DOI: 10.7860/JCDR/2019/41456.12985

Original Article

Orthopaedics Section

A Cross-sectional Study on Grip Ability Test and its Relation with "Hy" Band: Surrogate Marker for Amyloidosis in Patients with Rheumatoid Arthritis

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ABSTRACT

Introduction: Rheumatoid Arthritis (RA) is a chronic inflammatory disease of autoimmune origin. The disease has specific predilection for small joints of the body especially joints of the hand. Thus, by evaluating the hand grip ability, we can measure the severity of RA. The "Hy" band occurs due to an increase in prealbumin as shown by Serum protein electrophoresis. Few studies on Prealbumin show that increased prealbumin is directly associated with Amyloidosis. Amyloidosis being a known complication of RA drew attention towards "Hy" band.

Aim: To establish Grip Ability Test (GAT) as a predictor of RA severity and find its correlation with presence of "Hy" band.

Materials and Methods: This cross-sectional study was conducted at Government Villupuram Medical College, Tamilnadu, India. The study included 20 RA patients diagnosed by ARA/EULAR 2010 criteria, recruited from the Department of Orthopaedics. After due ethical clearance, all demographic data, DAS28 score, ESR, Duruoz Hand Index were obtained. GAT was performed using Handgrip Dynamometer. "Hy" band was detected by Serum electrophoresis using automated capillary zone electrophoresis. The values were pooled and statistical analysis was performed using epi info version 7.2.2 p-value <0.05 was considered significant.

Results: There was a statistically significant correlation between GAT and disease activity (p=0.001). Statistical significance for correlation between "Hy" band and GAT values was dull (p=0.7279 in dominant hand and 0.3337 in non-dominant hand).

Conclusion: GAT shows significant correlation with disease activity. Hence, GAT will serve as a reliable and objective method of measuring disease severity in RA. GAT may be used as a clinically simple performance based prognostic tool. The presence of "Hy" band shows no correlation with GAT scores.

Keywords: Disease activity score, Hand strength, Prognosis, Rheumatology, Serum electrophoresis, Transthyretin

INTRODUCTION

RA is notable for de-novo origin and haphazard progression. Any clue in understanding the disease further will help us tackle the challenges in therapy. RA has high affinity towards small peripheral joints. Hand involvement is characteristic of RA, leading to difficulties in Activities of Daily Living (ADL). GAT is a quick, easy and objective test for measurement of hand function [1]. Thus, 'Grip ability test' is a reliable measure of hand involvement in RA [2,3]. In addition, the grip strength is indicative of overall well being of the patient and denotes the muscle strength, built and endurance [4,5].

Chronic inflammatory diseases are known to produce perturbation of protein metabolism [6,7]. Hence, authors studied the protein electrophoretic pattern in patients with RA. The presence of "Hy" band which migrates with velocity greater than albumin was noted in the previous study [8]. This "Hy" band is a surrogate marker for the risk of Amyloidosis. "Hy" band lies in the prealbumin region indicating an obvious rise in prealbumin [9]. Elevated levels of prealbumin are directly linked with Amyloidosis as shown by previous studies [10,11]. The underlying mechanism is that the prealbumin protein-transthyretin in the wild form or when mutated gets deposited in tissues as amyloid deposits [12,13]. A possible intervention to prevent Amyloidosis is to scavenge the free prealbumin protein by administration of retinol. This is based on the principle that Transthyretin is involved in stabilisation of Retinol-RBP (Retinol Binding Protein) complex [14]. Authors confirmed the presence of this "Hy" band in 70% of RA patients in the previous study [8]. As a way ahead, our hypothesis was to find any relation between presence of "Hy" band and GAT.

MATERIALS AND METHODS

This cross-sectional study was conducted at Government Villupuram Medical College and Hospital. The sample size used was 21 based on a similar study [9]. Moreover, the presence of "Hy" band in serum of Rheumatoid arthritis was not a highlighted feature in the our parent article. The presence of "Hy" band was confirmed only in the synovial fluid in their study. So in order to confirm the presence of the band in serum, authors did a pilot study [8]. As a step further, authors did GAT for the same patients and tried to find its relation with "Hy" band. Hence, the study included 20 patients with active RA who were diagnosed according to the American College of Rheumatology/European League Against Rheumatism (EULAR) 2010 criteria [15]. The EULAR score was calculated at the first visit and monitored during subsequent follow-ups and those having a score below 6 are considered to be in the inactive stage of disease. The EULAR criteria is a comprehensive criteria which takes into account the number of joints involved, presence of RA factor, presence of Anti-CCP and duration of symptoms. It was developed for the purpose of selecting homogeneous populations for studies [16]. Patients having diabetes mellitus, metabolic diseases, diseases affecting neuromuscular function, renal diseases, hepatic diseases and other autoimmune diseases were excluded from the study.

Institutional ethical clearance for the study was obtained and the study was conducted for a period of two months from June 2018 to August 2018.

All relevant data such as duration of disease, presence of morning stiffness and treatment history were collected. The numbers of tender and swollen joints were counted and the patients were examined for

the presence of hand deformities. Duruoz Hand Index (DHI) is a questionnaire evaluating quality of hand function in ADL such as eating, dressing, personal hygiene, etc., [17]. It is suggestive of the overall well being of the patient [4,5] and hence used as a measure of General Health in calculating DAS28. The questionnaire was filled by interview method.

Disease activity was measured by Disease Activity Score 28 [18]:

DAS28=0.56*√TJC28+0.28*√SJC28+0.70*ln(ESR)*1.07 +0.014*GH

TJC 28=Tender joint count 28; SJC 28=Swollen joint count 28. The 28 joints are: Shoulder joint (2), Elbow joint (2), Knee joint (2), Wrist joint (2) and Hand's PIP and MCP joints (20). ESR was measured by Westergren method in the Physiology laboratory. DAS28 is a well known and reliable measure of the severity of Rheumatoid arthritis [18]. The patients were split into three categories based on DAS28 scores as mild (DAS<5), moderate (DAS 5 to7) and severe (DAS>7). After taking consent and following all aseptic precautions, 3 cc blood was collected from each patient and the blood was stored at 4°C for three hours. The serum protein electrophoresis was carried out by automated capillary zone electrophoresis.

GAT was performed using Handgrip Dynamometer. The tests were conducted after 10 am in order to eliminate the influence of morning stiffness. Hand dominance was enquired. Before starting the test, the patient was asked to hold the apparatus and if the patient was unable to hold the apparatus, the GAT scores are taken as zero. If the patient was capable of holding the apparatus, the test was carried out with patient in sitting position, elbow flexed and forearm supinated and the patient was asked to clench the handle of the apparatus. The values are noted in kilograms. Three trials were conducted for each hand and the mean value was noted.

STATISTICAL ANALYSIS

All the readings were tabulated and statistical analysis for correlation between GAT score and disease activity was performed by ANOVA. Student t-test was used for finding correlation between GAT scores and the presence of "Hy" band using epi info software version 7.2.2.

RESULTS

The study included 20 subjects with a male female ratio of 3:17. There was one patient with Juvenile Rheumatoid arthritis (JRA). On classifying patients based on DAS28 scores, three patients were in mild group, nine patients in moderate group and eight patients in severe group. The mean grip strength observed in dominant hand was 6.94±8.59 and in the non-dominant hand was 6.11±9.03 [Table/Fig-1]. On analysing the data using ANOVA test, there was a statistically significant correlation between disease activity and GAT with a p-value of 0.001 in both dominant and non-dominant hand [Table/Fig-2-4]. As stated earlier, "Hy" band was positive in 70% of cases (n=14) [Table/Fig-5,6]. The presence of "Hy" band showed no correlation with GAT scores with p-value of 0.7279 in Dominant hand and p-value of 0.3337 in non-dominant hand [Table/Fig-7,8]. Deformities were present in eight cases-Boutainnaire (n=8), Swan neck (n=1), Ulnar deviation (n=5), Rheumatic nodules (n=1). The presence of deformities showed no correlation with GAT scores in both dominant and non-dominant hand [Table/Fig-9,10].

	N	Minimum	Maximum	Mean	Std. deviation
Age	20	13.0	60.0	40.900	11.1019
DHI	20	16.0	86.0	49.550	19.8295
DAS28	20	4	8	6.51	1.207
ESR	20	9.0	68.0	22.750	13.2779
DOM_GAT	20	0.0	28.3	6.945	8.5918
NDOM_GAT	20	0.00	30.70	6.1120	9.03524
Valid N (listwise)	20				

[Table/Fig-1]: Descriptive statistics.

DISCUSSION

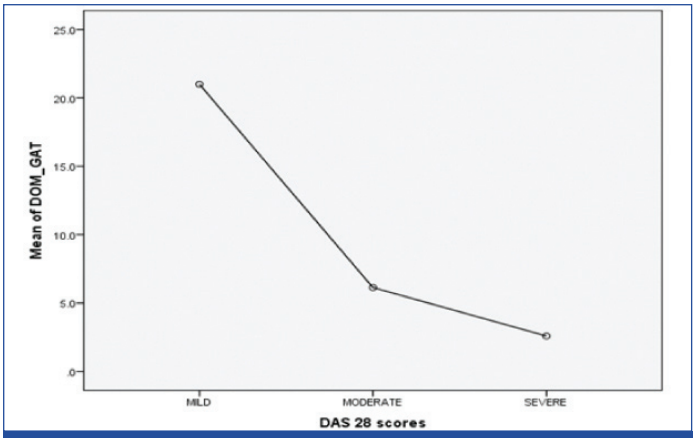
The relation between grip strength and general disability was established by previous studies [4,5]. GAT value of the dominant hand was found to have a significant positive correlation with handgrip [19]. This confirms the validity of GAT as a measure of handgrip strength. In the present study, authors compared GAT scores with disease activity. The present study revealed significant correlation with GAT and disease activity in both dominant and non-dominant hand. This is in line with a previous study [2] which found significant negative correlation with GAT and disease activity i.e., as Disease activity increases, GAT decreases.

		Sum of squares	df	Mean square	F	Sig.
DOM_GAT	Between groups	750.461	2	375.230	9.782	0.001
	Within groups	652.089	17	38.358		
	Total	1402.550	19			
NDOM_GAT	Between groups	913.785	2	456.893	12.188	0.001
	Within groups	637.292	17	37.488		
	Total	1551.077	19			

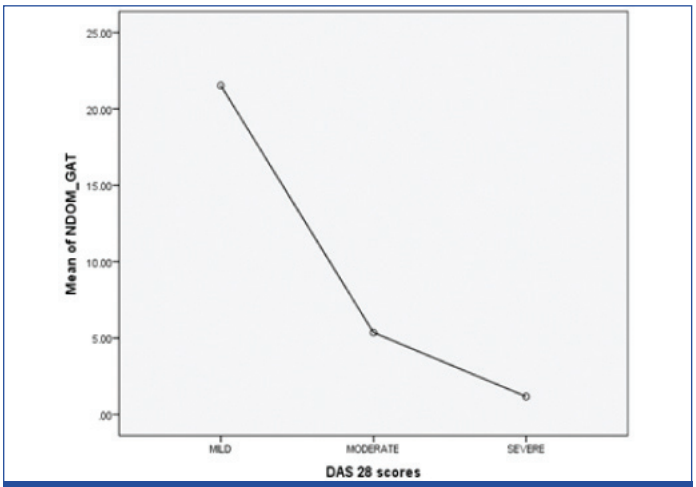
[Table/Fig-2a]: ANOVA results.

Tukey HSD Dependent variable			Mean difference (I-J)	Std. error	Sig.	95% Confidence interval	
						Lower bound	Upper bound
DOM_GAT	Mild	Moderate	14.8667*	4.1289	0.006	4.274	25.459
		Severe	18.4125*	4.1929	0.001	7.656	29.169
	Moderate	Mild	-14.8667*	4.1289	0.006	-25.459	-4.274
		Severe	3.5458	3.0094	0.482	-4.174	11.266
	Severe	Mild	-18.4125*	4.1929	0.001	-29.169	-7.656
		Moderate	-3.5458	3.0094	0.482	-11.266	4.174
NDOM_GAT	Mild	Moderate	16.17000*	4.08182	0.003	5.6987	26.6413
		Severe	20.36208*	4.14510	0.000	9.7284	30.9958
	Moderate	Mild	-16.17000*	4.08182	0.003	-26.6413	-5.6987
		Severe	4.19208	2.97511	0.359	-3.4401	11.8243
	Severe	Mild	-20.36208*	4.14510	0.000	-30.9958	-9.7284
		Moderate	-4.19208	2.97511	0.359	-11.8243	3.4401

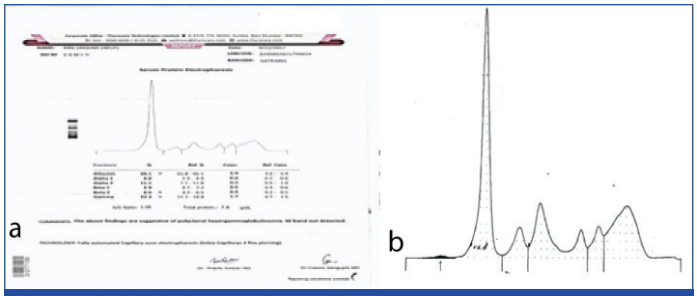
[Table/Fig-2b]: Multiple comparisons; showing the statistical relation between Grip Ability Test scores and Disease Activity Score 28 analysed using Analysis of Variance test.
*The mean difference is significant at the 0.05 level



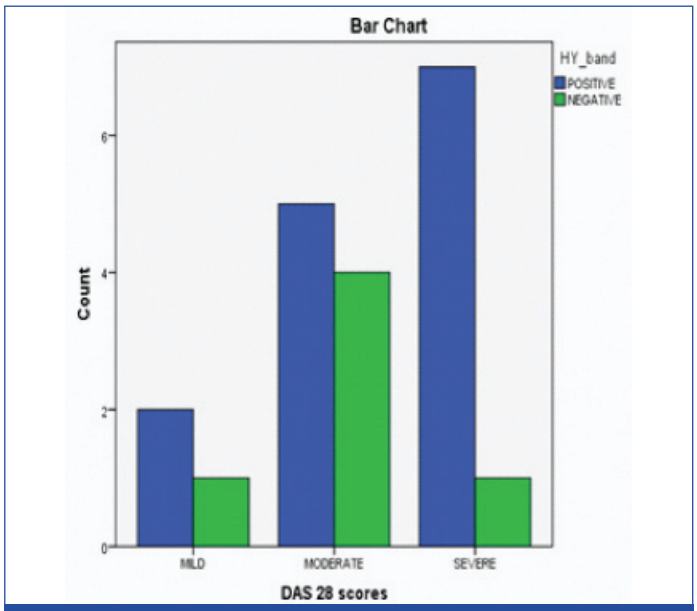
[Table/Fig-3]: Graph representing the relationship between GAT scores of Dominant hand and DAS28 scores. Note the fall in Handgrip strength/Grip Ability in severe group.



[Table/Fig-4]: Graph representing the relation between GAT scores of Non dominant hand and DAS28 scores. Note the fall in Handgrip strength/Grip Ability in severe group.



[Table/Fig-5]: a) Figure showing the presence of "Hy" band in the prealbumin region; b) Magnified version.



[Table/Fig-6]: The chart shows the number of people having "Hy" band in each group (Grouped according to Das28 scores).
Two sample 't' test with equal variances (DOM GAT, by "Hy" band)

Ha: diff <0	Ha: diff=0		Ha: diff >0			
Pr (T<t)=0.6360	Pr (|T|>|t|)=0.7279		Pr (T>t)=0.3640			
Group	Observation	Mean	Std. Err.	Std. Dev	[95% Conf. Interval]	
Present	14	7.4	2.451597	9.173037	2.103646	12.69635
Absent	6	5..883333	3.127047	7.733154	-2.232114	13.99878
Combined	20	6.945	1.921177	8.591763	2.923931	10.96607
Diff		1.516667	4.292371		-7.50127	10.5346

[Table/Fig-7]: Table showing statistical relation between GAT scores of dominant hand and "Hy" band.
Diff=Mean (present)-Mean (absent); t=0.3533; Ho: Diff=0; Degrees of freedom=18

Ha: diff<0	Ha: diff=0		Ha: diff>0			
Pr (T<t)=0.8332	Pr (|T|>|t|)=0.3337		Pr (T>t)=0.1668			
Group	Observation	Mean	Std. Err	Std. Dev.	95% Confidence interval	
Present	14	7.426429	2.757082	10.31606	1.470115	13.38274
absent	6	3.045	1.702711	4.170773	-1.331958	7.421958
Combined	20	6.112	2.020342	9.035244	1.883376	10.34062
diff		4.381429	4.41026		-4.884184	13.64704

[Table/Fig-8]: The table shows the statistical relation between Non Dominant hand Grip Ability Test scores and "Hy" band.
Diff=mean (present) – mean (absent); t=0.3533; Ho: diff=0; Degrees of Freedom=18

Variable	Coefficient	95% Confidence	Limits	Std. error	F-test	p-value
Deformity	2.137	-6.261	10.536	3.997	0.2859	0.599388
Constant	3.525	-10.528	17.578	6.689	0.2777	0.604637

Source	df	Sum of squares	Mean square	F-statistic	p-value
Regression	1	21.9308	21.9308	0.2859	0.5994
Residuals	18	1380.6188	76.7010		
Total	19	1402.5495			

[Table/Fig-9]: Table showing the analysis results of the correlation between Grip Ability Test scores of Dominant hand and presence of Deformity.
Linear Regression; Outcome variable: NDOM_GAT; Co-variates: Deformity; Dummy variables: -; Interaction terms: -; Include missing: False; Correlation Coefficient: r^2= 0.02

Variable	Coefficient	95% Confidence	Limits	Std. error	F-test	p-value
Deformity	4.637	-3.964	13.237	4.094	1.2829	0.272224
CONSTANT	-1.307	-15.698	13.085	6.850	0.0364	0.850853

Source	df	Sum of squares	Mean square	F-statistic	p-value
Regression	1	103.1937	103.1937	1.2829	0.2722
Residuals	18	1447.8833	80.4380		
Total	19	1551.0769			

[Table/Fig-10]: Showing relation between Grip Ability Test scores of Non–Dominant hand and presence of Deformity.
Linear Regression
Outcome variable: NDOM_GAT; Co-variates: Deformity; Dummy variables: -; Interaction terms: -; Include missing: False; Correlation Coefficient: r^2 = 0.07

Functional capacity of the patient decreases most rapidly at the early stages of the disease. The functional status and initiation of therapy in their first year of RA is predictive of long-term outcome [20]. In addition, the hand grip function is a sensitive measure of therapeutic response [21]. Hence GAT will serve as a quick and trustworthy tool for predicting prognosis and optimising therapy [Table/Fig-11].

[Table/Fig-11]: Photograph demonstrating the GAT.

The study included patients on regular medication and patients not under regular medication. The treatment compliance was enquired by history and those who were on regular follow-up (one visit per month for the past two years) were considered to be on regular medication. Most patients were on Methotrexate (n=15) and severe cases were on steroids (n=8). On observation, the patients who were said to be on regular medication were able to perform the GAT test more efficiently. Since most patients did not have proper treatment records, treatment status was not subjected to statistical analysis.

In the present study, the prime focus was to find out the relation between GAT scores (loss of hand function) and the presence of "Hy" band. RA being an autoimmune disorder is known for remissions and exacerbations. A previous study by present authors [8] was a cross-sectional study and investigated the cases only for a short period of time, authors could not asses the inflammatory features present before the time of investigation accurately and the DAS28 score is a subjective measure, calculated only from the patient's history. Hence there might be a memory recall bias. In order to reduce this bias, GAT scores can be used as a measure of disease activity. Thus, authors analysed the correlation between GAT scores and presence of "Hy" band. The present data revealed that there is no statistically significant relation between presence of "Hy" band and GAT scores.

LIMITATION

Further studies are required to reveal the exact chemical nature of "Hy" band and confirm its relation with Amyloidosis in case of Rheumatoid arthritis patients. The factors influencing the presence of "Hy" band in RA patients needs to be evaluated. The therapeutic effect of increasing the retinol and retinol binding protein levels in preventing Amyloidosis in Rheumatoid arthritis patients, must be evaluated in a longitudinal study.

CONCLUSION

Our study concludes that the loss of hand function measured by GAT has positive correlation with disease activity. "Hy" band the surrogate marker of Amyloidosis shows no association with GAT. The treatment status of the patient is a possible confounding factor in the study. Way ahead, studies investigating the factors influencing the presence of "Hy" band are needed.

ACKNOWLEDGEMENTS

The study did not receive funding from any organisation. We express our gratitude to the faculties of the Department of Physiology for encouraging us. We are grateful to the professors of community medicine for their support. We are indebted to each and every professor, and Asst. professor in the Department of Orthopaedics for their unconditional support.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Mar 16, 2019**
Date of Peer Review: **Apr 02, 2019**
Date of Acceptance: **May 15, 2019**
Date of Publishing: **Jul 01, 2019**