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A Clinical Study on Rheumatoid Arthritis with Reference to Ultrasonographic Evidence of Synovitis for Early Diagnosis

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ABSTRACT

Objectives: Early rheumatoid arthritis has been defined as a disease duration of 24 months or less, with a focus on the first 6 to 12 months. Ultrasound technology is more sensitive and accurate in the diagnosis of rheumatoid synovitis. The objective of this study is to assess ultrasonographic evidence of synovitis.

Methods: This hospital based, observational, single centre study was carried in 70 patients of rheumatoid arthritis taken from Rheumatology, Medicine and Orthopedics OPD or admitted in Medicine Department of Assam Medical College & Hospital from July 2021 to June 2022. The statistical analysis of data was performed using the computer program, statistical package for Social Sciences.

Results: The mean age of study population is 44.84±14.38 years. The maximum number of patients seen in the 41-50 age group. The male to female ratio was 1:3.67. Out of 70 patients rheumatoid factor was positive in 40(57.14%). Fifty two (74.29%) patients were having disease duration of <10years.Out of 1960 joints screened,1117(57%) joints showed synovial hypertrophy on the ultrasound grey scale. In the power doppler scan, 940(47.9%) joints had power doppler signal. In comparison between clinical joint involvement and joints with power doppler signal 23.37% had power doppler signal. 268 (26.54%) joints from the clinically nil group had synovial hypertrophy on grey scale ultrasound.

Conclusion: MSUS in rheumatoid arthritis helps in detection of subclinical synovitis which are not evident in conventional clinical examination and thus helps in treatment and prediction of disease relapse and structural progression.

Keywords: *Rheumatoid arthritis, Ultrasound, Synovitis*

1. INTRODUCTION

Early rheumatoid arthritis (RA) has been defined as a disease duration of 24 monthsor less, with a focus on the first 6 to12 months[1]. The main presenting features of RA are joint pain, morning stiffness, symmetrical swelling , tenderness of the joints and impaired physical function. Extra-articular manifestations include rheumatoid nodules, pulmonary, cardiac, ocular, neurological manifestations and vasculitis. In approximately two- thirds of patients, disease onset is insidious with fatigue, anorexia, generalized weakness and vague musculoskeletal symptoms appearing as typical sequelae, with the appearance of synovial inflammation following soon afterward[2].

Typically, the joints of the hands, wrists, knees and feet are affected gradually and symmetrically [3]. In 8% to 15% of individuals polyarthritis develops rapidly together with fever, lymphadenopathy and splenomegaly at a more acute beginning. About 15% to 20% of patients have an intermediate onset of symptoms in days to weeks[4].

0.5% to 1% of the world's population suffers from RA[5]. It occurs in all races with significant differences in prevalence in different populations. Women are affected 2-3 times more than men. The prevalence of RA is 0.75 % in India.

Diagnosis of RA is clinical and relies more on history and joint examination, supported by serological and radiological investigations. No single test confirms the diagnosis of RA. Diagnostic modalities include imaging (X-ray, Ultrasound, or Magnetic Resonance Imaging), Serology [rheumatoid factor (RF), anti-cyclic citrullinated peptide (CCP)] and measurement of acute phase reactants [Erythrocyte sedimentation rate (ESR) and C reactive protein (CRP)].

The clinical course in RA is unpredictable in many cases & the disease progresses to produce cartilage breakdown, joint injury and deformity over time[6]. RA patients typically take one of the following clinical paths - a) relapsing and remitting; b) chronic and progressive; c) remission or non-recurrence[7] .Various criteria are used to study the nature of disease progression, treatment response, prognosis and outcome[8]. The ultimate goal of treatment is to supress disease activity as low as possible to induce and maintain clinical remission and reduce joint damage and deformity and thus a more favourable long term outcome.

Historically, plain film radiography has been used to detect radiographic changes and various abnormalities. Local inflammation of the affected joints , the clinical disease activity in RA is measured by various joint indices like DAS 28,CDAI ,ACR 20, ACR 50 etc.

However, in the very early stages of RA , patients only have vague musculoskeletal symptoms. Additionally, it may be challenging to identify synovitis symptoms and signs, inflammatory biomarkers may not be detectable and X-ray results may be normal[9].

Ultrasound technology is non-invasive, in expensive, readily available, not associated with radiation and can be applied to almost all synovial joints within the framework of a single examination[10] . By using B-mode (grey scale ultrasound), it can also measure the thickness of the synovial membrane, target tendon sheaths, joints and bursae. It offers 44% sensitivity & 99% specificity which is as good as MRI (gold standard) for identifying tenosynovitis in RA[11].

As compared to a clinical, laboratory study and X-rays [12] alone , ultrasound is more sensitive and accurate in the diagnosis of rheumatoid synovitis [13,14].It offers high sensitivity for detecting minor bone erosion[15].

Power doppler aids in diagnosing synovial tissue hyperaemia[16].Both color Doppler ultrasound (CDUS) and power Doppler ultrasound (PDUS) detect synovial blood flow, which is a sign of synovial vascularization. The presence of intra-articular power Doppler aids in distinguishing between active synovitis and inactive intra-articular thickening [17].

As synovitis is the best predictive marker for future damage of joints in RA, we want to investigate in this north eastern part of the country the relationship between ultrasound measures with DAS28-ESR(Disease activity score 28-Erythrocyte sedimentation rate), CDAI (Clinical disease activity index), their components & other variables like pain and fatigue.

Aims and Objectives

The aims and objectives of the present study is to assess ultrasonographic evidence of synovitis in patients of rheumatoid arthritis as an aid for the treatment of the disease.

2. MATERIALS AND METHODS

The present study was carried out in the Department of Medicine, Assam Medical College & Hospital, Dibrugarh for 1 year from 1stJuly, 2021 to 30thJune 2022. This is a hospital based observational study.

Study Population: Diagnosed cases of RA attending Rheumatology OPD, Orthopedics OPD, Medicine OPD or admitted in Department of Medicine in Assam Medical College& Hospital, Dibrugarh satisfying inclusion criteria.

Sample Size: Considering 95% confidence interval with a precision of 10% and proportion of patients detected of synovitis to be 23% by both clinical and ultrasonographic examination, the sample size is calculated to be 70.

Inclusion criteria:

- Diagnosed rheumatoid arthritis patients.
- Age13 years and above.
- The patient who provided their informed consent.

Exclusion criteria:

- Patients not giving consent for the study.
- Patients with already deformed joints of all 4 limbs.

Informed consents were taken from all the patients or their attendants before enrolment of the study. Ethical clearance was obtained from the Institutional Ethics Committee (H) of Assam Medical College & hospital, Dibrugarh vide No. AMC/EC/PG/5574.

Data collection methodology:

Detailed history taking, clinical examination and laboratory investigations were done. Rheumatoid arthritis was diagnosed by 2010 ACR/EULAR diagnostic criteria. A score of more than or equal 6 indicated the presence of definite RA.

Assessment of synovitis :

Assessment of synovitis were done using grey scale and power Doppler ultrasound.

Grey scale imaging commonly referred as B(Brightness)mode is a 2-dimensional image in which organ or tissue of interest are depicted as point of variable brightness. The formation of a B mode image relies on the pulse echo principle, assuming the speed of sound remains constant, the position of a target of interest may be inferred by the time taken from emission to its return to the transducer.

Power Doppler ultrasound is a technique that encodes the power in Doppler signal in color.

This parameter is fundamentally different from the mean frequency shift. The frequency is determined by the velocity of the red blood cell, while the power depends on the amount of blood present. Providing an image of a different property of blood flow, power doppler has shown several key advantages over color doppler, including higher sensitivity to flow, better edge definition and depiction of continuity of flow.

Study equipment: Ultrasonography machine-SAMSUNG RS 80 A, Linear probe-L3-12A.

Assessment of disease activity in RA:

Scoring for B mode (grey scale ultrasound) for synovial hypertrophy (SH): Grade 0: No SH independently of the presence of effusion or normal.

Grade 1: Minimal hypoechoic SH up to the level of horizontal lines connecting bone surface or minimal between metacarpal head & the proximal phalanx.

Grade 2: Moderate hypoechoic SH extending beyond the joint line or: but with the upper surface concave (curved downwards) or hypertrophy extending moderate beyond the joint line but the upper surface flat.

Grade 3: Severe hypoechoic SH with or without effusion extending beyond the joint lines with the upper surface convex.

Scoring for Power Doppler Ultrasound:

- **Grade0:**No PD signal.
- **Grade 1:** 3 isolated spots or 2 confluent spots or 1 confluent spot and 2 isolated spots of signal.
- **Grade2:** >grade1 but ≤ 50% Doppler signals in total grey scale background.
- **Grade3:** >grade2 (>50% of total grey scale background).

Combined score:

Grade 0 (Normal):No SH and no PD signals.

Grade1(Minimal):Grade1hypoechoic SH and ≤ grade1PD signal.

Grade 2 (Moderate): Grade 2 hypoechoic SH and ≤ grade 2 PD signals ; or grade 1 SH and a grade 2 PD signal.

Grade 3(Severe): Grade 3 hypoechoic SH and ≤ grade 3 PD signal; or grade 1or 2 SH and a grade 3 PD signal.

Disease activity:

Clinical disease activity was determined by Disease activity Score (DAS) 28 score. DAS 28 was measured by determining the four clinical parameters-

1. Swollen joint count.
2. Tender joint count. 3.ESR.
4. Patients assessment of disease activity (0-10).

CBC, ESR, Urine R/E, Random blood sugar, Renal function tests, Liver function test, Serum electrolytes, C-reactive protein, Rheumatoid factor, Antinuclear antibody assay, Anti- CCP etc. were done in all patients.

Statistical analysis:

The statistical analysis of data was performed using the computer program, statistical package for social sciences (SPSS for windows, version 20.0. Chicago, SPSS Inc.) and Microsoft Excel 2010. Discrete data are expressed as number and percentage. Pearson's correlation coefficient (r) was used to measure the association among continuous variables. For all

analyses, the statistical significance was fixed at 5% level (p value <0.05).

Results and observations:

The following tables shows the essential features & results of the study.

Table1: Showing age distribution

Age group (in years)	Number (n)	Percentage (%)
≤20	0	0.00
21-30	10	14.29
31-40	18	25.71
41-50	23	32.86
51-60	10	14.29
61-70	5	7.14
>70	4	5.71
Total	70	100.00

* Mean (±S.D)of age = 44.84±14.38 years

The maximum number of patients seen in the 41-55 age group with 23 (32.86%) patients. The minimum age was 22 years while the maximum age was 88 years in the study population.

Table2: Gender distribution

Gender	Number (n)	Percentage (%)
Male	15	21.43
Female	55	78.57
Total	70	100.00
Ratio(Male : Female)	1:3.67	

Table3: Showing RA Factor

RA Factor	Number (n)	Percentage (%)
Positive	40	57.14
Negative	30	42.86
Total	70	100.00

64 patients (91.43%) presented with symmetrical joint involvement & 6 patients (8.57%) with asymmetrical distribution. Morning stiffness was seen in 65 patients (92.86%) and in 5 patients (7.14%) there were no morning stiffness.

Table4: Showing disease duration

Disease duration (in years)	Number (n)	Percentage (%)
Upto10	52	74.29
>10-20	13	18.57
>20-30	5	7.14
>30	0	0.00
Total	70	100.00

* Mean(±S.D.) of disease duration = 8.57±5.76 years

Table 5: The range, mean and S.D. of clinical and laboratory measures of Disease activity in RA patients

Disease activity parameter	Mean	±S.D.	Range	
			Min	Max
Patient's Global Assessment (PGA)	5.80	2.64	1	10
Evaluator's Global Assessment (EGA)	5.27	2.47	1	9
Visual Analogue Scale(VAS)-Pain	5.39	2.28	0	9
VAS-Fatigue	5.31	2.46	0	9
Clinical Disease Activity Index (CDAI)	28.07	16.68	2	64
ESR	59.91	21.59	12	106
Tender Joint Count 28	10.43	7.09	0	26
Swollen Joint Count 28	6.57	5.88	0	23
DAS28-ESR	5.14	1.30	2.67	7.30

Table6: Showing clinical disease activity index (CDAI)

CDAI		Number (n)	Percentage (%)
High activity	22.1-76.0	40	57.14
Moderate activity	10.1-22.0	16	22.86
Low activity	2.9-10.0	13	18.57
Remission	0-2.8	1	1.43
Total		70	100.00

* Mean(±S.D.)of CDAI=28.07±16.68

Table7: Showing DAS28-ESR

DAS28-ESR		Number (n)	Percentage (%)
High	>5.1	35	50.00
Moderate	3.2-5.1	29	41.43
Low	2.6-3.1	6	8.57
Remission	< 2.6	0	0.00
Total		70	100.00

* Mean (±S.D.) of DAS 28-ESR = 5.14±1.30

Table8: Distribution of joints as per Ultrasound Grey scale grading

Synovial hypertrophy	Joints						Total	
	PIP	MCP	Wrist	Elbow	Shoulder	Knee		
	(n)	(n)	(n)	(n)	(n)	(n)	(n)	(%)
Nil	281	292	63	74	78	55	843	43.0
Grade1	243	237	45	38	36	49	648	33.1
Grade II	147	143	27	23	22	30	392	20.0
Grade III	29	28	5	5	4	6	77	3.9
Total	700	700	140	140	140	140	1960	100.0

Table9: Distribution of joints as per Ultrasound Effusion

Ultrasound effusion	Joints						Total	
	PIP	MCP	Wrist	Elbow	Shoulder	Knee		
	(n)	(n)	(n)	(n)	(n)	(n)	(n)	(%)
Normal joints	527	567	99	120	121	116	1550	79.1
Effusion Joints	173	133	**41**	20	19	24	410	20.9
Total	700	700	140	140	140	140	1960	100.00

Table10: Distribution of joints as per Power Doppler Ultrasound grading

Power Doppler Grade	Joints						Total	
	PIP	MCP	Wrist	Elbow	Shoulder	Knee		
	n	n	N	N	n	n	n	%
Normal	354	368	66	80	78	74	1020	52.1

Grade I	236	226	50	41	42	45	640	32.6
Grade II	83	80	18	14	15	16	226	11.5
Grade III	27	26	6	5	5	5	74	3.8
Total	700	700	140	140	140	140	1960	100%

Table11: Correlations between clinical, laboratory and ultrasonographic features

	SHI	SHJC	PDI	PDJC	EJC
TJC28	0.614**	0.606**	0.452**	0.444**	0.753**
SJC28	0.555**	0.540**	0.419**	0.428**	0.709**
VAS pain	0.406**	0.439**	0.359**	0.361**	0.590**
VAS fatigue	0.528**	0.542**	0.405**	0.438**	0.666**
EGA	0.459**	0.486**	0.405**	0.398**	0.583**
PGA	0.510**	0.514**	0.393**	0.381**	0.686**
DAS28	0.599**	0.572**	0.452*	0.436**	0.781**
CDAI	0.606**	0.602**	0.462**	0.459**	0.765**
ESR	0.379**	0.326**	0.244*	0.253*	0.625**

SHI = Synovial hypertrophy Index, SHJC= Synovial hypertrophy Joint Count, PDI = Power Doppler Index, PDJC = Power Doppler Joint Count, EJC = Effusion Joint Count

**correlation is significant at the 0.01 level (2-tailed)

*correlation is significant at the 0.05level (2-tailed)

Ultrasound joint count & index for synovial hypertrophy was highly correlated with clinical and laboratory parameters. Also Ultrasound joint count for PD & PDI showed a high correlation with clinical and laboratory parameters.

3. DISCUSSION

The present study was conducted on70 patients with rheumatoid arthritis for one year period.

Age incidence:

In our study of 70 patients, the highest number 23 cases (32.86%) were in the age group 41-50 years. The mean age was 44.84±14.38 years. Younis AA *et al.* studied 50 patients and found the mean age of the patient was 45±8.2 years, ranging from 28-61years[18]. Richi*et al.* studied 61 patients with early RA <6 months duration and found the mean age of presentation was 54 years. Abd-Elazeem MI *et al.* studied 50 patients with RA and found that the mean age of presentation was 40±10.1years [19].

Sex incidence:

In the present study , out of 70 patients 55 were females and 15 were males. The female accounts for 78.57% and the male account for 21.43% in a ratio of 3.67:1. Younis AA *et al.* found 80% of patients were female and 20% were male, making the ratio 4:1[18].Qayyum *et al.* found in their study of 50 patients , 30 patients were female and 20 were male with female to male ratio of 2.5:1[20]. Makinen *et al* studied 195 patients with early RA (< 2 years duration) and observed that females were affected more[21].

Rheumatoid factor:

In our study population, rheumatoid factor was positive in 40 (57.14%) patients. Rest 30 (42.86%) patients were rheumatoid factor negative. Higami *et al* in a study of 82 patients of RA (<1 year duration) 77 patients (94%) were seropositive [22]. Younis AA *et al* found rheumatoid factor positive in 54% of the study population [18].

Clinical disease activity:

In this study population, 40 patients (57.14%) had high clinical disease activity,16 patients(22.86%)with moderate disease activity,13(18.57%) patients with low disease activity and 1(1.43%) in remission i.e. the mean CDAI being 28.07±16.68.

Younis AA *et al* found mean CDAI of 29.6±19.7[18] . Sanmarti *et al* observed high clinical disease activity in 83.3%, moderate in 16.7% at baseline. At 1 year, patients were improved clinically only 20% had high, 46.7% had moderate and 33.3% had low clinically disease activity[23].

In our study population, mean DAS28 score was 5.14±1.30. Damjanov N *et al* found average DAS 28 score 5.80±1.28 in 90 active RA patients[24] .

Joint involvement in grey scale ultrasound:

In our study ,out of the1960 joints screened for 70 RA patients,1117(56.99%) joints had synovial hypertrophy and rest 843(43.01%) were normal. However out of those involved joints,648(33.1%) joints had grade1 hypertrophy,392(20.0%) had grade II and rest 77(3.9%) had grade III synovial hypertrophy . Younis AA *et al* showed out of 1400 joints

,772(55.14%) had synovial hypertrophy[18]. Wakefield RJ *et al* studied 80 patients with 644 painful joints (with and without clinical synovitis). Ultrasound found 33% of 459 joints that were not clinically synovitis. Ultrasound detected synovitis in more joints than clinical examination in 64% patients. Ultrasound Scanning also found synovitis in 13% of the 826 asymptomatic (painless) joints [25].

Joint involvement in power Doppler ultrasound:

In this study, out of 1960 joints, 940(47.9%) joints had power doppler signals. Out of those involved joints 640(32.6%) showed grade I, 226 joints (11.5%) had grade II and 74 joints (3.8%) had grade III power doppler signal. This is similar to the study by Younis AA et al. where they found 46.57% joints showed power Doppler signal[18].

Comparison between synovial hypertrophy grading and grading per clinical groups:

In comparison between clinical joint counts and grey scale ultrasound for synovial hypertrophy , we found that 268(26.54%) joints from nil clinical groups had grade I,69(6.83%) had grade II and 11(1.09%) had grade III synovial hypertrophy. Younis AA et al. found 27.9% of joints from nil clinical groups had grade I and 4.2% joints had grade II synovial hypertrophy[18]. Naredo E et al. found that ultrasound showed significantly more joints with effusion and synovitis than clinical examination[26].In our study, joints with both swelling and tenderness, only 2 (0.50%) joints were without hypertrophy, the rest of 165 (40.84%) had grade I, 212 (52.48%) had grade II and 25 (6.18%) joints had grade III synovial hypertrophy. Rees JD et al. found that S+T group have highest number of synovial hypertrophy [27].

Comparison between power Doppler signals and grading for clinical groups:

In comparison between clinical joint involvement and joints with power Doppler signals, 757(74.95%) joints without symptoms did not have any power doppler signal, 236(23.37%) joints had grade I, 12(1.19%) joints had grade II and rest 5 (0.49%) had grade III power doppler signals. Younis AA et al. found that 23% of joints from the clinically nil group had grade I power doppler signal and 3.9% joints had grade II power Doppler signal [18]. In our study, among joints having both T+S only 19 joints (5.70%) did not have a power doppler signal, 208 joints (49.48%) had grade I ,147(37.38%) joints had grade II and 30(7.44%) joints had grade III power doppler signals. This study correlates with Younis AA et al[18].

Correlation between clinical and ultrasonographic features:

The Spearman's correlation between clinical, laboratory and ultrasound parameters were done. Ultrasound joint count and index for synovial hypertrophy showed high correlation withTJC28, SJC28, VAS (both pain and fatigue), EGA, PGA, DAS28, CDAI and ESR.

Also, PD joint count showed a high correlation with TJC 28, SJC 28, VAS (pain and fatigue), EGA, PGA, DAS28, CDAI and moderate correlation with ESR. PDI showed high correlation with TJC 28, VAS, EGA, PGA, CDAI and a moderate correlation with DAS 28 and ESR. EJC showed a high correlation with TJC 28, SJC 28, VAS, EGA, PGA, DAS 28, CDAI and ESR. Younis AA et al found ultrasound joint count and index for synovial hypertrophy high correlation with SJC 28, VAS (pain and fatigue),EGA,PGA,DAS 28, CDAI and ESR[18].

Limitation of the study:

- The study did not take into account the medication received by the patients. So, it does not evaluate the effect of various medication on synovitis.
- Follow up of the patient was not done. So, prognosis of the patient who was diagnosed early could not be assessed.

4. CONCLUSION

Measurement of clinical disease activity and musculoskeletal ultrasound are essential for monitoring disease progression and outcome in rheumatoid arthritis.

Traditional clinical signs used in the evaluation of disease activity maybe a different relation to the ultrasound features of synovitis. Joints with both swelling and tenderness are most likely to show ultrasound synovitis. Joints that are normal on

clinical examination may show ultrasound synovitis.Also, composite ultrasound count and indices for synovial hypertrophy and power doppler relate significantly to DAS 28, CDAI and its component and VAS for pain and fatigue.

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