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Correlation of level of expression of Wnt Signaling Pathway Inhibitor Dickkopf-1 with disease activity in Elderly patients of Rheumatoid Arthritis: A cross sectional study

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ABSTRACT

Objective: To correlate the level of Dickkopf-1 (DKK-1) and its role in rheumatoid arthritis (RA) patients of elderly age group.
Methods: Serum samples were collected elderly RA patients fulfilling the inclusion criteria coming to Geriatric outdoor clinic between June 2018 to September 2018. DKK-1 was detected by ELISA. Serum C-reactive protein (CRP) levels, erythrocyte sedimentation rates (ESR), rheumatoid factor (RF) titers, and anti-cyclic citrullinated peptide antibody were also measured in patients with RA.
Results: Twenty one patients were enrolled in study period. The serum level of DKK-1 was significantly higher in patients with severe RA with high DAS score ($p < 0.01$); The serum DKK-1 level was correlated with T-score ($r= -0.588$; $p = 0.005$), Z-Score($r= -0.458$, $p = 0.037$) and the larson score of radiologic change ($r = +0.673$, $p = 0.001$) in RA, however not correlated significantly with ESR, CRP.
Conclusion: DKK-1 may serve as a biomarker of bone erosion and correlates with the disease activity in RA patients of elderly age group.

Keyword: DKK 1, Rheumatoid arthritis, Geriatric, Osteoporosis.

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INTRODUCTION

Rheumatoid arthritis (RA) is commonest form of symmetric peripheral polyarthritis involving predominantly small joints of the hands and feet. It is an autoimmune disorder characterized by chronic inflammation of synovial joints, which leads to articular destruction and functional disability. Bone erosion which is hallmark of RA is due to imbalance between bone formation and resorption for which osteoclasts play a major role.[1] Growth and differentiation of osteoblasts is controlled by Dickkopf-1 (DKK-1) of Wingless (Wnt) signaling pathway.[2] Dickkopf-1 (DKK-1) is an endogenous, secreted inhibitory factor in the canonical Wnt signaling by binding the Wnt coreceptor LRP5/65.[3]DKK-1 could increase the expression of the osteoclast differentiation factors by enhancing RANKL/RANK interaction[4]. Further, DKK1 also plays an important role in the promotion of synovial angiogenesis[5]. Data regarding role of DKK-1 in RA elderly patients in bone destruction and inflammation in RA and its correlations with disease activity and laboratory characteristics of RA patients, have not been thoroughly clarified.

MATERIAL AND METHODS

A cross sectional study was done between June 2018 to September 2018 in Department of Geriatric Medicine, Sir Sunderlal Hospital BHU, a tertiary centre in eastern Uttar Pradesh, India after taking approval from Institute's ethical committee. Informed consent was taken from the patients. All RA patients of age >50 years diagnosed by 2010 ACR/EULAR criteria.(American rheumatology criteria) were included in study. Exclusion criteria included patients of age less than 50 years, patients on treatment of disease modifying anti rheumatic drug, evidence of steroid use in past 1 month, calcium supplement in last 3 months and presence of Diabetes Mellitus, or any chronic illness. No formal method of sample size calculation was made it being a pilot study.

Clinical history and examination of all patients was done for the study. Routine investigations included complete blood counts, liver function test, random blood sugar, RA titre, CRP titre, anti-cyclic citrullinated peptide(anti CCP_2) was obtained.

X-ray of various joints of hand, wrist and feet was obtained and Larsen scoring was done for each.[6] Bone marrow density

(BMD) was obtained for each sample.[7] Disease Activity was measured by disease activity Score (DAS28) along with Modified Health assessment Questionnaire (MHAQ) score for all patients.[8,9]

DKK1 measurement was done by RayBio® Human DKK-1 ELISA Kit with intra-assay coefficient of variation percent (CV %), <10% and inter-assay CV %, <12%).

Statistical Analysis:

The data was analysed by software SPSS version 23.0. Continuous variables are presented as Mean±standard deviation (SD) and categorical variables are presented as numbers and/or percentages. Kolmogorov–Smirnov test was used to test the normality of distribution of continuous variables. The association between continuous variables was analysed by Pearson's or Spearman's correlation coefficients.

RESULT

Twenty one patients fulfilled the inclusion criteria in study period. Out of 21 cases, there were 15(71.4%) female and 6 (28.57%) male patients. Mean age was 57.62±9.00 years. Comparison of various hematological and biochemical parameters of cases is shown in table 1.

Mean DKK1 was 445.91 & DAS score was 2.19±0.87. Table 2 show mean values of age, Larson score, Bone mineral density(BMD), DAS score, T and Z score, MHAQ score, CRP and ESR parameters and their correlation with DKK-1.

DKK-1 level was correlated with T-score (r= -0.588; p = 0.005), Z-Score(r= -0.458, p = 0.037), DAS28 score(r = +0.460, p = 0.036) and the larson score of radiologic change (r = +0.673, p = 0.001) in elderly RA patients, however it was not correlated significantly with ESR, CRP.

Table 1: Hematological and biochemical parameters of patients

Variable(N=21)	Mean ± S.D
Age	57.62 ± 9.00
Hemoglobin (gm%)	10.37± 2.02
Total Leucocyte count(TLC)	10050.29 ± 3160.35
Platelet	2.79 ± 2.60
Creatinine	0.92 ± 0.20
Serum Calcium	8.71 ± 0.93
Urea	28.95 ± 12.95

Table 2: Correlation of Dickkopf-1 (Dkk-1) with different Parameters

Variable (N=21)	Mean± SD	Pearson correlation Coefficient value (r)	P-value
Age	57.62 ± 9.00	+0.508	**0.019***
Larsen Score	3.52 ± 1.16	+0.673	**0.001***
BMD (Bone mineral density)	0.88 ± 0.28	-0.139	0.548
T-Score	-3.10 ± 1.17	-0.588	**0.005***
Z-Score	-2.20 ± 0.95	-0.458	**0.037***
DAS Score	2.19 ± 0.87	+0.460	**0.036***
MHAQ- Score	1.95 ± 0.97	+0.397	0.074
CRP	8.23 ± 21.46	+0.210	0.360
ESR	42.62 ± 21.86	+0.181	0.432

Note:

1. 0.1< I<rI <0.3 Small/Weak
2. 0.3< I<rI <0.5 Medium/Moderate
3. 0.5< I<rI Large/Strong Correlation

DISCUSSION

Bone erosion and joint deformation is hallmark of inflammatory joint disease. DKK-1 has the strongest inhibitory effect on the Wnt pathway[10]. Previous studies have demonstrated that DKK-1 promote osteolytic lesions in vivo by enhancing osteoclastogenesis. Studies have shown that DKK1 is higher in healthy population with osteoporosis than non-osteoporosis. So it can be used as marker of osteoporosis. The infiltration of immunocompetent cells and proliferation of synovial fibroblasts in synovial lining leads to the formation of pannus tissue, which invades the articular cartilage and subchondral bone as a characteristic of RA. The above features were all associated with DKK-1. [11]

Mean haemoglobin level found to lower side in study group was 10.37± 2.02 mg/dl. Previous studies have shown that anaemia develops in 30%-70% of patients with RA.[12,13] From above results it's concluded anaemia is common in patient with rheumatoid arthritis and usually anaemia of chronic disease was seen.

Mean calcium level was found to have at lower level in study group was 8.71±0.93 mg/dl. It was in accoradnace with previous studies and suggest that rheumatoid arthritis patient have low calcium level with disease affecting the joint destruction and erosion, needs to supplement calcium along with other treatment options in RA.[13]

In our study mean DKK1 level was found to be high in patients with osteoporosis as found in other studies. In our study, significantly correlated with T and Z Score.[14] Above results suggests that as rheumatoid arthrtis is chronic disease of bone having bone destructive effect so DKK1 in RA patient will be higher with osteoporosis than non osteoporosis. It suggest it can be used as a marker for bone destruction and follow up.

DKK1 level shows positive correlation in RA patient with radiological progression. Larsen score for which was ; r value 0.673 and p value of 0.001 ,which is statistically significant. In a study by Raphaèle Seror et al mean baseline DKK-1 level was higher among RA patients with radiological changes than without radiological progression (29.6 ± 13.3 vs 26.63 ± 12.4 pmol/L) (p = 0.0084).[14]

CONCLUSION

Results suggest that with increase in disease progresions and bone distruction, serum level of DKK1 will increase. Hence serum DKK1 can used as marker for bone destruction and osteoporosis.

Conflict of interest: None

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