Acceptance: **Aug 06, 2022**
Date of Publishing: **Sep 01, 2022**