Evaluation of Cardiac Involvement by ECG and ECHO in Different Grades of Disease Activity in Rheumatoid Arthritis and Its Relation to Activity and Nontraditional Risk Factor

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Abstract: Objective: Patients with RA have systemic inflammation and increased risk of cardiovascular (CV) events, including thrombosis. The aim of this work to assess cardiac involvement by ECHO and ECG in different grades of disease activity in (RA) rheumatoid arthritis patients and to correlate these finding to disease activity and fibrinogen as the most important nontraditional cardiovascular risk. **Methods:** Patients with RA and controls were recruited at Benha university faculty of medicine rheumatology department. Disease activity was evaluated using standard indices. Fibrinogen, ESR, CRP, ECHO and ECG were done for all patients and controls. **Results**: A total of 100 RA patients and 50 controls were studied. Among patients with RA, disease activity ranged from inactive to highly active disease. There were Significant difference between moderately, highly active and inactive RA as regarding cardiovascular risk variables fibrinogen, CRP, ESR P< 0. 01. Also there was significant cardiac involvement in different grades of disease activity in RA patients as regarding both ECG and ECHO and these findings correlate to grades of disease activity. A statistically significant +ve correlation between serum fibrinogen level and cardiac involvements were found in all RA. **Conclusion:** cardiac involvement by ECHO and ECG are present in different grades of disease activity, RA patients in inactive state exhibit cardiac findings compared with controls with significant different, There is Significant correlation of fibrinogen as the most important nontraditional cardiovascular risk to cardiac involvement by ECG and ECHO.

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Introduction:

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by joint swelling, tenderness and destruction of synovial joints, leading to severe disability and premature mortality **[1]**. Excessive cardiovascular events observed in RA individuals are not fully explained by traditional risk factors [2]. Hence, there is an increasing interest in identifying "nontraditional" [3] novel risk factors (i. e., genetic polymorphisms, autoantibodies, medication, duration of RA, high disease activity, and many others) in order to explain the development of early endothelial dysfunction, increased intima-medial thickness (IMT), and finally accelerated atherosclerosis [4]. The finding and understanding of these predisposing factors will allow us to better describe cardiovascular sub phenotypes including hypertension, stroke, coronary artery disease (CAD), angina, myocardial infarction (MI), arrhythmias, ventricular diastolic dysfunction, congestive heart failure (CHF), and thrombosis [5]. Elevated fibrinogen levels have been observed in a number of inflammatory diseases including RA. Plasma fibrinogen levels have been shown to parallel disease activity and acute phase markers (ESR, CRP, Acute phase serum amyloid A (A-SAA) [6].

Several thrombotic variables have been linked to the future risk of developing myocardial infarction or stroke. Fibrinogen is best established of these [7].

The aim of the work: to assess cardiac involvement by ECHO and ECG in RA patients in different grades of disease activity and to correlate these finding to disease activity and fibrinogen as the most important nontraditional cardiovascular risk.

2. Patients and Methods:

This study included 100 patients with rheumatoid arthritis (RA), defined according to American College of Rheumatology (ACR) revised criteria [**8].** These patients were divided into 2 groups according to DAS-28[9].

Group I:

Included 50 patients in active state according to disease activity score (DAS-28 ≥ 3. 2). They were classified into highly, moderate and minimally active according to DAS-28 values, if greater than 5. 1 indicate highly active disease, values between 3. 2 and

5. 1 moderately active disease, and values not greater than 3. 2 minimally active disease. DAS28 < 2. 6 can be used to define remission [9].

Group II:

Included 50 patients in a controlled state according to disease activity score (DAS-28<3. 2) DAS-28 < 2. 6 can be used to define remission. In addition to 50 healthy subjects of the same age and sex were taken as a control group. Exclusion criteria: Careful history and clinical examination were carried out to exclude the following: Any other disease accompanied by inflammation (chronic infection, psoriasis, IBD, hepatitis), pregnancy, DM, uncontrolled hypertension (> 150 / 90). Prednisone dose > 10 mg / day, current or recent lipid lowering therapy, significant anemia, renal impairment, smoking, elevated liver enzymes. Informed consent was obtained from all patients before evaluation. All the patients were subjected to a full clinical examination according to standardized rheumatologic sheet including, history taking, assessment of RA disease activity for patients: through assessment of DAS- 28[9], [10]. The following laboratory tests were done for all the patients and controls. Erythrocyte sedimentation rate (ESR) using Westergren method. C-reactive protein (CRP) using enzyme-linked immunosorbent assay (ELISA) method. Rheumatoid factor (RF) in the serum, using the latex fixation test. Cholesterol assessment by enzymatic colorimetric method. Triglycerides assessment by enzymatic colorimetric method. Fibrinogen assessment by coagulation method using fibrotic FIB. Radiological investigation including Plain x-ray of both hands. ECHO and ECG for detecting any cardiac affection were done for RA patients and control. Radiographic grading of disease severity for both hands and wrists was done [11]. Stanford Health Assessment Questionnaire (HAQ) was done for all patients [12].

3. Results:

This study was carried out on 100 rheumatoid arthritis patients with variable degrees of severity and activity, 50 patients were in an active state (28 in moderate activity and 22 in high activity) added to 50 patients in an inactive state, all patients were taken from the outpatient clinic of rheumatology – Benha university hospital, compared to 50 normal healthy subjects 46 female and 4 male of, the mean age of patients of both groups was 52. 3 ± 8. 2 and 51. 8 ± 5. 9 for the controls, and they were 46 female to 4 male in both group of patients with no significant different, the mean disease duration in active group was 3. 6± 1. 2 and 3. 5 ± 1. 1 in inactive group with no significant different. All patients were subjected to full history taking and clinical examination, diagnosed according to ACR, also laboratory investigations including ESR, CRP, serum cholesterol, triglycerides, RF, and serum fibrinogen were done added to plain X- ray, ECHO and ECG after obtaining the results, they were tabulated, subjected to statistical analysis from which we have found the following:

As regard to nontraditional cardiovascular risk factors ESR, CRP, Fibrinogen. There were statistically significant difference between RA patients and controls as regarding laboratory variables including ESR, serum fibrinogen, CRP. (P < 0. 01) **Table 1**. There were significant difference between moderately, highly active and inactive RA as regarding cardiovascular risk variables fibrinogen, CRP, ESR. **Table 2**.

A significant cardiac involvement in RA patients as regarding both ECG and ECHO in comparison` to control **Table3, 5**, there was a significant difference between active and inactive RA patients as regarding the same variables **Table 4, 6**. A statistically significant +ve correlation between serum fibrinogen level and CVD in all RA patients **Table 7, 8.**

Table-1 Comparison between RA patients and controls as regarding some of the laboratory findings

		Patients (n=100)	Controls (n=50)	Student t test	
				T	p
ESR		22. 5 ± 20. 4	6. 8 ± 3. 0	4. 8	< 0. 01
Cholesterol		236. 9 ± 18. 0	188. 2 ± 9. 9	1. 5	< 0. 01
Triglycerides		173. 7 ± 32. 6	102. 1 ± 39. 5	1. 87	< 0. 01
Fibrinogen		432. 2 ± 18. 1	218. 3 ± 30. 9	9. 4 5	< 0. 01
CRP		22 ±1. 3	7±1. 4	13. 3	< 0. 01
				Chi-square test	
				X2	P
RF	+	91	1	20. 6	>0. 05
	-	9	19		

P< 0. 01 Significant difference between RA patients and controls as regarding ESR, fibrinogen, CRP and insignificant different for Rh factor

Table-2 Comparison between patients with active and inactive RA as regarding some of laboratory findings

	Active grade I (n =28)	Active grade II (n = 22)	Inactive (n=50)	One Way ANOVA	
				F	P
ESR	22. 4 ± 25. 2	42. 7 ± 10. 5	8. 7 ± 2. 4	26. 8	< 0. 01
Fibrinogen	308. 8 ± 14. 9	412. 0 ± 28. 2	293. 4 ± 24. 7	1. 2	< 0. 01

CRP		23 ±1. 2	30±3. 2	17±2. 1	4. 6	< 0. 01
					Chi-square test	
					X2	P
RF	+	24	20	49	1. 7	0. 42
	-	2	2	1		

P < 0. 01

Significant difference between active and inactive RA as regarding ESR, CRP and fibrinogen

Table-3- Comparison between patients and controls as regarding the ECG findings

	Patients (n=100)	Controls (n=50)
Normal	69	50
Arrhythmia	13	-
Ischemia	10	-
LV Hypertrophy	8	-

Cardiac involvement in RA patients and controls as regarding the ECG findings.

Table- 4- Comparison between patients with active and inactive RA as regarding the ECG findings

	Active grade I n=28	Active grade II n=22	Inactive (n=50)	Chi-square test	
				X2	P
Normal	15	10	44	8. 5	< 0. 01
Arrhythmia	4	6	3		
Ischemia	3	5	2		
LV Hypertrophy	3	4	1		

P < 0. 01

Significant difference between active and inactive RA patients as regarding the ECG findings.

Table-5 Comparison between RA patients with controls as regarding the Echocardiographic findings

	Patients (n=100)	Controls (n=50)
Normal	66	50
Arrhythmia	14	-
Ischemia	11	-
LV Hypertrophy	9	-

Cardiac involvement in RA patients as regarding the Echocardiograph findings.

Table-6 Comparison between patients with active and inactive disease regarding the Echocardiographic findings

	Active (n=50)	Inactive (n=50)	Chi-square test	
			X2	P
Normal	25	41	5. 1	P < 0. 01
Arrhythmia	10	4		
Ischemia	8	3		
LV Hypertrophy	7	2		

P < 0. 01

Significant difference between active and inactive RA patients as regarding the ECHO findings.

Table-7 Relation of fibrinogen level to the ECG findings in patients with RA

	Fibrinogen in High and moderately active	One way ANOVA	
		F	P
Normal	273. 2 ± 12. 9	4. 05	P < 0. 05
Arrhythmia	335. 6 ± 38. 6		
Ischemia	343. 0		
LV Hypertrophy	399. 0 ±18. 1		

P < 0. 05

Significant correlation between fibrinogen level and ECG findings RA patients

Table-8 Relation of fibrinogen level to the ECHO findings in active RA patients

	Fibrinogen In highly &moderately active	One way ANOVA	
		F	P
Normal	245. 4 ± 28. 9	3. 33	P < 0. 01
Arrhythmia	412. 0 ± 35. 2		
Ischemia	393. 0 ± 12. 5		
LV Hypertrophy	455. 0 ± 6. 3		

P < 0. 01

Significant correlation between fibrinogen level and ECHO findings in active RA patients.

4. Discussion:

Patients with RA may be at a special risk of sudden thrombotic arterio-occlusive events in the absence of warning symptoms **[13].** It is known that platelets can produce fibrinogen, and platelet activation is a potential factor implicated in heightened CV risk and thrombotic events in RA [6]. Fibrinogen is an acute – phase protein, participating in the systemic response to inflammation. Inflammation plays a key role in the development of athermanous plaque [14]. Monocytes infiltrating the plaque differentiate into macrophages that release cytokines, such as interleukin – 6, that increase plasma fibrinogen[15].

In our study, serum levels of fibrinogen, ESR and CRP which are a biomarkers connecting thrombosis, inflammation and CV risk were elevated in RA patients compared with healthy controls with a P value <0. 01, this was near to other study which measured serum level of acute phase reactants in 147 patients with rheumatoid arthritis and 50 healthy controls and found that the mean level of ESR, CRP and fibrinogen in RA patients were all significantly higher than in healthy controls (for ESR; P <0. 001 and for fibrinogen; p < 0. 05) [16].

Also another study found that serum level of fibrinogen in 105 RA patients and 62 controls was (median 466 Vs 367 mg / dl) with a P value of < 0. 001 [17].

Our study revealed that a significant result between acute phase reactants, fibrinogen and the degree of disease activity according to DAS -28 and which go hand in hand with other study which found a strong positive correlation between DAS- 28 score and serum CRP and fibrinogen [16].

In accordance to our results we found that cardiac finding by ECG in RA patients was about 8% of RA had Hypertrophy, 10 % had Ischemia and 13 % had Arrhythmia and cardiac involvement By ECHO was 9% of RA had LV Hypertrophy, 11% had Ischemia, and 14% had Arrhythmia.

There were significant finding by ECG and ECHO In RA in comparison to controls, also significant different between these finding and different grades of activity in RA patients. Our work were confirmed by many authors who studied 76 RA patients and 64 controls from north Glasgow Monica and reported that a higher prevalence of angina in RA (P = 0. 03) patients compared with controls. In addition about 30 % of RA patients had chest pain more than controls (15%). RA patients were more likely to have suffered from stroke than controls (P = 0. 08) which means that RA patients had significantly higher prevalence of angina and stroke but the difference did not reach statistical difference [18]. Also, According to the results obtained by our study, there was a correlation between the level of plasma fibrinogen and both ECG and ECHO findings in different grades of rheumatoid activity (arrhythmia, ischemia and ventricular hypertrophy). The results of our work confirmed by other research which studied 196 coronary heart disease patients which were grouped into 71 with acute myocardial infarction, 64 with unstable angina and 61 with stable angina. They were 114 males and 82 females with an average age of 55.7 years. From this study, he declared that fibrinogen Concentration in patients with acute myocardial infarction, unstable and stable angina are higher than those of the control group (P < 0. 05). These results indicated that plasma fibrinogen is related to the incident coronary heart disease [19].

our study confirmed by result which found a correlation between fibrinogen level and cardiovascular complications. where he stated that elevated levels of fibrinogen in persons aged 25 – 37 were associated with an increased prevalence of CAC (coronary artery calcification) added to CIMT (carotid intimal medial thickness) after 13 years follow up (age 38 – 50)[20].

Fibrinogen is also a downstream component of the inflammatory cascade increasingly implicated in the pathogenesis of atherosclerosis, myocardial injury and heart failure. Many epidemiological studies and several meta - analyses have reported that elevated plasma fibrinogen level is associated with coronary artery disease, stroke and other adverse cardiovascular event [21], [22]. Again it was declared that elevated fibrinogen has also been demonstrated to be associated with incident heart failure. However, the underlying pathphysiological mechanisms have not been well elucidated [23].

Based on the results of our study, this may raise some important issues. Importance of cardiovascular (CV) evaluation in RA patients and follow up by ECG and / or ECHO. Cardiac findings are present in all grades by ECHO and ECG and significantly correlated with activity so we could considered activity as nontraditional risk factor risk factor. Serum fibrinogen level were elevated in all patients even in inactive group so evaluation in RA patients may be of a great value in impending CV events, This may be a fruitful area for research, therefore, when fibrinogen levels are high, reducing those levels should be the goal of therapy. We recommend for this study to be extended on a larger number of patients with different grades, severity, duration and correlate this with CV events.

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