IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 19, Issue 11 Ser.10 (November. 2020), PP 31-37
www.iosrjournals.org

To Study the Association between Serum Vitamin D Level and Disease Activity in Patients with Rheumatoid Arthritis

Dr.Linda Marangmei[1],Dr.Ravi Nishad[2],Dr.Ningthoukhongjam Reema[3], Dr.Saitluanga Sailo[4],Dr. ThingbaijamShanti Devi[5],Dr. Prof. Santa Naorem[6]
[2,3](Senior Resident, Department of Medicine, Regional Institute of Medical Sciences, RIMS, Imphal, India)
[1.5](Assistant professor, Department of Medicine, RIMS, Imphal, India)
[4](JuniorResident, Department of Medicine, RIMS, Imphal, India)
[6](Professor, Department of Medicine, RIMS, Imphal, India)
Corresponding author: Dr Ningthoukhongjam Reema

Abstract
Background*: Rheumatoid arthritis (RA) is a chronic, inflammatory, autoimmune disease of unknown etiology affecting approximately 1% of the world population,0.75% in India and 0.2% in Manipur. The hallmark swelling, bony erosions and synovial thickening reflect the underlying inflammatory and auto immune processes of RA.Deficiency of vitamin D is studied for its involvement in the pathogenesis of RA, as well as for correlating with disease activity of RA.Therefore,we conducted this study to derive the correlation between serum vitamin D level and RA disease activity specifically from the cohort population of Manipur,India.*
Methods:*Rheumatoid arthritis patients who were attending Medicine OPD,Rheumatology OPD or admitted inthe General Medicine wards at Regional Institute of Medical Sciences (RIMS), Imphal, Manipur from 2017 to 2019. Total 52 diagnosed cases of RA(2010 ACR-EULAR criteria) were included andserum vitamin D and other related blood investigations were studied.*
Results:*Vitamin D deficiency was found in 17 patients (32.7 %).20 patients had vitamin D insufficiency and remaining 15 patients have normal serum vitamin D level.According to DAS-28 ESR scoring system, 38(73.1%) patients fall under moderate to severe disease activity and 16 of them had vitamin D deficiency, while 3 of them had normal vitamin D level.*
Conclusion:*There was significant association between vitamin D deficiency and disease activitysuggesting Vitamin D deficiency as an independent risk factor for disease severity in RA. Therefore, all RA patients must be given vitamin D supplementation in order to reduce the severity of the disease process.*
Keywords*: Autoimmune disease,DAS-28 ESR ,Rheumatoid arthritis, , vitamin D deficiency,*

Date of Submission: 10-11-2020 Date of Acceptance: 26-11-2020

I. Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory, autoimmune disease of unknown etiology affecting approximately 1% of the world population.[1] It is a systemic autoimmune disease that frequently results in joint deformities and subsequent disabilities.The population prevalence of RA in India is 0.75%.[2] The prevalence of RA in the state of Manipur in northeast India is estimated to be 0.2%.[3]Clinically,themain characteristic feature of established RA is persistent inflammatory synovitis, usually involving small peripheral joints in a symmetrical distributioncausing cartilage damage, bone erosion and joint destruction.

A renewed interest in area of RA research has been the association of dietary and supplemental vitamin D with RA incidence & disease severity .Higher intake of vitamin D was inversely associated with risk of RA.[4]It may be mentioned that worldwide one billion people are estimated to have vitamin D deficiency or insufficiency.[5] Whereas the deficiency of vitamin D in India is very common (50-90%) in all age groups,[6-8]more than ninety percent individuals above 50 years of age have vitamin D deficiency in India.[9] 1,25-dihydroxyvitamin D3 (1,25(OH)2D3) the active metabolite of vitamin D3, is regulator of bone and calcium metabolism. It also exerts immunomodulation via the nuclear vitamin D receptor (VDR) expressed in antigen-presenting cells (APC) and activated T/B cells.[10] Main target of vitamin D immunomodulation are the dendritic cells (DCs) as indicated by inhibition of DC differentiation and maturation. This ultimately leads to vitamin D induced inhibition of DC-dependent T-cell activation.[10] VDR agonists also inhibit the T-cell production of IL-17 which is a pro-inflammatory cytokine produced by Th17 cells in models of organ-specific autoimmunity in the brain, synovium, heart, and intestines.[11] The net effect of the vitamin D is an enhancement of innate immunity with multifaceted regulation of adaptive immunity.[12] Rheumatoid arthritis (RA) is an immune-mediated disease,

mainly driven by Th1 cells. These immunomodulatory activities of vitamin D might be particularly efficient in RA patients and support a therapeutic role of 1,25(OH)2D3 in such a disease.

Deficiency of vitamin D is involved in the pathogenesis as well as disease activity of RA. The decrease of vitamin D is related to older age, female gender and a higher degree of RA activity.[13-14] So, we conducted this study to find out the correlation between rheumatoid arthritis disease activity and serum vitamin D level.

II. Material and methods

This is a cross sectional study conducted in Rheumatoid arthritis patients who were attending Medicine OPD, Rheumatology OPD or admitted in the General Medicine wards at Regional Institute of Medical Sciences (RIMS), Imphal, ManipurfromSeptember 2017 to August 2019.We enrolled 52 patients of Rheumatoid arthritis patients following the criteria.

a. **Inclusion criteria:** Diagnosed cases of rheumatoid arthritis according to 2010 ACR-EULAR criteria[15]with age >18years were included in the study after taking informed consent.

b. **Exclusion criteria:**

Obese patients (BMI >30kg/m^2), patients on glucocorticoids, those with liver/kidney/thyroid diseases, malabsorption syndrome and other auto-immune or chronic diseases were excluded from the study.

Personal details including a detailed history of presenting symptoms, past history and personal history were recorded in proper proforma along with age, sex, body mass index (BMI),disease duration, C-reactive protein (CRP)Erythrocyte sedimentation rate (ESR), serum vitamin D level, Rheumatoid factor (RF) and Anti-CCP antibody level. A detailed relevant clinical examination of every subject was also done. We also noted Tender joint count (TJC),Swollen joint count (SJC), general health by Visual analogue scale 0-100 (VAS-0-100) and disease activity assessed by DAS28ESR.

Study tools:

1.Anti-CCP antibody was estimated by electrochemiluminescence immunoassay (ECLIA) All values >17 IU/ml is considered positive with>51IU/ml as highly positive.

2.Rheumatoid factor: IgM RF was determined by immunoturbidimetry/ nephelometry. A value of <15.9IU/ml was considered normal.

3.C-reactive protein was estimated by latex agglutination method and a value 1-3 mg/dl considered as normal.

4.Erythrocyte sedimentation rate (ESR): determined using Westergren method and expressed in millimeters at the end of first hour. A value of >20mm/1^{st} hour in males and >30mm/1^{st} hour in females wereconsidered high.

5.Serum vitamin D was measured by using ELISA reader at wavelength 450nm using ELISA test kit of Immunodiagnostic Germany by method of Hollis BW. A value of $\geq$ 30 ng/ml is taken as optimal, 20-29 ng/ml as insufficiency and<20 ng/ml as deficiency.

6.Other investigation like kidney function test, liver function test, complete hemogram were done .X-Ray, MRI and USG were done as and when required.

7.**DAS28-ESR** was used to assess disease activity score using parameters of Tender joint count (TJC-28), swollen joint count (SJC-28), erythrocyte sedimentation rate (ESR) and general health
or Visual analogue scale (VAS) (0-100) and classified as follows:

< 2.6 : Remission
2.6-3.1 :Mild disease activity
3.2-5.1 : Moderate disease activity
>5.1 : Severe disease activity

Statistical analysis: Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD and results on categorical measurements are presented in Number (%). p value of < 0.05 was considered statistically significant. Student t test (two tailed, independent),Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

Statistical software: The Statistical software namely SPSS 22.0 and R environment ver.3.2.2 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc**.**

Approval of Research Ethics Board and Informed consent: The study was approved by Research Ethics Board Regional Institute of Medical Sciences, Imphal.

III. Result

The mean age of the study population was 49.63±12.60 years and majority (57.6%) of the them were of 41 to 60 years of age. 47 (90.4%) patients were females while males constituted the remaining 9.6 %. The female to male ratio in our study is 9.4:1. Vitamin D deficiency was found in 17 patients (32.7 %). 20 patients (38.5%) with vitamin D insufficiency and remaining 15 patients (28.8%) had normal vitamin D levels (table 1).

Out of total 52 patients, 40 (76.9%) were <60years of age and11(64.7%) of them were having vitamin D deficiency,16(40%) had vitamin D insufficiency while 13 (32.5%) hadnormal vitamin D levels. 12 patients were above 60 years of age and 6(50%) of them were having Vitamin D deficiency. As per visual analogue scale, out of the 15(28.8%) patients were having > 50 score VAS, 8 of them had vitamin D deficiency, while the rest 7 patients had vitamin D insufficiency(table2).

According to DAS-28 ESR scoring system, 38(73.1%) patients fall under moderate to severe disease activity and 16 of them had vitamin D deficiency, while 3 of them had normal vitamin D levels (table 3).Out of the 52 patients, 18(34.6%) of them had 5 or more tender joints, among them 10 patients(56.8%) had vitamin D deficiency and none of them had a normal vitamin D level. 8(15.4%) patients out of the 52 patients had 5 or more swollen joint counts and among them 5 had vitamin D deficiency and none of them had a normal vitamin D level. 30(57.7%) patients had raised ESR and 16(94.1%) patients among them had vitamin D deficiency(table 4).Out of 52 patients 17 patients had vitamin D deficiency and among them only 2(11.8%) were males (table 5). All the parameters are showing significant p value <0.005, in relation to vitamin D levels and DAS except age parameter.(table 6,7).

Table 1: Serum vitamin D distribution in study population

Serum vitamin D levels	No. of patients	%
Deficiency	17	32.7
Insufficiency	20	38.5
Normal	15	28.8
Total	52	100.0

Table 2: Visual Analogue scale in relation to Serum Vitamin D levels of patients studied

Visual Analogue scale	Serum vitamin D n (%)			Total n (%)
	Deficiency	Insufficiency	Normal	
1-10	0(0%)	1(5%)	14(93.3%)	15(28.8%)
11-20	1(5.9%)	3(15%)	0(0%)	4(7.7%)
21-30	2(11.8%)	1(5%)	1(6.7%)	4(7.7%)
31-40	1(5.9%)	1(5%)	0(0%)	2(3.8%)
41-50	5(29.4%)	7(35%)	0(0%)	12(23.1%)
>50	8(47.1%)	7(35%)	0(0%)	15(28.8%)
Total	17(100%)	20(100%)	15(100%)	52(100%)

Table 3: Association of DAS 28 in relation to Serum Vitamin D levels of patients studied

Variables	Serum vitamin D n(%)			Total (n=52) n(%)	P value
	Deficiency (n=17)	Insufficiency (n=20)	Normal (n=15)		
DAS28					
• Remission	0(0%)	0(0%)	9(60%)	9(17.3%)	<0.001
• Mild	1(5.9%)	1(5%)	3(20%)	5(9.6%)	
• Moderate	13(76.5%)	18(90%)	3(20%)	34(65.4%)	
• Severe	3(17.6%)	1(5%)	0(0%)	4(7.7%)	

Table 4: Tender joint count, Swollen Joint count and ESR in relation to Serum Vitamin D levels of patients studied.

Joint counts	Serum vitamin D n (%)			Total (n=52) n (%)	P value
	Deficiency (n=17)	Insufficiency (n=20)	Normal (n=15)		
Tender joint count					
• 0	0(0%)	0(0%)	11(73.3%)	11(21.2%)	<0.00
• 1	1(5.9%)	3(15%)	3(20%)	7(13.5%)	

• 2-4	6(35.3%)	9(45%)	1(6.7%)	16(30.8%)	
• 5 or more	10(58.8%)	8(40%)	0(0%)	18(34.6%)	
Swollen joint count					
• 0	3(17.6%)	4(20%)	14(93.3%)	21(40.4%)	<0.001
• 1	1(5.9%)	2(10%)	1(6.7%)	4(7.7%)	
• 2-4	8(47.1%)	11(55%)	0(0%)	19(36.5%)	
• 5 or more	5(29.4%)	3(15%)	0(0%)	8(15.4%)	
ESR					
• Male <20; Female <30	1(5.9%)	6(30.0%)	15(100.0%)	22(42.3%)	<0.001
• Male >20; Female >30	16(94.1%)	14(70.0%)	0	30(57.7%)	

Table 5: Association of age and gender in relation to Serum Vitamin D levels of patients studied.

Variables	Serum vitamin D n (%)			Total (n=52) n (%)	P value
	Deficiency (n=17)	Insufficiency (n=20)	Normal (n=15)		
Age in years					
• 21-30	0(0%)	3(15%)	1(6.7%)	4(7.7%)	0.880
• 31-40	2(11.8%)	3(15%)	4(26.7%)	9(17.3%)	
• 41-50	6(35.3%)	5(25%)	4(26.7%)	15(28.8%)	
• 51-60	5(29.4%)	6(30%)	4(26.7%)	15(28.8%)	
• 61-70	2(11.8%)	2(10%)	2(13.3%)	6(11.5%)	
• 71-80	2(11.8%)	1(5%)	0(0%)	3(5.8%)	
Gender					
• Male	2(11.8%)	2(10%)	1(6.7%)	5(9.6%)	1.000
• Female	15(88.2%)	18(90%)	14(93.3%)	47(90.4%)	

Table 6: Comparison of clinical variables in relation to Serum Vitamin D levels of patients studied

	Serum vitamin D (Mean + SD)			Total (Mean + SD)	P value
	Deficiency	Insufficiency	Normal		
Age in years	53.71±12.84	48.75±12.39	46.20±12.14	49.63±12.60	0.228
Tender joint count	5.88±3.20	4.10±2.17	0.33±0.62	3.60±3.17	<0.001
Swollen joint count	2.82±2.13	2.45±1.96	0.07±0.26	1.88±2.06	<0.001
ESR	54.29±13.32	46.75±17.27	14.13±7.30	39.81±21.54	<0.001
Visual Analogue scale	52.35±16.69	46.50±17.93	6.00±6.21	36.73±24.78	<0.001
DAS 28	5.22±0.89	4.77±0.84	2.02±0.53	4.13±1.57	<0.001
Serum vitamin D level	15.71±2.93	24.95±3.39	41.00±8.27	26.56±11.29	<0.001

Table 7: Comparison of clinical variables in relation to DAS 28 of patients studied.

Variables	DAS28 levels (Mean + SD)				Total (Mean + SD)	P value
	Remission	Mild	Moderate	Severe		
Age in years	43.22±10.27	47.80±15.87	50.09±11.95	62.50±12.58	49.63±12.60	0.079+
Tender joint count	0.22±0.44	1.40±2.61	4.12±2.45	9.50±1.91	3.60±3.17	<0.001
Swollen joint count	0.00±0.00	0.80±1.30	2.15±1.88	5.25±1.71	1.88±2.06	<0.001
ESR	11.89±6.07	30.00±21.51	46.68±18.38	56.50±7.23	39.81±21.54	<0.001

Visual Analogue scale	4.33±3.71	16.20±20.24	44.71±19.07	67.50±5.00	36.73±24.78	<0.001
DAS 28	1.81±0.35	3.00±1.50	4.67±1.03	6.10±0.34	4.13±1.57	<0.001
Serum vitamin D level	42.56±9.49	32.40±11.28	22.47±7.61	18.00±2.58	26.56±11.29	<0.001

IV. Discussion

Vitamin D deficiency increases the risk of developing autoimmune diseases such as multiple sclerosis, inflammatory bowel disease, type I diabetes mellitus and especially RA [16-18]where low vitamin D level is implicated as an independent risk factor in RA development[4].Althoughthe exact etiology is still unknown, many environmental and genetic factors play an important role. RA which is the most common chronic systemic polyarthritis ismediated by Th1 cells.Vitamin D has immunoregulatory activity and vitamin D receptors are present in a number of cells of the immune system, antigen presenting cell, activated T lymphocyte and activated B lymphocyte.Vitamin D leads to induction of regulatory T cell and NK T cell and inhibits TH1 cell response so, vitamin D suppresses experimental autoimmunity[19]. Monolagas et al[20] found that significantly greater proportion of seropositive RA patients (76%) had lymphocyte possessing vitamin D receptor compared with healthy controls (18%). Cherniak[21] also studied 84% prevalence of vitamin D insufficiency (serum level <30 ng/ml) in RA patients. In our study, vitamin D deficiency or insufficiency was indirectly related to severity of RA.

Regarding the disease activity, numerous studies had linked low vitamin D level with increased disease activity in RA.[4,22-25] We found that patients of RA having high disease activity(with increased inflammatory burden) had significantly low vitamin D level compared to patients of RA having low disease activity. Patel et al[22] also found similar results which showed inverse association between disease activity and vitamin D metabolite concentration in early polyarthritis patients. Kerr GS et al[26] also concluded that 25(OH) vitamin D deficiency, but not insufficiency, was independently associated with higher tender joint counts and highly sensitive CRP levels.We also found a significant negative correlation between diseases activity measured by DAS-28 score and serum vitamin D level. Our results are compatible with the study done ofTurhanoglu et al[27] which also showed significant negative correlation between disease activity measured by DAS-28 score and vitamin D level.

Regarding the age of patientin our study, increased in age does not correlate with vitamin D deficiency in RA patient (p value- 0.228). However, NajiaHHet al[28] reported that the low level of vitamin D were associated with increase in age. The sex ratio for RA is typically around 3:1 as per Wolfe AM et al[29].But in our study, it is 9:1 ratio.With respect to ESR, in our study we have found that increase in age was directly related to the rise in ESR in RA patient. Siemons L et al[30]showedthat age and sex are independently associated with the levels of both acute phase reactants in early RA, emphasizing the need to take these external factors into account when interpreting disease activity measures.

Sanjeev Patel et al[22]showed there was an inverse relationship between 25(OH)D levels and the tender joint count and DAS28 score. Each 10-ng/ml increase in the level of 25(OH)D was associated with a decrease in the DAS28 score of 0.3 and in the CRP level of 25%. In our study, DAS 28 score is showing direct relationship with vitamin D deficiency with p value of < 0.001. Tamrakar BK et al[31], found that in RA patientsserum 25-hydroxy vitamin D levels were negatively correlated to anti-CCP antibody levels (rs = 0.72, p <0.001), and ESR (rs = 3.95, p <0.005). Similar result is also shown in our study that vitamin D deficiency level is inversely proportional to ESR value with p value of <0.001.

Patel et al[22]reported vitamin D level was an independent predictor of greater disability in persons with active RA, even after controlling for age, race and disease activity. Vitamin D deficient patients had six times the odds of needing assistance with activities of daily living. In patients with moderate to high disease activity, vitamin D deficiency was associated with higher DAS scores, pain and disability.In our study both swollen joint count and tender joint count are more with decrease in vitamin D level with a significant p value of <0.001. Sherif R Elbassiony et al[32]found SJC, TJC, VAS-pain and DAS28-CRP were significantly higher in RA patients with Vitamin D deficiency as compared to patients with insufficiency or normal Vitamin D levels. Many studies reported inverse significant associations between Vitamin D and DAS28, pain, SJCand TJC in RA patients[33,34]. Kerr et al[26] found that serum vitamin D correlated with TJC only in patients with deficiency but not in those with 25(OH)D insufficiency. Although TJC and VAS-pain were inversely associated with Vitamin D concentration in the univariate analysis, these associations failed to meet significance following multivariate adjustments whereas SJC and DAS28-CRP remained statistically significant following adjustments for age and sex, suggesting that the association of TJC and VAS-pain is explained primarily by the disease activity.Sherif R Elbassiony et al[32] showed that SJC and DAS28-CRP were significant predictors of Vitamin D levels.

V. Conclusion

There was significant association between vitamin D deficiency and disease activity (assessed through DAS28-ESR score) as well as ESR, TJC and SJC. Hence, we proposed that Vitamin D deficiency is an independent risk factor for increasing the severity of the disease process in RA. Therefore, all RA patients must be given vitamin D supplementation in order to reduce the severity of the disease process.

Declarations:
Funding: None
Conflict of Interest: None declared
Approval of research ethics board**:** Taken

References

[1]. Gibofsky A. Overview of epidemiology, pathophysiology and diagnosis of rheumatoid arthritis. Am J Manag Care 2012;18(13):295-302.
[2]. Malaviya AN, Kapoor SK, Singh RR, Kumar A, PandeI. Prevalence of rheumatoid arthritis in the adult Indian population. Rheumatol Int 1993;13(4):131-4.
[3]. Chopra A. Disease burden of rheumatic disease in India: copcord perspective. Indian J Rheumatol 2015;10(2):70-7.
[4]. Merlino LA, Curtis J, Mikuls TR, Cerhan JR, Criswell LA, Saag KG. Iowa women's health study. Arthritis Rheum 2004;50:72–7.
[5]. Hollick MF. Vitamin D deficiency. N Engl J Med 2007;357:266-81.
[6]. Harinarayan CV, Joshi SR. Vitamin D status in India-its implications and remedial measures. J Assoc Phys India 2009;57:40-8.
[7]. Marwaha RK, Sripathy G. Vitamin D and bone mineral density of healthy school children in northern India. Indian J Med Res 2008;127:239-44.
[8]. Harinarayan CV. Prevalence of vitamin D insufficiency in postmenopausal South Indian women. Osteoporos Int 2005;16:397-402.
[9]. Marwaha RK, Tandon N, Garg MK. Vitamin D status in healthy Indians aged 50 years and above. J Assoc Phys India 2011;59:706-9.
[10]. Van EE, Mathieu C. Immunoregulation by 1,25-dihydroxyvitamin D3: basic concepts. J Steroid Biochem Mol Biol 2005;97:93–101.
[11]. Steinman L. A brief history of TH17, the first major revision in the TH1/TH2 hypothesis of T cell-mediated tissue damage. Nat Med 2007;13:139–45.
[12]. Adorini A, Penna G. Control of autoimmune diseases by the vitamin D endocrine system. Nat Clin PractRheumatol2008;4:404–12.
[13]. Song GG, Bae SC, Lee YH. Association between vitamin D intake and the risk of rheumatoid arthritis: A meta-analysis. Clin Rheumatol2012;31:1733-9.
[14]. Kim TH, Choi SJ, Lee YH, Song GG, Ji JD. Combined therapeutic application of mTOR inhibitor and vitamin D(3) for inflammatory bone destruction of rheumatoid arthritis. Med Hypotheses 2012;79:757-60.
[15]. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/ European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010 Sep;62(9):2569-81.
[16]. Cantorna MT, Hayes CE, DeLuca HF. 1,25-Dihydroxyvitamin D3 reversibly blocks the progression of relapsing encephalomyelitis, a model of multiple sclerosis. Proc Natl Acad Sci USA 1996;93:7861–4.
[17]. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr2004;80:1678–88.
[18]. Kamen DL, Cooper GS, Bouali H, Shaftman SR, Hollis BW, Gilkeson GS. Vitamin D deficiency in systemic lupus erythematosus. Autoimmun Rev 2006;5:114–7.
[19]. Jones G, Strugnell SA, DeLuca HF. Current understanding of themolecular actions of vitamin D. Physiol Rev 1998;78:1193–231.
[20]. Manolagas SC, Werntz DA, Tsoukas CD, Provvedini DM, Vaughan JH. 1,25-dihydroxyvitamin D3 receptors in lymphocytes from patientswith rheumatoid arthritis. J Lab Clin Med 1986;108:596–600.
[21]. Cherniack EP. A ray of hope for tender joints: vitamin D and rheumatoid arthritis. J Rheumatol2011;38:5-7.
[22]. 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;56:2143–9.
[23]. Liao KP, Alfredsson L, Karlson EW. Environmental influences on risk for rheumatoid arthritis. CurrOpinRheumatol2009;21:279-83.
[24]. Nielen MM, van Schaardenburg D, Lems WF. Vitamin D deficiency does not increase the risk of rheumatoid arthritis. Arthritis Rheum 2006;54:3719-20.
[25]. Costenbader KH, Feskanich D, Holmes M, Karlson EW, Benito GE. Vitamin D intake and risks of systemic lupus erythematosus and rheumatoid arthritis in women. Ann Rheum Dis 2008;67:530-5.
[26]. Kerr GS, Sabahi I, Richards JS, Caplan L, Cannon G, Reimold A, et al. Prevalence of vitamin D insufficiency/ deficiency in rheumatoid arthritis and associations with disease severity and activity. J Rheumatol 2011;38(1):53–9.
[27]. Turhanoglu AD, Güler H, Yönden Z. The relationship between vitamin D and disease activity and functional health status in rheumatoid arthritis. Rheumatol Int 2009;10:1393-6.
[28]. Najia HH, Nada M, Fadoua A, Hanan R, Kenza H, Ihsane H, et al. Evaluation of vitamin D status in rheumatoid arthritis and its association with disease activity. Intern J Rheumatol2017;67:1-8.
[29]. Wolfe AM, Kellgren JH, Masi AT. The epidemiology of rheumatoid arthritis: a review of incidence and diagnostic criteria. Bull Rheum Dis 1968;19(3):524-9.

[30]. Siemons L, Klooster PM, Vonkeman HE, Vanriel PL, Glas CA, Vandelaar MA. How age and sex affect the erythrocyte sedimentation rate and C-reactive protein in early rheumatoid arthritis. BMC MusculoskeletDisord. 2014;15:368.
[31]. Tamrakar BK, Karki D, Nagila A. Decreased level of vitamin D is associated with rheumatoid arthritis patients from Western Region of Nepal. J-GMC-N 2018;11(2)46-50.
[32]. Elbassiony SR, Tawhid Z, Ahmad HS, Sabry A. Serum 25-hydroxy vitamin D levels in Egyptian patients with rheumatoid arthritis: association with disease activity, functional disability and radiological damage. Egypt Rheumatol 2016;38(1):133-9.
[33]. Craig SM, Yu F, Curtis JR, Conn DL, Jonas B, Callahan LF, et al. Vitamin D status and its associations with disease activity and severity in African Americans with recent-onset rheumatoid arthritis. J Rheumatol2010;37:275–81.
[34]. Haque UJ, Bathon JM, Giles JT. Association of vitamin D with cardiometabolic risk factors in rheumatoid arthritis. Arthritis Care Res (Hoboken) 2012;64(10):1497–504.

Dr Ningthoukhongjam Reema, et. al. "To Study the Association between Serum Vitamin D Level and Disease Activity in Patients with Rheumatoid Arthritis." *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 19(11), 2020, pp. 31-37.