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General Medicine

A PROSPECTIVE STUDY COMPARING ULTRASONOGRAPHIC FINDINGS AND INFLAMMATORY MARKERS AS A PREDICTOR OF JOINT EROSIONS IN RHEUMATOID ARTHRITIS.

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ABSTRACT Rheumatoid arthritis is chronic inflammatory disease that affects the joints. This results in painful joints, swelling and stiffness in the joints. The present prospective comparative study aimed to compare the USG Doppler findings with the inflammatory marker levels in being a better predictor of joint erosions in rheumatoid arthritis. Total 50 patients coming rheumatology and medicine OPD were studied for inflammatory markers and ultrasonography findings. Radiological investigations such as High resolution USG power Doppler (4-12 MHz) and x-ray of the affected joints were carried out. Majority of participants (60%) belonged to 31-50 years of age group and female gender (86%). The change in inflammatory markers were found to be poorly correlated to joint erosions, while that of USG erosions was found to be strongly positively correlated with the same. Multivariate regression analysis showed that in presence all others also only delta USG erosion significantly impacts delta VDH, or the gold standard(X Ray) for evaluation joint erosion This strongly proves that USG erosion is a better predictor of joint erosions than the other independent variables(inflammatory markers).

KEYWORDS : Rheumatoid arthritis, inflammatory markers, ultrasonographic findings, joint erosion.

Introduction

Rheumatoid arthritis is a chronic inflammatory disease of unknown etiology. It is characterised by a symmetric polyarthritis and is the most common form of chronic inflammatory arthritis whose incidence being 0.4 per 1000 females and 0.2 per 1000 males, with a rising incidence rate with time. It is diagnosed and classified with the help of the 2010 ACR/EULAR criteria which includes different clinical and laboratory parameters which are described later in this paper. The pathological hallmarks of Rheumatoid arthritis are synovial inflammation and proliferation, focal bone erosions, and thinning of articular cartilage.[1]

In rheumatoid arthritis (RA), synovitis appears to be the primary abnormality responsible for structural joint damage[2]. Doppler ultrasound (US) can detect pathological vascularization within joints and changes in the periarticular soft tissues, and thus can demonstrate the presence of active inflammation, which can be correlated with the neoangiogenesis in the synovium. Power Doppler (PD) is a valid tool for the detection and quantification of synovial vascularization.[3]Early diagnosis of RA is important because early aggressive treatment reduces the long-term disability.[4]Clinical examination, and laboratory tests are limited in their usefulness. Radiographic changes occur late and may not be detected early in the disease course.[5, 6] In the early course of RA, application of US including both PD and gray scale imaging has been shown to be more sensitive than clinical examination in determining synovitis.[7]Conventional radiography has been the imaging modality of choice in RA primarily because of its reproducibility and feasibility with respect to detecting structural damage[2-4]. However, radiography can provide only indirect information on synovial inflammation, and the technique is insensitive to early inflammatory bone involvement and bone damage. Another helpful tool that aids us get a fair idea of the extent of disease activity are our serological inflammatory markers, namely ESR (Erythrocyte Sedimentation Rate), CRP (C - reactive protein) and to some extent, the platelet count, released by the cells of inflammation as a response to the ongoing inflammatory process, the very essence of the pathogenesis of the disease, these are some of the wide range of serum derived 17 markers, the tools which tell us the overall condition of the inflammatory state the body is in. Albeit nonspecific, they are highly sensitive markers, sensitive for assessing the level of inflammation, as has been seen in previous studies.[8] Natural course of the disease, when persistently active, often results in articular cartilage and bone destruction, thereby causing functional disability. Thus it is vital to diagnose and treat this disease early and aggressively before damage ensues, causing irreversible damage to the joints leading to significant impairment in functionality and quality of life. With two big instruments at hand, radiological and biochemical inflammatory markers, eg ESR and CRP, diagnosis and assessment of severity and progression of the disease eases out, and makes way for timely intervention, to curb the disease progression and resultant morbidity. We endeavoured to find here, whether the aforementioned inflammatory markers gave us a better overview of the ongoing joint activity changes, or is it that the grey scale and Doppler ultrasonographic findings were more sensitive in picking up the early changes that signifies ongoing activity, that would help us ascertain whether there is a mismatch between the findings of the two, or which one is a better predictor of inflammatory activity at the rheumatoid joints. Thus, this study aims at comparing the USG Doppler findings with the inflammatory marker levels in being a better predictor of joint erosions in rheumatoid arthritis.

Materials and methods

Study setting and study population:

This study was prospective observational study conducted among the patients attending the General Medicine and Rheumatology OPD of Medical College & Hospital, Kolkata. Patients attending medicine these OPDs and fulfilling inclusion criteria were selected for the study.

Inclusion criteria:

- Patients who have been diagnosed with rheumatoid arthritis as per ACR/EULAR 2010 criteria.
- Patients between 16 and 75 years of age
- Patients who give consent for the study
- Patients with disease duration less than 2 years
- DMARD use less than 6 months.

Exclusion criteria:

- Patients with a history of fever at onset of the study
- Patients with any accompanying organ failure
- Severely deformed rheumatoid patients
- Suspicion of any overlapping disease
- Patients with any chronic infections which would affect the inflammatory markers.

Study duration and sample size: The present study was carried out during February 2018 to August 2019. Based on previous years' records, we took the sample size around 50 patients. Consecutive sampling method was used to these 50 patients from OPDs.

Methodology:

Patients fulfilling inclusion/exclusion criteria were included in study after taking written informed consent. Detailed medical history and clinical examination of patients were done using general assessment scoring and DAS28 scoring. All patients were subjected to laboratory tests such as Rheumatoid factor, serum ACPA, ESR, CRP and platelet count. Following clinical and laboratory parameters were considered during conduction of this study. Radiological investigations such as High resolution USG power Doppler (4-12 MHz) and x-ray of the affected joints were carried out.

Ethical Issues:

Ethical approval was taken institutional ethics committee of medical college, Kolkata. Written informed consent was taken from each patient after explaining the study purpose. Confidentiality of data was maintained. Those having clinical disease were given appropriate treatment.

Statistical analysis

The statistical software SPSS version 20 was used for the analysis. Continuous variables were expressed as Mean, Median and Standard Deviation, and compared across the groups using Mann-Whitney U test/Kruskal Wallis Test as appropriate. Associations between Continuous variables were captured using Spearman's Rank Correlation Coefficient. An alpha level of 5% was taken, i.e. if any p value is less than 0.05 it was considered as significant and a p value of >0.05 as insignificant.

Results

Age distribution in the study population of 50 patients majority were in the fourth and fifth decade (30% each). Followed by sixth decade (18%), third decade (16%), and the least in the seventh decade of life(6%). Above chart shows the sex distribution of study population most of the patients were females (86%), with only 7 males (14%). (Table 1)

Table. 1. Distribution of study population according to baseline characteristics (n=50)

Variable		Frequency (N=50)	Percent
Age group in years	21-30	8	16.0
	31-40	15	30.0
	41-50	15	30.0
	51-60	9	18.0
	61-70	3	6.0
Sex	Male	7	14
	Female	43	86
Smoker	No	46	92
	Yes	4	8

The mean ESR at baseline (mean± s.d.) of patients was 38.31 ± 15.1. The mean ESR after 8 months (mean± s.d.) of patients was 33.15 ± 15.18. Distribution of mean ESR at baseline and 8 months after was statistically significant (p=0.002). The mean CRP at baseline (mean± s.d.) of patients was 16.89 ± 8.37. The mean CRP after 8 months (mean± s.d.) of patients was 12.50 ± 8.83. Distribution of mean CRP at baseline and 8 months after was statistically significant (p<0.001). Similarly, the mean platelet count was also statistically significant (p<0.001). The mean ± s.d. DAS28 score at baseline and after 8 months was 5.29 ± 0.79 and 5.29±0 .79respectively.(Table 2)

Table 2 : Distribution of various Clinical parameters amongst the study population.(n=50)

Variable	At baseline Mean(±S.D.)	After 8 months Mean(±S.D.)	p-value
ESR	38.31(±15.1)	33.15(±15.1)	0.002
CRP	16.89(±8.3)	12.50(±8.8)	<0.001
Platelet count	3.9(±1.2)	3.15(±.94)	<0.001
DAS28	5.3(±0.79)	3.4(±1.1)	<0.001

The mean USG Synovial Proliferation at baseline (mean± s.d.) of patients was 9.94 ± 3.513. The mean USG Synovial Proliferation post 8 months (mean± s.d.) of patients was 4.32 ± 3.728. Distribution of mean USG Synovial Proliferation according to baseline and after 8 months was statistically significant (p<0.001). Distribution of mean USG Synovial to baseline and after 8 months was statistically significant (p<0.001) with baseline mean (± s.d.) 10.28 (± 3.7.) and after 8 month mean (± s.d.) value 4.80 (± 3.796); also the USG Synovial Vascularity , Joint Erosion were having statistically significant (P value <0.001).

The mean Xray Soft Tissue Swelling at baseline (± s.d.) of patients was 9.92 (± 5.78). The mean Xray Soft Tissue Swelling after 8 months (± s.d.) of patients was 5.42 (± 4.68). Distribution of mean Xray Soft Tissue Swelling was statistically significant at baseline and after 8 months .All other X ray findings as we can appreciate in table no.3 were statistically significant. (Table 3)

Table 3: Distribution of study population according to radiological findings (n=50)

Variable	At baseline Mean(±S.D.)	After 8 months Mean(±S.D.)	p-value
USG Synovial Proliferation	9.94(±3.5)	4.32(±3.7)	<0.001
USG Synovial Effusion	10.28(±3.7)	4.8(±3.7)	<0.001
USG Synovial Vascularity	9.92(±9.92)	4.94(±3.96)	<0.001
USG Joint Erosion	5.06 (±4.4)	11.50 (±4.3)	<0.001
Xray Soft Tissue Swelling	9.92(±5.788)	5.42(±4.686)	<0.001
Xray Juxtaarticular Osteoporosis	9.64(±5.9)	5.68 (±5.501)	<0.001
Xray Marginal Erosions	7.26(±7.3)	12.22(±7.9)	<0.001
Xray Joint Space Narrowing	1.68(±2.29)	2.34(±2.3)	<0.001
VDH Score	8.98(±9.3)	14.56(±9.90)	<0.001

Table 4 shows correlation between the change(delta) of inflammatory markers(ESR,CRP, platelet) and change (delta) USG joint erosions, with change of (delta) gold standard (X Ray joint erosion, or VDH Score). It shows that the inflammatory markers were poorly correlated: with delta ESR/delta VDH had a correlation of 0.212(least), delta platelet/delta VDH had a correlation coefficient of 0.246(less), and with delta CRP/delta VDH had a correlation coefficient of 0.252 (less). The change in(delta) USG joint erosion finding, on the other hand, was strongly positively correlated with change in(delta) gold /standard, i,e, delta VDH , with a correlation coefficient of 0.645, with a P value of <0.001

Table 4: Correlational matrix showing strength of correlation between the change (delta) of inflammatory markers and USG joint erosions, with gold standard (X Ray joint erosion, or VDH Score).

		Delta VDH
Delta CRP	Correlation coefficient	0.252
	p-value	0.078
Delta ESR	Correlation coefficient	0.212
	p-value	0.139
Delta Platelet	Correlation coefficient	0.246
	p-value	0.085
Delta USG erosion	Correlation coefficient	0.645
	p-value	<0.001

Table 5 shows multivariable regression analysis showing how change (before-after study) in XRay VDH scores [delta VDH] simultaneously depends on the change in other variables: the inflammatory markers (CRP/ESR/platelet) and USG findings of joint erosions . It shows in presence all others also only delta USG erosion significantly impacts delta VDH for evaluation joint erosion.(regression coefficient 0.770, with P value <0.001. `

Table 5. Mulitvariable regression analysis between inflammatory markers, USG erosion and VDH score.

	Coefficients	P-value	95% confidence interval	
			Lower Bound	Lower Bound

Constant	-0.023	0.986	-2.722	2.675
Delta CRP	-0.024	0.860	-0.299	0.250
Delta ESR	0.039	0.590	-0.107	0.185
Delta Platelet	0.68	0.201	-0.375	1.735
Delta USG erosion	0.77	<0.001	0.454	1.085

Dependent variable: VDH

Discussion

Rheumatoid arthritis disease being chronic inflammatory disease mostly seen in elderly people; in our study with a sample size of 50, age distribution analysis showed that majority were in the fourth and fifth decade(30% each), followed by sixth decade(18%) , and the least in the seventh decade of life(6%). This is in accordance with a study by D.Mainland et al[9], where 32% were in the fifth decade, 22% in the sixth, 21 % in the fourth , 11% in the third and 4% in second. In evaluating the sex distribution of study population, most of the patients were females (86%), with only 7 males (14%). Likewise, in a study by Cooper C et al[10] it was also found that the sex ratio was equally skewed, with around 20% male patients, while the rest 80% were females. Other studies also showed that the sex distribution was roughly 2:1 to 3:1 females: males.[11,12,13,14]

Next, the variables that were prospectively studied at presentation and after an average of 8 months, were checked for pre and post study change. It was found that all these pre-post changes were statistically significant with ESR pre-post change having a P value of 0.002, and all the rest(prepost CRP, pre-post platelet levels, pre-post DAS28 level, pre-post USG synovial effusion/proliferation/vascularity and joint erosions, pre-post X Ray soft tissue swelling/juxta articular osteopenia/marginal erosions/joint space narrowing/ VDH score) significantly changing pre and post study, with a P value of <0.001. Then we embarked on our quest of the true essence of the study, to find out which one of these parameters more sensitively predicted joint erosions. For that, the change in values (delta) of inflammatory parameters (ESR/CRP/platelet) and the change in USG joint erosions were compared against the gold standard, here taken as X Ray changes, in terms of the change in (delta) Van de Heijde et al[15] score(VDH score), for correlation, and it is their strength of correlation that would give us which one is a better predictor of joint erosions. For that, we did the correlation study, found out the correlational coefficients(r) and their respective 95 levels of significance (P value). The one with the higher r value would be more strongly correlated and thereby more sensitively assess the change of the joint erosions (i,e from the gold standard, X Ray), and be a better predictor of joint erosions. This would be again substantiated by a regression analysis to show the ability to predict joint erosions (dependant variable: gold standard to look for joint erosions, i,e, X Ray VDH score , and independent variables: inflammatory markers- ESR/CRP/platelets and USG joint erosion findings). This regression analysis has been done to validate the robustness of the association of the dependent with the independent variables. In the correlational analysis, we found that the change of inflammatory markers were poorly correlated with the change in joint erosions, (as evidenced by X Ray findings-VDH score), while the change in USG joint erosions was positively correlated with the change in X Ray erosions(VDH): The delta ESR/delta VDH had a correlation coefficient (r) of 0.212(poor correlation), delta platelet/delta VDH an r of 0.246(poor), and delta CRP/delta VDH an r of 0.252(poor) whereas the change in(delta) USG joint erosion/VDH had a correlation coefficient of 0.645, with a P value of < 0.01 for all) proving that there is a discordance has been between clinical improvement and progression of radiological erosion scores, signifying the importance of regular radiological assessment for joint erosions, that is more sensitive than the inflammatory markers and clinical activity scores in assessing joint erosions. In radiological evaluation, both USG and MRI have significant contribution towards evaluating joint erosions and disease progression, as seen in previous studies: In a study by Maxime dugados et al[16], evaluation of several ultrasonography scoring systems for synovitis and comparison to clinical examination: results from a prospective multicentre study of rheumatoid arthritis, they concluded that US evaluation of synovitis as an outcome measure is at least as relevant as physical examination. They also concluded that further studies are required in order to achieve optimal US scoring systems for monitoring patients with RA in clinical trials and in clinical practice. In another study by Terslev et al[17], titled Estimation of inflammation by Doppler ultrasound: quantitative changes after intra-articular treatment in rheumatoid arthritis, it was found that ultrasound doppler seems to be a promising tool for estimating synovial activity in arthritis. Scott D et al[18], in their study, progression of radiological changes in rheumatoid arthritis, found that there was a divergence between deterioration in radiological features and improvements in the ESR and functional capacity, though patients with a persistently low ESR had less radiological progression. These studies provide evidence that treatment may be associated with a reduced rate of radiological progression but suggest that changes in radiological progression and clinical and laboratory measurements may result from different mechanisms. Thus the reliability of radiological investigations, especially USG power Doppler in identifying joint erosions and its superiority over inflammatory markers in determining the same has been seen in some previous studies. In a study by Scheel AK et al[19], a prospective 7 Year Follow up imaging study comparing radiography, ultrasonography, and magnetic resonance imaging in rheumatoid arthritis, finger joints, on following up a rheumatoid cohort of 60 patients for 7 years, detected an increase of bone erosions by all imaging modalities whereas, clinical improvement and regression of synovitis were seen only with US and MRI. Brown et al[20] in his study, presence of significant synovitis in rheumatoid arthritis patients with disease-modifying antirheumatic drug-induced clinical remission: evidence from an imaging study may explain structural progression also reported that in imaging, synovitis occurred frequently in patients with RA who fulfilled the clinical criteria for remission, suggesting a 'floor effect' for the clinical detection of joint inflammation below which subclinical inflammation can only be revealed by imaging. In this study, improvements in imaging synovitis (MRI and US) and osteitis (MRI) were concordant with reductions in C reactive protein, functional scores and joint counts, as would be expected. This is consistent with the findings of other studies which have also reported both MRI and US to be more sensitive for detecting synovitis than clinical assessment.[21]

Conclusion

In this hospital based prospective comparative observational study, majority of patients belonged to fourth and fifth decade (30% each). Most of the patients were females (86%), with only 7 males (14%). The change in inflammatory markers were found to be poorly correlated to joint erosions, while that of USG erosions was found to be strongly positively correlated with the same, thereby proving that USG findings are much more sensitive in assessing the joint erosions as well as predicting further changes in erosions, than are inflammatory marker counterparts. Multivariate regression analysis showed that in presence all others also only delta USG erosion significantly impacts delta VDH, or the gold standard(X Ray) for evaluation joint erosion This strongly proves that USG erosion is a better predictor of joint erosions than the other independent variables(inflammatory markers).

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