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RESEARCH ARTICLE

Correlation between Vitamin D Deficiency and Rheumatoid Arthritis Patients.

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Abstract

The main aim and objective of this study was to determine the prevalence of Vitamin D deficiency in patients with rheumatoid arthritis (RA) and compare the serum Vitamin D levels to healthy controls and also establish relationship between 25-hydroxyvitamin D (25(OH)D) with disease activity and disability. A cross sectional study was designed to include 50 RA patients (case) and 50 (controls), from Rajiv Gandhi Hospital & Research Center from duration 2012-2015. All patients had serum 25(OH) D measured in a laboratory and Vitamin D levels were analyzed in correlation with disease activity, functional impairment. The main objective of this study to determine Vitamin D level in Rheumatoid Arthritis (RA) patient and healthy controls and to estimate the prevalence of Vitamin D deficiency in patients in Rheumatoid Arthritis (RA) as compared to healthy controls and to analyze the association between 25-hydroxyvitamin D (25(OH) D) with disease activity.

The study includes 50 RA patients (case) and 50 (controls), from Rajiv Gandhi Hospital & Research Center from duration 2012-2015. All enrolled patients had serum 25(OH) D measured in a laboratory under set conditions. The percentage of RA patients with vitamin D deficiency (25(OH) D level <20 ng/ml) was 33.5%, where as in control group percentage observed was (18.6 %). In RA patients, 25(OH) D levels were negatively correlated with the Health Assessment Questionnaire Disability Index, Disease Activity Score (DAS28), and Mobility Activities of daily living score. Significantly lower 25(OH) D values were found in patients not in disease remission or responding poorly to treatment, and with the highest Stein rocker functional state. It was also found that Body mass index (BMI) was good predictors of 25(OH) D values ($P < 0.001$). The association between disease activity or functional scores and 25(OH) D levels remained statistically significant even after adjusting 25(OH) D levels for both BMI.

In RA patient's vitamin D deficiency is quite common, disease activity and disability scores are inversely related to 25(OH) D levels. The study concluded Overweight RA patients, with high BMI and raised DAS score and disable RA patients has low titers of Vitamin D deficiency and the same could be a proposed cause for rapid bone loss in RA patients besides autoimmune factor. Based on the merits of results obtained this study may be a recommended guideline in management of RA patients, where it is proposed that Vitamin D supplementation should be included in Reverse pyramid regimen in management of RA patients and regular monitoring of Vitamin D levels every 6 months should be emphasized for PCP .

Introduction:-

Vitamin D is a hormone which plays vital role in bone and calcium metabolism. The key player in calcium homeostasis, involved in calcium absorption from the G.I system.¹ The hormone synthesis site is in the skin by the use of ultraviolet irradiation^{2, 3}. Extra skeletal effect of Vitamin D is immunomodulatory actions⁴ Vitamin D deficiency correlated with the appearance of autoimmune diseases, such as diabetes mellitus type 1 and multiple sclerosis⁵

Vitamin D deficiency is extremely common in Northern hemisphere where more than 90% of elderly people are affected⁶⁻¹⁰ Vitamin D deficiency is also frequent among all age groups.: 25-hydroxyvitamin D (25(OH)D) levels lower than 20 ng/ml have recently been reported in Italy in almost a third of apparently healthy women¹¹

Vitamin D receptors are found on several immune cells and *in vitro* studies have shown that vitamin D metabolites modulate T cell proliferation and dendritic cell function¹²⁻¹³ Epidemiological data also imply that vitamin D deficiency could be a risk factor for development of autoimmune and other chronic diseases^{8, 14}

More recently, vitamin D deficiency was found in 42 out of 145 postmenopausal women with RA in the USA, with the highest prevalence among African Americans¹⁵⁻¹⁶

Aims & Objectives:-

A critical study on Vitamin D deficiency in patient with Rheumatoid Arthritis was designed to conduct study Rajiv Gandhi Hospital & Research Center from duration 2012-2015. The main objective of this study was

To determine Vitamin D levels in Rheumatoid Arthritis (RA) patients and healthy controls And estimate the prevalence of vitamin D deficiency in patients with Rheumatoid Arthritis (RA) as compared to healthy controls Analyze the association between 25-hydroxyvitamin D (25(OH)D) with disease activity.

Rheumatoid arthritis (RA) is an autoimmune disease of unknown etiology¹⁷. T and B cells lymphocytes play role in pathogenesis of RA Patients and so are therapeutic targets for treatment of RA.

Vitamin D deficiency may increase the risk for the development of RA¹⁸. Recently, the role of vitamin D deficiency in the pathogenesis of RA, as well as the relationship between vitamin D deficiency and the activity of RA is discussed¹⁹.

The present study & research work would help to analyse, Vitamin D deficiency as a risk factor for the development of RA, its role in pathogenesis and correlation between Vitamin D levels and RA disease activity. RA is an inflammatory disease characterized by flares and remissions, flares being characterized by pain. Vitamin D deficiency is also known to be associated with diffuse musculoskeletal pain²⁰. As a confounding factor pain in RA patients will be titrated to Vitamin D levels.

Rheumatoid arthritis (RA), Autoimmune disease in which synovial inflammation with continuous erosion of bone is the cause of joint loss.²¹ Possible etiological causes of the disease could be genetic, hormonal, environmental, and infectious factors²². Vitamin D can put in consideration as an environmental factors related to RA disease²³. The effects of vitamin D and the may elucidate the associations between the vitamin and RA.^{24, 25}

Vitamin D has immunomodulatory and immune-regulatory properties. Detection of vitamin D receptors in the immune system cells and Vitamin D role in cellular proliferation and differentiation and survival of cells in immunity disorders could suggest role of Vitamin D deficiency as a possible cause for bone loss in RA patients.²⁶⁻³¹ Previous outcomes were also achieved in Saudi Arabia as published by Attar³² and Atwaet al.³³. Vitamin D levels will be studied in RA patients and their correlation will be explored in this research work.

Symptoms, Antibodies, and Inflammatory biomarkers are cardinal diagnostic factors in RA. Genetic and Environmental factors are useful prognostic factors.³⁴

Blaney et al.³⁵ assumed that vitamin D could be used as clinical biomarker in RA disease and other autoimmune diseases. As per present status of work there is no scale to measure the optimal vitamin D cutoff point related to RA

disease activity. Therefore, this study is novel on finding out the optimal vitamin D cutoff point in predicting activity of RA disease.

RA classification criteria as defined by American College of Rheumatology and European League against Rheumatism (ACR/EULAR) at 2010³⁶ were adopted for diagnosis of RA patients in present studies. The inclusion and exclusion criteria is incorporated here under :

Exclusion Criteria:-

Age > 70 years old,
 Mal-absorption Syndrome
 Kidney Disease with GFR less than 40 mL/min/1.73 m²
 Tumors,
 T2DM,
 Osteoporosis,
 Systemic lupus erythematosus,
 Hyperthyroidism,
 Celiac disease,
 Inflammatory bowel diseases,
 Pregnancy & lactation
 Immobility,
 Steroid medication,
 Vitamin D supplementation
 Bypass surgery

Inclusion Criteria:-

All RA patients fulfilled the 1987 American College of Rheumatology (ACR) revised criteria for RA. The only inclusion criteria were a diagnosis of established RA and an age less than 75 years, irrespective of menopausal status.

Clinical evaluation:-

After Informed consent ,patients meeting inclusion criteria are enrolled in the study .

All patients were interviewed ,case history built with physical exam and current treatment modalities taken in to consideration as part of data gathering .Onset of the disease, disease duration, disease severity, extra-articular manifestations are prime considerations at the time case histories.

28 tender joint count (TJC28) and 28 swollen joint counts (SJC28) The three-variable Disease Activity Score (DAS 28) was calculated using C-reactive protein (CRP) and the Nijmegen formula: $DAS28 = (0.56 * \sqrt{TJC28}) + 0.28 * \sqrt{SJC28} + 0.36 * \ln(CRP+1)) * 1.10 + 1.15$ ³⁷

.Patient in remission defined as per ACR CRITERIA.

Clinical measures of disease related functional impairment included Health Assessment Questionnaire Disability Index (HAQ), Steinbrocker functional state and the mobility activities of daily living (ADL)⁴⁸⁻⁵⁰ RA specific treatment were collected and included in drug history.

The patients were interviewed regarding current use of drugs affecting bone metabolism including bisphosphonates, calcium and vitamin D supplements. Vitamin D supplements taken during the previous year were carefully evaluated and expressed as mean daily dose. Body weight and height were assessed and the body mass index (BMI = kg/m²) was calculated in all subjects.

Materials and Methods:-

Study Design: Cross Sectional case-control:-

Out of 600 case pools, 100 patients with measured plasma 25-hydroxy vitamin D (25(OH) D) were selected and enrolled in the study after informed consent process. Ethics approval was obtained from the Hospital Ethics Board, at the Rajiv Gandhi Hospital & Research Center.

Patient subjects were categorized in case and control groups; 50 patients with rheumatoid arthritis as per Inclusion criteria, as well as 50 patients as controls from Rajiv Gandhi Hospital & Research Center from duration 2012-2015. Information on age, sex, BMI, plasma 25(OH)D, vitamin D and calcium supplement use, serum calcium, serum phosphate, erythrocyte. Sedimentation rate (ESR), C-reactive protein (CRP), glomerular filtration rate (GFR) were collected and recorded. We also collected data on disease activity score (DAS 28-ESR) only in cases with rheumatoid arthritis. DAS28-ESR is a quantitative measure of disease activity in rheumatoid arthritis, calculated by using a formula that considers the number of tender joints and swollen joints within 28 joints, as well as ESR. The disease activity is considered high with the score of >5.1 , low with <3.2 score, and the score of <2.6 for diseases in remission.

Independent *t*-test was used to evaluate the differences between patients in case and control group. Pearson correlation was used to determine the relationship between disease activity and serum vitamin D status in RA cases. We used the threshold of 50 nmol/L to define vitamin D deficiency based on recent literature. To evaluate distribution of cases and controls across vitamin D status groups (deficient and optimal), Chi-square test was applied. Logistic regression was used to identify the association between vitamin D status and disease (autoimmune vs. non-auto immune). Data manipulation, cleaning, and creation of new variables and statistical analyses were done using SPSS IBM (Version 19, Armonk, NY, USA). In all analyses, alpha was set at the level of 0.05.

Results:-

The characteristics of participants in case and control groups are presented in Table 1. In the control group (50), most patients were Non RA. In case group, ($n = 50$), all patients are RA patients as per the RA classification criteria as defined by American College of Rheumatology and European League against Rheumatism (ACR/EULAR) at 2010

Table 1:-Characteristics of Participants in Case and Control groups.

	Case Group (n=50)		Control Group(n=50)	
	Mean	SD	Mean	SD
Age*	53.5	11	63	11.5
BMI	28	7.8	28.6	5.1
Total 25 vitamin D Value (nmol/L)*	63.8	28.6	84.8	36.9
Vitamin D Supplement use (IU)	1041.4	647.3	1006	663.7
Serum Calcium*	2.1	0.1	2.3	0.1
Calcium Supplement use (mg/day)	453.7	435	713.4	586
ESR	21.76	19.7	18.17	14.3
CRP*	11.7	19.1	6.03	9.2
Creatinine	71.8	43.7	77.6	33.7
GFR	67.9	27.3	70.9	19.7

*Significant difference ($p < 0.05$), independent student *t*-test

Patients in case group were significantly in their fifth and sixth decade. Only 12 participants were males (2 in control group and 10 in case group). Although most patients in both case (90.7%) and control (82.9%) groups reported taking approximately 1000 IU vitamin D supplement intake (median of 1000 IU in both case and control group), the mean plasma 25(OH)D was significantly lower in patients with autoimmune rheumatic diseases compared to control patients ($p < 0.05$) (Figure 1 & 2). Also, serum calcium was lower in case group ($p = 0.01$). In case group, 90.7% of participants reported vitamin D supplement use, among them 46.5% had vitamin D supplement prescription. The significantly higher CRP in patients with autoimmune rheumatic disease may indicate the higher disease activity in those patients ($p = 0.035$). A negative correlation was observed between plasma 25(OH)D and CRP with a borderline significance, probably due to a small sample size ($r = -0.2$, $p = 0.087$).

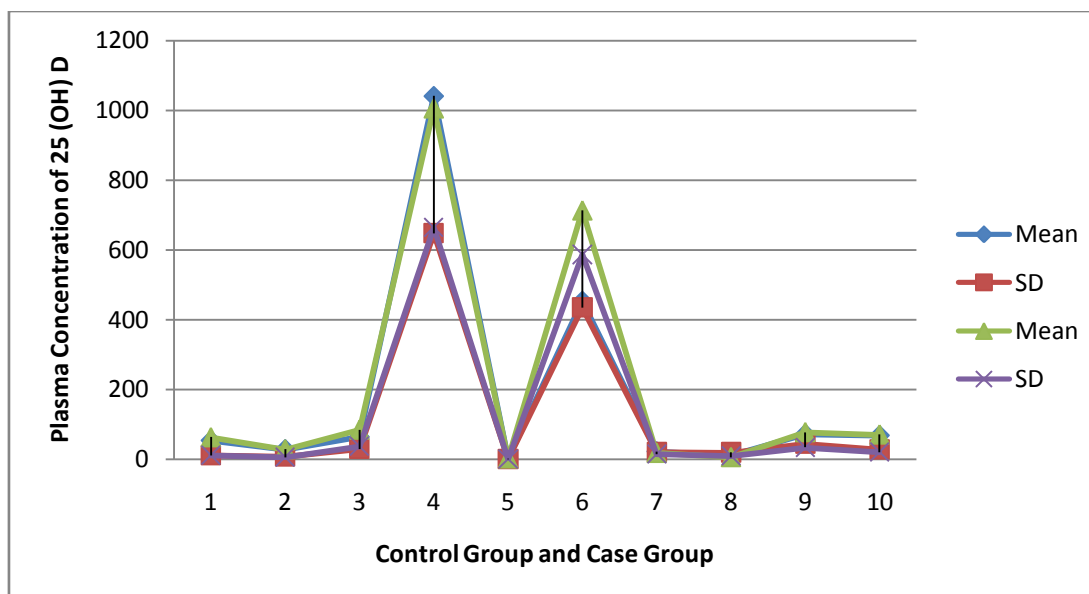


Figure No. 1:- *Significant difference ($p < 0.05$), independent student t-test

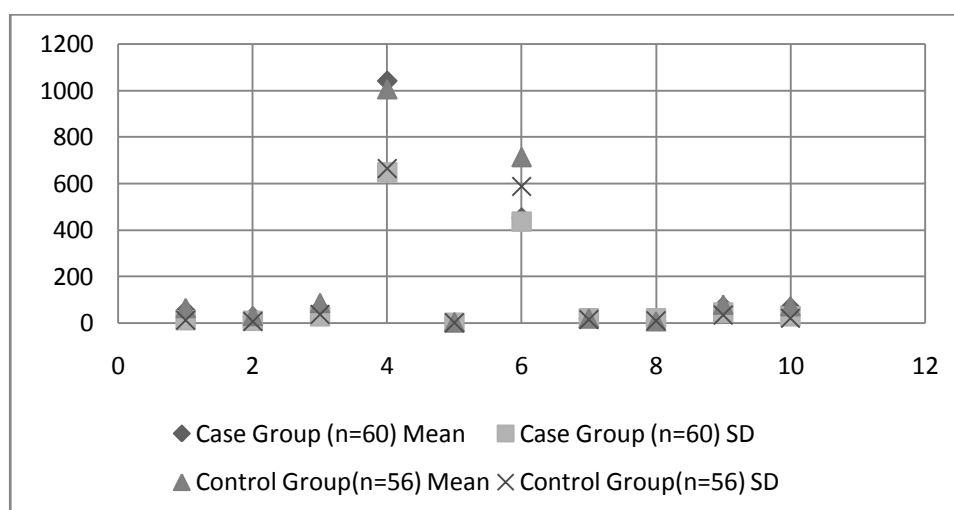


Figure No 2:-Plasma concentration of 25(OH) D across case and control groups.

In the control group 10 patients (18.6%) with no autoimmune diseases were vitamin D deficient (plasma 25(OH)D < 50 nmol/L). Whereas in the case group, 19 patients (33.5%) were vitamin D deficient. The distribution of patients across plasma 25(OH)D groups (deficient, optimal) presented a borderline significant difference ($p = 0.05$) between case and control groups with higher distribution of patients with autoimmune diseases in deficient vitamin D group.

A considerable proportion of RA cases (58.6%) had a disease activity score of above 2.6 (cut off for disease remission). Further, the significant negative correlation between plasma 25(OH)D and disease activity ($r = -0.43$, $p = 0.01$) may indicate lower disease activity with increase in plasma 25(OH)D. In logistic regression analyses to evaluate the association between vitamin D status and disease activity in RA cases, adjusted for age, sex, the odds of having active disease was 5.12 times higher in patients with low plasma 25(OH)D compared to those with adequate vitamin D (OR = 5.15 95% CI 1.16, 22.9; $p = 0.031$).

Discussion:-

In the present study vitamin D levels were found to be low in a group of patients with RA. Vitamin D levels were found to be negatively correlated with disease activity in RA.

Vitamin D levels have been studied in RA. Vitamin D deficiency, may be considered as a risk factor in the development and progression of bone damage in RA patients.

The Iowa Women's Health Study by Merlino and colleagues⁴¹ analyzed data from a prospective cohort study of 29,368 women aged 55–69 years. Merlino and colleagues found that greater intake of vitamin D might be associated with a lower risk of RA. Through 11 years of follow up, 152 cases of RA were reported.

In contrast, in two cohort studies conducted by Costenbader and colleague's vitamin D intake was not found to be associated with the risk of RA.⁵⁸ The first cohort included 91,739 women followed from 1980 to 2002 in the Nurses' Health Study, and the second included 94,650 women followed from 1991 to 2001 in the Nurses' Health Study II. They observed no associations between cumulative average vitamin D intake and the risk of RA. In a meta-analysis of studies assessing the association between vitamin D intake and the risk of RA Song and colleagues showed an association between vitamin D intake and RA incidence without between study heterogeneity.⁴² The cohort studies considered included 215,757 participants and 874 cases of RA.

Individuals in the highest group for total vitamin D intake were found to have a 24.2% lower risk of developing RA than those in the lowest group. Subgroup meta-analysis also showed a significant association between vitamin D supplement intake and RA incidence. By contrast, a recent study did not find an association between vitamin D intake and the risk of RA.⁴⁴ In the present study, lower levels of vitamin D were found in RA patients as compared with a control group.

In the present study an inverse association was observed between vitamin D levels and RA disease activity. Several studies have evaluated the association between vitamin D levels and RA activity. In a study involving 1191 patients with RA and 1019 controls, Rossini and colleagues found an inverse association between vitamin D levels and disease activity in RA.⁴⁵ Welsh and colleagues and Kerr and colleagues found that vitamin D deficiency is linked with disease activity in RA.^{46,47} Also Cutolo and colleagues and Haque and Bartlett found an inverse relationship between vitamin D levels and disease activity in RA.^{48,49} By contrast, others did not find a relationship between vitamin D deficiency and disease activity in RA.^{51,52,53} In the study by Braun-Moscovici and colleagues they found no correlation between vitamin D levels and disease activity among 85 patients with RA.⁵³ However, overall, their subjects had high disease activity and low 25(OH)D₃ levels, accounting for a high vitamin D deficiency rate, which might have influenced the study outcome and the lack of correlation with disease activity. Given the increased risk for the development of cardiovascular disease in RA, Haque and colleagues further investigated the matter and found an association of vitamin D deficiency with cardio metabolic risk factors.^{49,50}

Vitamin D is responsible for immunologic tolerance.⁵⁴ Thus, vitamin D deficiency may induce the development of autoimmune diseases, such as RA. Vitamin D has immunomodulatory properties, acting on the immune system both in an endocrine and in a paracrine manner.⁵⁵ It appears to regulate the immune response by a variety of mechanisms, such as decreasing antigen presentation⁵⁶, inhibiting the proinflammatory T helper type 1 profile and inducing regulatory T cells.⁵⁷ 1,25(OH)₂D₃ suppresses proliferation and immunoglobulin production and retards differentiation of B-cell precursors into plasma cells.⁵⁸ These data support a role for vitamin D deficiency in the development and progression of autoimmune inflammatory conditions in general, and in particular RA. Earlier data from animal models indicate that the 1,25(OH)₂D₃ metabolite and its analogues may suppress collagen-induced arthritis.⁵⁹ Other data suggest that vitamin D receptor agonists may also prevent and suppress established collagen-induced arthritis.⁶⁰ Having said that, however, there are data showing that vitamin D may be negatively affected in acute response, that is, its levels may decrease in the setting of inflammation, such as in active RA.⁶¹ Despite that, treatment with rituximab in RA did not affect vitamin D levels, although it decreased indices of inflammation.⁶²

Supplementation with vitamin D has been proposed as a means to induce immune tolerance and thus prevent the development of autoimmune diseases.⁶³ Recently, the combination of antirheumatic drugs with vitamin D has been suggested for RA. Patients with RA are prone to osteoporosis and suffer from pain when the disease is in flare. Vitamin D supplementation has been proposed for patients with RA for the prevention and treatment of osteoporosis as well as for its possible effects on disease activity. From a careful analysis of a large number of epidemiological

studies it was recently found that the optimal 25(OH)D concentrations for bone health and extra-skeletal benefits are between 36 to 40 ng/ml%⁶³

BMI is a well established risk factors for vitamin D deficiency and these associations are confirmed in the present study⁶⁴

The scope of this study was to evaluate to what extent vitamin D deficiency was related in RA patients with the severity of the disease. The inverse relationships between vitamin D levels and disease activity or functional impairment are of interest but not of obvious interpretation. Similar relationships have been found also by others. Cutolo *et al.* reported a significant inverse association between 25(OH)D and DAS28 in patients with active RA and Patel *et al.* found an inverse relationship between 25(OH)D levels and tender joint count, DAS28, and HAQ score only at disease onset, but not in patients with a disease duration longer than one to two years⁶⁵

Conclusions & Recommendations:-

In this study we found that:-

Vitamin D deficiency is quite common in RA patients as compared to healthy control population eliminating all confounding factors as exclusion criteria.

Inverse co-relation has been established between RA disease activity and disability scores and vitamin D levels.

The causality of these associations remain to be assessed in longitudinal studies aimed at evaluating the clinical response to a vitamin D supplementation dose regimen large enough to increase 25(OH)D levels over 38 ng/ml⁶⁵

In conclusion, it appears that vitamin D deficiency is highly prevalent in patients with RA, and that vitamin D deficiency may be linked to disease severity in RA. As vitamin D deficiency has been linked to diffuse musculoskeletal pain, these results have therapeutic implications. Vitamin D supplementation may be needed for the prevention of osteoporosis and for pain relief in patients with RA. Greater intake of vitamin D lowers down bone losses in RA patients. Inverse associations were apparent for both dietary and supplemental vitamin D.

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