Low Vitamin D Levels in Rheumatoid Arthritis Patients is Associated with Poor Disability Index and Increased Patient Global Disease Assessment Score

Niharika Agarwal¹, Ghan Shyam Pangtey²*, Ritu Singh³, SK Sharma⁴

Abstract

Background: Rheumatoid arthritis (RA) is a chronic inflammatory connective tissue disorder with wide spectrum of presentation from polyarthritis to multisystem involvement. Apart from bones, muscles and other soft tissues, Vitamin D receptors have been found on many immune cells and tissues. The most vital function of Vitamin D is calcium and phosphorus absorption but it can also act as an immune-modulator hormone, which can affects both innate and adaptive immune responses leading to autoimmune diseases.

Objectives: To study the relationship of vitamin D insufficiency with disease activity and functional disability in patients of Rheumatoid Arthritis.

Material and Methods: The present study was an observational, cross sectional study done in a tertiary care hospital in New Delhi, India. The inclusion criteria comprised of patients attending the inpatient (IPD) and outpatient department (OPD), age above 18 years and fulfilling 1987 American college of Rheumatology (ACR) criteria for RA. The exclusion criteria was patients suffering from any other connective tissue disorder (CTD) and patients who were taking vitamin D supplements for past 6 months. Thirty patients were enrolled in the study after satisfying inclusion and exclusion criteria and appropriate clinical data and blood sample were collected after informed consent. Joint examination were performed and swollen joint count (SJC), tender joint count (TJC), patient global assessment (PGA) and evaluator global assessment (EGA) scores were recorded. Disease activity using DAS28ESR, DAS28CRP and CDAI were calculated and disability index was assessed using Short Fries Health Assessment Questionnaire.

Results: In our study mean vitamin D level was 18.93 ng/ml (S.D. 6.64 ng/ml). Mean DAS28 ESR was 4.57±1.48. Mean Disability Index was 0.52±0.89. All the study population had low Vitamin D level (100%), while 50% patients had vitamin D level in deficiency range (<20ng/ml). On analysis by student t-test, statistically higher PGA (p value 0.024) and Disability Index (p value < 0.001) in vitamin D deficient patients, compared to vitamin D insufficient patient group was observed, however there was no significant difference in disease activity between the groups.

Conclusion: Low Vitamin D levels are common in Indian rheumatoid arthritis patients. Mean PGA significantly increased, and disability index significantly increased in Vitamin D deficient group compared to insufficient group suggesting vitamin D deficient patients poor wellbeing and more disability.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory connective tissue disorder with wide spectrum from polyarthritis to multisystem extra-articular involvement. The specific cause or trigger for the disease is still unknown, but the prevalent concept revolves around multifactorial aetiology; including genetic and environmental interaction that lead to this autoimmune disorder. Vitamin D is a steroid hormone, its receptors have been found on many cells including immune cells, and therefore vitamin D has been characterized as an immunomodulatory hormone. It can modify both innate and adaptive immune responses. It also suppresses T cell function and dendritic cell proliferation and inhibit expression of pro-inflammatory cytokines like Interlukin-2 (IL-2). By these properties, Vitamin D has been proposed as a major factor responsible for immune tolerance, and hence people suffering from vitamin D deficiency may be at risk for development of autoimmune illnesses.¹

The present work aims to study the relationship of disease activity and functional disability in patients suffering from rheumatoid arthritis and hypovitaminosis D. Secondary aim of the study was to find the proportion of hypovitaminosis D in RA patients.

Methods and Material

The present study was an observational, cross sectional study in a tertiary care hospital setting. Period of study was seventeen months from Nov 2011 to March 2013. Inclusion criteria comprised all patients attending the IPD and OPD departments, above 18 years of age who fulfil the 1987 American college of Rheumatology (ACR) criteria for RA. Exclusion criteria was patients suffering from systemic lupus erythematosus (SLE) and other...
connective tissue disorders (CTDs), non-consenting patients and patients already taking vitamin D supplements for past three months. The proposal was approved by the ethical committee of the institution.

The patients were subjected to a battery of blood investigations which included complete blood counts with ESR done by Westergreen method. Routine biochemical investigations, liver and kidney function tests, serum electrolytes, total protein, albumin, calcium, phosphorus, serum alkaline phosphatase were performed in all patients. These investigations were done on fully automated analyser CX-9 using standard reagents and quality control sera. Anti-nuclear antibody (ANA) and rheumatoid factor (RF) qualitative assay was done using Latex Agglutination method. TSH test was done by chemiluminescence assay on Access 2 Beckmann analyser using standard reagents. 25(OH) Vitamin D levels in serum were done using DRG 25(OH) Vitamin D by ELISA method. A serum vitamin D value of 30 – 100ng/ml was considered normal; deficiency: <20ng/ml, insufficiency is 20-30ng/ml; toxicity is >100ng/ml. CRP was measured using Calbiotech hsCRP ELISA kit.

**Disease Activity and Indices**

Patient global assessment (PGA): Patients were asked to assess themselves over last one week and to mark themselves on a paper scale of 0 – 10; score of zero being very good and 10 being worst disease status. Patients were then examined for swollen joint count (SJC) and Tender joint count (TJC) for calculation of disease activity scores. Afterwards they were evaluated on another scale of 0 – 10, 0 being good and 10 being worst by an independent evaluator (physician) and Evaluator global assessment (EGA) scores were recorded. Disease activity was measured for CDAI and DAS28ESR/ DAS28CRP according to below formula-

1. CDAI (clinical disease activity index) = SJC+TJC+PGA+EGA. Value lies between 0 and 76.

[Remission < 2.8, Low disease activity (LDA) ≤ 10, Moderate disease activity (MDA) ≤ 22, High disease activity (HDA) ≥ 22]

2. DAS 28 ESR and DAS 28 CRP were calculated using the following formula with DAS calculator

\[ \text{DAS 28} = 0.56 \sqrt{\text{tender joints}} + 0.28 \sqrt{\text{swollen joints}} + 0.70 \ln(\text{ESR}/\text{CRP}) + \text{Patient Global assessment (PGA)} \]

Values lies between 0.49-9.07

[Remission < 2.6; LDA < 3.2; MDA ≤ 5.1; High disease activity (HAD)>5.1]

**Disability Index (DI)**

Disability index was calculated using *Short Fries Health Assessment Questionnaire (short HAQ).* It is one of the first patient self-reporting based functional status (disability) score and has become mandated outcome measure in many rheumatoid arthritis trials and one of the most widely used in rheumatology. There are 20 questions in 8 sections of disability assessment: dressing, arising, eating, walking, hygiene, reach, grip, and activities. Scoring within each section is from 0 (without any difficulty) to 3 (unable to do). The disability index (DI) was calculated by summing up scores of all the 8 sections and dividing it by 8, a score below 0.5 is considered normal whereas a score > 1.5 indicates severe disability.

**Statistical Analysis**

Variables were examined and transformed to approximate normal distribution. Frequencies were calculated for categorical variables and mean and standard deviation for continuous variables. Pearson’s correlation was used to assess relationship between vitamin D levels and marker of disease activity and disability. Multivariate linear regression was used to estimate the independent contribution to disability after controlling for covariates and potential co-founders. Analysis was done using Microsoft Excel 2010 and SPSS version 20.

**Observations and Results**

A total of 73 patients who fulfilled ACR 1987 criteria were subjected to inclusion and exclusion criteria. Out of these, only 30 were enrolled in the study after fulfilling inclusion and exclusion criteria. In our study group, maximum (53.3%) patients were young (< 40 years age) and average age of the patient group was 39.9 ± 12.1 years. The majority of enrolled patients were females 90% females in our study and only 10% (3/30) males. In our study group 83.3% (25/30) patients were seropositive for rheumatoid factor. Suggesting a cohort of predominantly young female RA patients.

There were 36.7% of our patients on low dose steroids and out of them around 27.3% were in remission by DAS28ESR. Only 10% (3/30) of our patients were on biological DMARDs in addition to conventional DMARDs. Although 2/3rd patients on biologicals were in remission compared to 25.9% without biological, but it was not statistically significant (p value 0.144). There was no significant difference in disease activity according to DAS 28 ESR for patients on single (n = 4), combination (n = 8) or triple drug therapy (n =18).

Deformities were present in 56.7% (17/30) of our patients. Mean duration of illness was around 8.5 years in group with deformity and 4 years for those without deformities. There was significant correlation between deformities and the increasing duration of illness (p value 0.005).

Surprisingly, vitamin-D levels of all patients (30/30) were found to be low (<30ng/ml), half of them were having levels of Vitamin-D in deficient level (< 20 ng/ml) and 50% were having insufficient level (20-30 ng/ml).

In our study mean vitamin D level was 18.93 ng/ml (S.D.+6.64 ng/ml). Mean DAS28 ESR was 4.57±1.48, mean DAS28 CRP was 3.21±1.22 and mean CDAI was 15.57±14.28. Mean Disability Index was 0.52±0.89, suggestive of mild difficulty to moderate disability (Table 1).

All the patients were divided in two groups of vitamin D deficiency and Vitamin D insufficiency group and analysed for disease activity, patient global assessment and disability index. Using student t-test, we found
Vitamin D is a group of fat-soluble secosteroids hormones. Vitamin D₃ (Cholecalciferol) is produced in the skin on ultraviolet B light from the sun or artificial sources and occurs naturally in a small range of foods. Vitamin D is proposed to have immunoregulatory properties. Vitamin D Receptor (VDR), a member of the nuclear hormone receptor superfamily, has been identified in primary lymphoid organs (bone marrow and thymus) and isolated from mononuclear cells, dendritic cells, antigen-presenting cells, and activated T and B lymphocytes. Quiescent CD4+ T cells express VDRs at low concentrations, which increases five-fold after their activation. Vitamin D inhibits T-lymphocyte proliferation, particularly Th1 cell proliferation and cytokine production, which includes IL-12, IFN-γ, IL-1, IL-6, TNF-α and promotes IL-5 and IL-10 production, which further shift the T cell response towards Th2 dominance. It also retards the expression of the IL-6, an important factor that stimulates Th17 cells. Th17 cells are a critical component of the autoimmune reaction. In B cells, vitamin D has been shown to inhibit antibody secretion and autoantibody production. In vitro, 1,25(OH)₂D₃ stimulates phagocytosis of the autoimmune reaction. In B cells, vitamin D has been shown to inhibit antibody secretion and autoantibody production. In vitro, 1,25(OH)₂D₃ inhibits T-lymphocyte proliferation, particularly Th1 cell proliferation and cytokine production, which includes IL-12, IFN-γ, IL-1, IL-6, TNF-α and promotes IL-5 and IL-10 production, which further shift the T cell response towards Th2 dominance. It also retards the expression of the IL-6, an important factor that stimulates Th17 cells. Th17 cells are a critical component of the autoimmune reaction. In B cells, vitamin D inhibits T-lymphocyte proliferation, particularly Th1 cell proliferation and cytokine production, which includes IL-12, IFN-γ, IL-1, IL-6, TNF-α and promotes IL-5 and IL-10 production, which further shift the T cell response towards Th2 dominance. It also retards the expression of the IL-6, an important factor that stimulates Th17 cells. Th17 cells are a critical component of the autoimmune reaction. In B cells, vitamin D has been shown to inhibit antibody secretion and autoantibody production. In vitro, 1,25(OH)₂D₃ stimulates phagocytosis and killing of bacteria by macrophages by increasing differentiation of macrophages, increasing chemotaxis and phagocytosis, increasing antimicrobial protein cathelicidin, and of IL-12 secretion. In vitro, 1,25(OH)₂D₃ is one of the most efficient blockers of dendritic cell differentiation and of IL-12 secretion. In vitro, 1,25(OH)₂D₃ stimulates phagocytosis and killing of bacteria by macrophages by increasing differentiation of macrophages, increasing chemotaxis and phagocytosis, increasing antimicrobial protein cathelicidin, and of IL-12 secretion. In vitro, 1,25(OH)₂D₃ is one of the most efficient blockers of dendritic cell differentiation and of IL-12 secretion. In vitro, 1,25(OH)₂D₃ stimulates phagocytosis and killing of bacteria by macrophages by increasing differentiation of macrophages, increasing chemotaxis and phagocytosis, increasing antimicrobial protein cathelicidin, and of IL-12 secretion. In vitro, 1,25(OH)₂D₃ is one of the most efficient blockers of dendritic cell differentiation and of IL-12 secretion. In vitro, 1,25(OH)₂D₃ stimulates phagocytosis and killing of bacteria by macrophages by increasing differentiation of macrophages, increasing chemotaxis and phagocytosis, increasing antimicrobial protein cathelicidin, and of IL-12 secretion. In vitro, 1,25(OH)₂D₃ is one of the most efficient blockers of dendritic cell differentiation and of IL-12 secretion. In vitro, 1,25(OH)₂D₃ stimulates phagocytosis and killing of bacteria by macrophages by increasing differentiation of macrophages, increasing chemotaxis and phagocytosis, increasing antimicrobial protein cathelicidin, and of IL-12 secretion. In vitro, 1,25(OH)₂D₃ is one of the most efficient blockers of dendritic cell differentiation and of IL-12 secretion.
autoimmune disease such as type 1 Diabetes Mellitus, systemic lupus erythematosus (SLE), Multiple sclerosis (MS), Inflammatory bowel disease (IBD) and RA.1,16

Studies have shown association of vitamin D deficiency and SLE and increase autoimmune response of vitamin D deficiency in patients of SLE.17,18 Association of vitamin D deficiency has been observed in multiple sclerosis19 and studies have also shown reduction in progression of relapsing disease with 1,25(OH)2D3 administration.20 Study by Orbach et al.21 show that patients with autoimmune diseases have lower levels of 25(OH) vitamin D levels than healthy adults. In Finnish birth cohort study, authors provided strong evidence that vitamin D deficiency in early life increases risk of type 2 DM whereas dietary vitamin D supplementation reduces risk to develop disease later in life.22 There are studies that shows latitudinal variation in incidence of RA with higher incidence in North Europe and North America compared to South Europe and South America.23,24

An observational study on disease activity in RA and climate, reported higher RA disease activity in spring and lower activity in autumn with circannual variation in disease activity suggesting possible role of solar light and thus Vitamin D.25 Hypovitaminosis is very prevalent even in healthy individuals in India. In a recent study by Goswami R et al. from New Delhi, India, the reported hypovitaminosis was as high as 90 % in healthy individuals.26,27 In another prevalence study of Vitamin D in RA patients by Baykal T et al.28 from Turkey, they found very high 91% hypovitaminosis D (<30ng/ml). Similar high prevalence of vitamin D insufficiency was found in our study of RA patients also.

Haga et al.29 measured 25(OH) vitamin D levels in 176 outpatients with RA and recorded disease activity by DAS28ESR, they didn’t found any statistical correlation between the two. Baykal et al.26 determined 25(OH)D3 concentration in 55 RA patients but didn’t found any significant correlation between disease activity and vitamin D levels. Baker et al.30 measured 25(OH) Vitamin D in 499 patients with active RA and in their study also, vitamin D deficiency was not associated with statistically greater DAS28 scores. Haga et al.31 measured 25 (OH) vitamin D in 302 patients of RA and found no significant correlation of vitamin D with DAS28.

Similar to above studies, in our study population also, we didn’t find any statistically significant correlation between vitamin D levels and the disease activity indices DAS28ESR, DAS28CRP and CDAI. We divided our study population in two groups of, vitamin D deficient(<20ng/ml) and insufficient groups (20-30ng/ml), we observed higher SJC counts, TJC counts, DAS28 ESR and DAS28CRP and CDAI in deficient group then insufficient group, but the differences were not statistically significant.

In our study, we found statistically significant inverse correlation between vitamin D levels and disability index (r = -0.552, p value < 0.05). There was statistically significant higher PGA (patient global assessment) 4.47±3.40 in vitamin D deficient group compared to insufficient group 1.80±1.01 (p value 0.024) and significantly higher disability scores in deficient group mean value of 1.01±1.06 compared to insufficient group mean value 0.03±0.10 (p value <0.001). In a similar study by Turhanoglu AD et al.21 found significant negative correlation of vitamin D with disability index. So, although there was no statistically significant correlation between vitamin D and disease activity, but higher proportion of hypovitaminosis in this group of autoimmune RA patients may be directly related to significantly higher Patient Global Assessment(PGA) of disease. Higher incidence periarticular symptoms of soft tissue rheumatism and fibromyalgia is common in Vitamin D insufficient patients. These hypovitaminosis-D patients may incorrectly perceive themselves as having active joint disease and having less response to DMARDs despite having remission/ low disease activity in their joint. This can have major implication for subsequent management RA and RA disease activity scoring, as overall PGA is included in most of disease activity scoring methods. Similarly the higher disability index due to vitamin D deficiency may also lead to falsely higher disease activity scoring. However because of small sample size, this study cannot be directly extrapolated to larger population and therefore large scale studies are required to further evaluate any correlation between vitamin D levels, disease activity and patient global assessment of RA. One interesting finding of 100% hypovitaminosis D was found in our patients, this may have some important role in autoimmunity, leading to or triggering inflammatory arthritis susceptible host.

**Conclusion**

All our 30 RA patients enrolled in the study had hypovitaminosis D, 50% were deficient and 50% were insufficient. Vitamin D deficiency may have some role in autoimmune inflammatory arthritis. All patients of Rheumatoid Arthritis should be regularly supplemented with vitamin D and monitored. Patients with vitamin D deficiency have significantly higher Patient global assessment (PGA) of disease and higher Disability score and this could have major implication for subsequent management of RA.

**References**


