

 ISSN NO. 2320-5407	Journal Homepage: - www.journalijar.com INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR) Article DOI: 10.21474/IJAR01/7961 DOI URL: http://dx.doi.org/10.21474/IJAR01/7961	 INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR) ISSN 2320-5407 Journal Homepage: http://www.journalijar.com Article DOI: 10.21474/IJAR01/7961
---	--	---

RESEARCH ARTICLE

VITAMIN D LEVELS IN PATIENTS OF RHEUMATOID ARTHRITIS AND CORRELATION WITH DISEASE ACTIVITY.

Dr. Shahoodajaz kakroo¹, Prof. Abdul khaliq², Dr. Owaisahmed wani¹, Shaheera Ajaz³, Manalabdullateef³, Showkatnazir Wani³, Drjavaid Chachoo⁴ and Dr. Manzoor teli⁴.

1. PG Scholar, Postgraduate department of general medicine government medical college, srinagar.
2. Professor of Medicine and Rheumatology, Postgraduate department of general medicine government medical college, srinagar.
3. Senior resident , Skims
4. Lecturer, Postgraduate department of general medicine government medical college, srinagar.

Manuscript Info

Abstract

Manuscript History

Received: 17 August 2018

Final Accepted: 19 September 2018

Published: October 2018

Copy Right, IJAR, 2018,. All rights reserved.

Introduction:-

Rheumatoid arthritis(RA) is a chronic inflammatory disease of unknown etiology marked by a symmetric, peripheral polyarthritis¹.It is a systemic disease and hence results in a variety of extra articular manifestations like fatigue, subcutaneous nodules, lung involvement, pericarditis, vasculitis and hematological abnormalities².

One of the most recent factors found to be associated with autoimmunity is vitamin D deficiency. Circulating 25(OH)D concentrations decreases with the evolution of the systemic inflammatory response³. The immunoregulatory effects of 1,25(OH)₂D₃ are a result of its action on regulating immune cells, including macrophages and lymphocytes, to suppress the production of IL-17, IL-23 and TNF- α , and to augment the expression of IL-4 and IL-10^{4,5}. Therefore, it is plausible to hypothesize that vitamin D deficiency may play a role in immunological dysfunction.

The IL-23 – IL-17 axis is a significant mediator of inflammation³¹. Studies have reported that increased IL-17 and IL-23 are associated with increased disease activity in patients with RA^{6,7}, but there is little evidence to show whether vitamin D status is associated with serum levels of IL-17 and IL-23 in RA patients?Recent evidence demonstrates that vitamin D may correlate inversely with occurrence, development, disease activity and flare ups of RA^{8,9,10}. The anti-inflammatory and immunomodulatory roles of vitamin D have gradually become apparent^{11,12}. In the adaptive immune system,vitamin D downregulates expression of proteins involved in T helper type 1 (Th1) cell driven autoimmunity, and participates in inhibition of antigen-presenting activity, antibody production, lymphocyte proliferation, dendritic cell differentiation and release of cytokines such as interleukin-2 (IL-2), IL-6, interferon- γ (IFN- γ) and tumor necrosis factor- α (TNF- α)^{13,14,15}. In addition, vitamin D reinforces the development of monocytes into macrophages and then further influences their chemotaxis and cytokine expression¹⁶. Most autoimmune diseases, including inflammatory bowel disease, insulin-dependent diabetes mellitus, multiple sclerosis and rheumatoid arthritis, are Th1 cytokine-mediated disorders¹⁷. By dampening Th1 responses, vitamin D helps redirect the T cell response towards an immunosuppressive state.

Corresponding Author:-Shahoodajaz kakroo.

Address:-PG Scholar, Postgraduate department of general medicine government medical college, srinagar.

Vitamin D levels might influence RA disease activity, as assessed by the 28-joint DAS (DAS28₄)¹⁸, however, some studies have reported no significant associations between vitamin D insufficiency and joint pain or disease activity¹⁹. These inconsistencies may be due to differences in factors such as study population, design, sample size and analytical methods. This allowed us to summarize the increased wealth of evidence now available and ask whether vitamin D concentrations can be clearly correlated with disease activity of RA?

Aims And Objectives:-

1. To estimate vitamin D levels in patients with rheumatoid arthritis.
2. To evaluate the correlation between disease activity and vitamin D levels in the study population

Materials And Methods:-

After obtaining the ethical clearance from the institutional ethical committee, the present cross-sectional study was performed at Postgraduate Department of Medicine, SMHS Hospital, an associated hospital of Government Medical College, Srinagar over a period of one and a half years.

Inclusion Criteria

Patients diagnosed with rheumatoid arthritis (RA) in-line with the criteria laid by American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR), 2010.

Exclusion Criteria

1. Patients having any form of vitamin D supplementations during previous three months.
2. Patients who were diagnosed cases of parathyroid disease, hyperthyroidism, kidney or liver diseases.
3. Pregnant females.

Methodology:-

Patients attending Outpatient Department of Medicine at SMHS Hospital were evaluated for a history of thyroid disease, parathyroid, kidney or liver disease, vitamin D supplementation during previous 3 months and pregnancy. Blood samples were obtained for the measurement of serum 25 OH vitamin D levels by Chemiluminescent micro-particle immunoassay (CMIA) method. DAS-28₄ was used to measure RA activity and patients were categorized accordingly into three groups: low activity (DAS28₄ ≤ 3.2), moderate activity (3.2 < DAS28₄ ≤ 5.1) and high activity (DAS28₄ > 5.1) groups. Mean Vitamin D levels of each group was determined and correlated with disease activity.

Baseline Analysis

Clinical data of patients in the RA group were collected, including gender, age, swollen joint count, tender joint count, C reactive protein (CRP), erythrocyte sedimentation rate (ESR), and rheumatoid factor (RF). Anti CCP, Vitamin D levels, Global impact of disease on patients health on VAS (0-100mm) and Disease Activity Score-28 (DAS28₄) of RA patients was calculated.

CRP was done by CRP-Latex Slide agglutination method with reference value upto 6 mg/L, taken as negative.

ESR was done by Westergren method and levels from 0-15 mm and 0-20 mm in first hour in males and females respectively was taken as normal.

Rheumatoid factor (RF) was done by RF-Latex Slide agglutination method with reference value upto 8 IU/ml, taken as negative.

Anti CCP was done by ELISA method and values of less than 6.25 IU/ml were taken as negative.

Analysis of Serum 25(OH)D Concentration

25 hydroxy vitamin D assay is a chemiluminescent micro particle immunoassay (CMIA) for the quantitative determination of 25(OH) vitamin D in human serum.

Biological Principles of the Procedures

1. 25(OH) vitamin D assay is a quantitative delayed one step competitive immunoassay to determine the presence of vitamin D in human serum using CMIA technology with flexible assay protocols, referred to as Chemiflex.
2. 3mL blood samples, assay diluent and paramagnetic anti-vitamin D coated micro-particles are combined. 25(OH) vitamin D present in the sample is displaced from the vitamin D binding protein and binds to anti-vitamin D coated micro-particles, forming an antigen antibody complex.
3. After incubation, a conjugate containing acridinium-labeled vitamin D is added to the reaction mixture and binds to unoccupied binding sites of the anti-vitamin D coated microparticles.
4. After further incubation and washing, Pre-Trigger and Trigger Solutions are added to the reaction mixture.
5. Pre-Trigger solution containing 1.32% (W/V) hydrogen peroxide.
6. Trigger solution containing 0.35N sodium hydroxide.
7. The resulting chemiluminescent reaction is measured as relative light units (RLUs). There is a relationship between the amount of 25(OH) vitamin D in the sample and the RLUs detected by the iSystem Optics. Results are calculated automatically based on the previously established calibration curve.

Specimen Types

1. Verified specimen types were collected in serum separator tubes (SSTs).
2. Vitamin D levels of 30-100 ng/ml were taken as normal and values of less than 30 ng/ml were taken as low.

Statistical Analysis

Continuous variables were summarised as mean and standard deviation. Categorical variables were summarised as frequency and percentage. The mean vitamin D level across three disease activity groups were compared using one-way ANOVA followed by Bonferroni Post-hoc comparison. Correlation between two continuous variables was analyzed using Pearson's correlation. Analysis was done using EpiInfo 7.0 and a p value of < 0.05 was considered statistically significant.

Results:-

The relationship between Vitamin D levels and Rheumatoid arthritis is a debatable subject. The present study was designed to see the serum levels of vitamin D in Rheumatoid arthritis patients and correlation with the disease activity (DAS28₄-ESR).

A total of 100 rheumatoid arthritis patients with the mean age of 41.13±11.528 years were taken for the study after formal informed consent which matched with the age group of the study population taken by **Turhanoglu AD et al²⁰**, **Zakeri Z et al²¹** and **Abbourazzak FE et al²²**. Gender distribution of patients in our study included 77% females and 23 % male patients which matched with the gender distribution of the study population taken by **Attar SM²³** and **Zakeri Z et al²⁴**. There were no significant differences between age and sex with the serum vitamin D levels.

It was found that the inflammatory markers ESR and CRP were raised in 73% and 65% patients respectively. However, RF was ≥3 times elevated in 70% and <3 times elevated in 21% while as it was negative in 9% of patients. Anti CCP was ≥ 3 times elevated in 80% and <3 times elevated in 11% of patients while as it was negative in 9% of the patients.

Low levels of serum vitamin D were found in 63% of the patients recruited in the study which matched with the study conducted by **Haque UJ et al²⁵** and **NajiaHajjaj-Hassouni et al²⁶**. Serum mean Vitamin D levels in the study population was 29.52 ng/ml which matched with the study population conducted by **Zakeri Z et al²⁷** and **NajiaHajjaj Hassouni²⁸**.

Serum mean Vitamin D levels in the high, moderate and low disease activity groups was 21.14±14.844, 27.29±8.156 and 40.03±16.161 respectively which matched with the study population conducted by **Attar SM²⁹** and **Mahdi Fakharan et al³⁰**. The observation was statistically significant (p < 0.001).

Serum 25-OH Vitamin D levels were found to be low in 24 (85.7%) patients in the high disease activity group, 30 (73.2%) patients in the moderate disease activity group and 9 (29%) patients in the low disease activity group. Serum Vitamin D levels were negatively correlated with the disease activity which matched with the study

conducted by AyseDicle et al³¹, Turhanoglu et al³², Attar SM³³, Ifigenia et al³⁴, Hans-Jacob Haga et al³⁵, Mahdi Fakharan et al³⁶, Sharma et al³⁷, Abourazzak FE et al³⁸, and NajiaHajjaj-Hassouni et al³⁹. The observation was statistically significant ($p < 0.001$).

There was also negative correlation between CRP levels and Serum Vitamin D levels which matched with the study conducted by AyseDicle et al⁴⁰, Turhanoglu et al⁴¹ and Ifigenia et al⁴². There was no significant association between age, sex with the disease activity (DAS28₄).

Epidemiological studies suggest that adequate vitamin D levels decrease the risk of developing autoimmune diseases such as multiple sclerosis, inflammatory bowel disease, RA, and type I diabetes mellitus^{43,44}. Recently, preventive treatment with vitamin D of individuals considered at high risk of developing autoimmune diseases has been proposed. On the other hand, a large epidemiological study did not find any association between vitamin D intake and the risk developing RA. Therefore, the role of vitamin D deficiency in the pathogenesis of RA is far from clear.

Discussion:-

In our study, a total of 100 rheumatoid arthritis patients in-line with the criteria laid by American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR), 2010 were recruited with the mean age of 41.13 ± 11.528 years, which included 77% females and 23 % male patients. Our aim was to estimate serum vitamin D levels in the study population and correlate it with disease activity (DAS 28₄). There were no significant differences between age and sex with the serum vitamin D levels. Inflammatory markers ESR and CRP were raised in 73% and 65% patients respectively. Low levels of serum vitamin D were found in 63% of the patients recruited in the study.

Serum mean Vitamin D levels in the study population was 29.52 ng/ml. Serum mean Vitamin D levels in the high, moderate and low disease activity groups was 21.14 ± 14.844 , 27.29 ± 8.156 and 40.03 ± 16.161 respectively which negatively correlated with the disease activity (DAS 28₄) and CRP levels. The observation was statistically significant ($p < 0.001$). There was no significant association between age, sex with the disease activity (DAS28₄).

Conclusion:-

Our study concludes that serum vitamin D levels are lower in rheumatoid arthritis patients and are inversely associated with RA disease activity. Further studies with larger sample sizes and more standardized unbiased methods are required to elucidate a causal role of vitamin D in RA and thus to bring about new approaches for prevention and treatment of this disease.

Bibliography:-

- McInnes I and Schett G. The pathogenesis of rheumatoid arthritis. *NEJM* 2011; 365: 2205-2219.
- Young A, Koduri G. Extra-articular manifestations and complications of rheumatoid arthritis. *Best Pract Res Clin Rheumatol.* 2007; 21(5): 907–927.
- Reid D, Toole BJ, Knox S et al. The relation between acute changes in the systemic inflammatory response and plasma 25-hydroxyvitamin D concentrations after elective knee arthroplasty. *Am J Clin Nutr* 2011; 93: 1006-11.
- Arnson Y, Amital H, Shoenfeld Y. Vitamin D and autoimmunity: new aetiological and therapeutic considerations. *Ann Rheum Dis* 2007; 66: 1137-42.
- Mathieu C, Adorini L. The coming of age of 1,25-dihydroxyvitamin D3 analogs as immunomodulatory agents. *Trends Mol Med* 2002; 8: 174-19.
- Duvallet E, Semerano L, Assier E, Falgarone G, Boissier MC. Interleukin-23: a key cytokine in inflammatory diseases. *Ann Med* 2011; 43: 503-11.
- Lubberts B. Th17 cytokines and arthritis. *Semin Immunopathol* 2010; 32: 43-53.
- Guo YY, Wang NZ, Zhao S et al. Increased interleukin-23 is associated with increased disease activity in patients with rheumatoid arthritis. *Chin Med J* 2013; 126: 85-04.
- Dehghan A, Rahimpour S, Soleymani-Salehabadi H, Owlia MB. Role of vitamin D in flare ups of rheumatoid arthritis. *Zeitschrift fur Rheumatologie.* 2014; 73(5): 461–4.
- Gatenby P, Lucas R, Swaminathan A. Vitamin D deficiency and risk for rheumatic diseases: an update. *Current Opinion in Rheumatology.* 2013; 25(2): 184–91.
- Braun-Moscovici Y, Toledano K, Markovits D, Rozin A, Nahir AM, Balbir-Gurman A. Vitamin D level: is it related to disease activity in inflammatory joint disease? *Rheumatology international.* 2011; 31(4): 493–9.

12. Neve A, Corrado A, Cantatore FP. Immunomodulatory effects of vitamin D in peripheral blood monocyte-derived macrophages from patients with rheumatoid arthritis. *Clinical and Experimental Medicine* 2014; 14(3): 275–83.
13. Szodoray P, Nakken B, Gaal J, Jonsson R, Szegedi A, Zold E, et al. The complex role of vitamin D in autoimmune diseases. *Scand J Immunol.* 2008; 68(3):261–9.
14. Maruotti N, Cantatore FP. Vitamin D and the immune system. *J Rheumatol.* 2010; 37(3):491–5.
15. van Etten E, Mathieu C. Immunoregulation by 1,25-dihydroxyvitamin D₃: basic concepts. *The Journal of steroid biochemistry and molecular biology.* 2005; 97(1–2):93–101.
16. Zold E, Barta Z, Bodolay E. Vitamin D deficiency and connective tissue disease. *Vitamins and Hormones* 2010; 86:261–86.
17. Rossini M. Vitamin D deficiency in rheumatoid arthritis: prevalence, determinants and associations with disease activity and disability. *Arthritis Res Ther* 2010; 12: 2169.
18. Craig SM, Yu F, Curtis JR et al. Vitamin D status and its associations with disease activity and severity in African Americans with recent-onset rheumatoid arthritis. *JRheumatol* 2010; 37: 275-81.
19. Cutolo M, Otsa K, Laas K, Yprus M, Lehtme R, Secchi ME, et al. Circannual vitamin d serum levels and disease activity in rheumatoid arthritis: Northern versus Southern Europe. *ClinExpRheumatol.* 2006; 24(6):702–4.
20. Patel S, Farragher T, Berry J, Bunn D, Silman A, Symmons D. Association between serum vitamin D metabolite levels and disease activity in patients with early inflammatory polyarthritis. *Arthritis Rheum.* 2007 Jul; 56(7): 2143-9.
21. AyseDicleTurhanoflu, HayalGüler, ZaferYönden, Fatma Aslan, AyhanMansuroglu, Cahit Ozer. The relationship between vitamin D and disease activity and functional health status in rheumatoid arthritis. *RheumatolInt* 2011; 31: 911-914.
22. Haque UJ, Bartlett SJ. Relationships among vitamin D, disease activity, pain and disability in rheumatoid arthritis. *ClinExpRheumatol* 2010 Sep-Oct; 28(5): 745-7.
23. Rossini M, MaddaliBongi S, La Montagna G, Minisola G, MalavoltaN, Bernini L et al. Vitamin D deficiency in rheumatoid arthritis: prevalence, determinants and associations with disease activity and disability. *Arthritis Res Ther.* 2010;12(6):R216.
24. Kerr GS, Sabahi I, Richards JS, Caplan L, Cannon GW, Reimold A et al. Prevalence of vitamin D insufficiency/deficiency in rheumatoid arthritis and associations with disease severity and activity. *JRheumatol.* 2011 Jan;38(1):53-9.
25. Turhanoglu AD, Güler H, Yönden Z, Aslan F, Mansuroglu A, Ozer C. The relationship between vitamin D and disease activity and functional health status in rheumatoid arthritis. *Rheumatol Int.* 2011 Jul;31(7):911-4.
26. Attar SM. Vitamin D deficiency in rheumatoid arthritis. Prevalence and association with disease activity in Western Saudi Arabia. *Saudi Med J* 2012 May; 33(5): 520-5.
27. IfigeniaKostoglou-Athanassiou, Panagiotis Athanassiou, AikateriniLyraki, IoannisRaftakis and Christodoulos Antoniadis. Vitamin D and rheumatoid arthritis. *Therapeutic Advances in Endocrinology and Metabolism* 2012; 3(6): 181-187.
28. Hans-Jacob Haga, Anne Schmedes, Yusuf Naderi, Alicia Martin Moreno and Elisabeth Peen. Severe deficiency of 25-hydroxyvitamin D₃ (25-OH-D₃) is associated with high disease activity of rheumatoid arthritis. *ClinRheumatol* 2013; 32: 629-633.
29. Higgins MJ, Mackie SL, Thalayasingam N, Bingham SJ, Hamilton J, Kelly CA. The effect of vitamin D levels on the assessment of disease activity in rheumatoid arthritis. *ClinRheumatol.* 2013 Jun; 32(6): 863-7.
30. Sabbagh Z, Markland J, Vatanparast H. Vitamin D status is associated with disease activity among rheumatology outpatients. *Nutrients.* 2013; 5(7):2268–75.
31. Gheita TA, Sayed S, Gheita HA, Kenawy SA. Vitamin D status in rheumatoid arthritis patients: relation to clinical manifestations, disease activity, quality of life and fibromyalgia syndrome. *Int J Rheum Dis.* 2014.
32. Mahdi Fakharan, AnoushehHaghighi, Mohsen Arabi, Maryam Loghman. Investigating the levels of serum vitamin D in patients with rheumatoid arthritis referred to Rasoul-Akram Hospital During 2011-2012. *Iran J Med Sci* 2014; 39(5): 476-479.
33. Sharma R, Saigal R, Goyal L, Mital P, Yadav RN, Meena PD, Agrawal A. Estimation of vitamin D levels in rheumatoid arthritis patients and its correlation with the disease activity. *JAssoc Physicians India.* 2014 Aug;62(8):678-81.

34. Qiong Hong, Jianhua Xu, Shengqian Xu, Li Lian, Mingming Zhang and Changhai Ding. Associations between serum 25-hydroxyvitamin D and disease activity, inflammatory cytokines and bone loss in patients with rheumatoid arthritis. *Rheumatology* 2014; 53: 1994-2001.
35. Firas Sultan Azzeh and Osama Adnan Kensara. Vitamin D is a good marker for disease activity of rheumatoid arthritis disease. *Hindawi Publishing Corporation Disease Markers* 2015; Article 260725, 6 pages.
36. Abourazzak FE, Talbi S, Aradoini N, Berrada K, Keita S and Hazry T. 25-hydroxy vitamin D and its relationship with clinical and laboratory parameters in patients with rheumatoid arthritis. *Clin Rheumatol* 2015; 34: 353-357.
37. Raczkiewicz A, Kisiel B, Kulig M, Thustochowicz W. Vitamin D status and its association with quality of life, physical activity, and disease activity in rheumatoid arthritis patients. *J Clin Rheumatol*. 2015 Apr; 21(3): 126-30.
38. Zahra Zakeri, Mahnaz Sandoughi, Mohammad A. Mashhadi, Vajihollah Raeesi, Sogol Shahbakhsh. Serum vitamin D level and disease activity in patients with recent onset rheumatoid arthritis. *International Journal of Rheumatic Diseases*. 2016 April; Vol. 19, Issue 4: Pg 343-347.
39. Najia Hajjaj-Hassouni, Nada Mawani, Fadoua Allali, et al. Evaluation of Vitamin D Status in Rheumatoid Arthritis and Its Association with Disease Activity across 15 Countries: "The COMORA Study". *International Journal of Rheumatology* 2017; Vol. 2017, Article ID 5491676, 8 pages.
40. Hollick MF. Vitamin D deficiency. *N Engl J Med* 2007; 357:266-281.
41. Hollick MF. High prevalence of vitamin D inadequacy and implications for health. *Mayo Clin Proc* 2006; 81: 353-373.
42. Cantorna MT, Zhu Y, Froicu M, Wittke A. Vitamin D status, 1, 25-dihydroxyvitamin D₃, and the immune system. *Am J Clin Nutr* 2004; 80: 1717-1720.
43. Harel M, Shoenfeld Y. Predicting and preventing autoimmunity, myth or reality? *Ann NY Acad Sci* 2006; 1069: 322-345.
44. Costenbader KH, Feskanich D, Benito-Garcia E, Holmas M, Karlson E. Vitamin d intake and risks of systemic lupus erythematosus and rheumatoid arthritis in women. *Ann Rheum Dis* 2007; 31:446-447.