Evaluation of Cardiac Changes in Hyperlipidaemic Rheumatoid Arthritis Patients

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Abstract: Objectives: To evaluate the prevalence of echocardiographic evidence of cardiac lesions among rheumatoid arthritis (RA) patients free of cardiac complaints and its relation to the presence of dyslipidemia and disease activity scores. **Patients & Methods:** The study comprised 100 patients with RA fulfilling ACR criteria. All patients underwent clinical evaluation of disease activity using the disease activity score, using a 28 joint score (DAS-28), pain visual analogue scale (VAS) and calculation of the Disability Index (DI). Then, all patients underwent trans-thoracic Echocardiography and gave fasting blood samples for estimation of serum lipids. **Results:** Lipid profile assessment defined 33 dyslipidemic RA patients (Group A) and 67 RA patients with near normal lipid profile (Group B). Dyslipidemic RA patients were significantly older with significantly longer disease duration and significantly higher DAS-28 and pain VAS scores. Fifty-nine RA patients had valvular affection; 27 patients were non-dyslipidemic and 24 were dyslipidemic RA patients with significantly higher frequency of patients had valvular diseases in dyslipidemic RA patients. Fifty-three (53%) patients had myocardial affection in the form of left ventricular diastolic dysfunction, wall motion abnormalities and dilatation of the wall. The frequency of myocardial affection in group A was significantly higher compared to its frequency in group B. Sixteen patients showed evidence of pericarditis; 6 in group A (18.2%) and 11 in group B (16.4%) with non-significantly higher frequency in group A. **Conclusion:** RA patients free of cardiac complaints are at a definite risk of having hidden or quiescent cardiac affection especially if they were dyslipidemic. The obtained results spotlight on the necessity for cardiac screening programs for RA patients for early detection of cardiac affection prior to be symptomatized and control of both RA activity and dyslipidemia is mandatory for minimizing the cardiac risk in RA patients

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1. Introduction

Rheumatoid arthritis (RA) is a chronic systemic disease affecting primarily the synovium, leading to joint damage and bone destruction. RA causes significant morbidity as a result of loss of function and associated disability, and increased energy expenditure. Epidemiological studies have shown a reduced life expectancy in patients with RA compared to general population and is mainly due to cardiovascular (CV) disease. In active RA, the majority of cardiovascular deaths result from accelerated atherosclerosis ***(Solomon et al., 2010)***.

Etiopathogenesis of RA-associated enhanced CV risk is unknown, but inflammation is thought to play an important part, (**Choi *et al.*, 2002, Libby, 2002**). Several possibilities have been suggested for the underlying pathophysiological mechanism; acute-phase proteins might deteriorate ‘‘fatty streaks’’ into (instable) plaques, destabilize plaques and cause plaque ruptures, give complement activation or facilitate deterioration of the lipid profile ***(Boers et al., 2003, Libby & Ridker, 2004, Ridker et al., 2004)*.**

Dyslipidemia may be responsible for the increased CV risk in patients with RA. Several investigators have shown that active RA is associated with unfavorable lipid profile resulting in a less favorable atherogenic index, suggesting a relationship between inflammation and dyslipidemia ***(Toms et al., 2010a)***.

In RA, the heart can be affected in its three layers. Pericarditis is the cardiac manifestation most readily recognized, but myocardial disease, coronary vasculitis, diastolic dysfunction, accelerated atherosclerotic disease and valvular lesions can also be found. The prevalence of RA valvular heart disease is variable in the literature varying from 3% to 70%. This high variability may be due to different genetic backgrounds of the studied population and to different methods used in the detection of valvular disease. In some studies the occurrence of valvular heart disease is associated with male gender and presence of rheumatoid nodules, age, disease duration and degree of inflammatory activity ***(Coskun et al., 2005, Kamiński et al., 2005, Kitas et al., 2001)***.

Even though the CV risk in RA is well-recognized, a major challenge is detection, treatment, and prevention of CV disease in RA subjects who are less likely to report symptoms of angina, more likely to

experience unrecognized myocardial infarction and are twice as likely to experience sudden deaths, indicating that the first presentation of CV disease in RA subjects may be a sudden cardiac death ***(Mohammad et al., 2010; Rovenský et al., 2010)***. Therefore, the present study aimed to evaluate the prevalence of cardiac lesions as identified using echocardiography among RA patients free of cardiac complaints and its relation to the presence of dyslipidemia and disease activity scores on the other side.

2. Patients & Methods

This prospective double-blinded study was conducted at Departments of Rheumatology, Physical Medicine & Rehabilitation, Cardiology and Internal Medicine, Faculty of Medicine, Al-Azhar University since Jan 2009 till May 2010. The study comprised 100 patients with RA. Only patients who fulfilled either four of seven ACR criteria or having morning stiffness ≥60 minutes, symmetrical arthritis and small joint arthritis (metacarpo-/metatarso-phalangeal joints/ wrists) for at least 6 months were included in the study. Acute phase reactions were measured by erythrocyte sedimentation rate and C-reactive protein using standard laboratory methods and performed at hospital laboratory. Patients had diabetes mellitus, hypertension, smoking, obesity, thyrotoxicosis, hyperuricemia, cystenuria and other cardiac risk factors were excluded from the study

All patients underwent clinical evaluation of disease activity as assessed by the disease activity score, using a 28 joint score (DAS-28), as follows: ≤3.2: inactive, >3.2-≤5.1: moderate activity and >5.1: very active disease ***(Prevoo et al., 1995***). Pain was assessed by a 0–100 mm horizontal visual analogue scale (VAS), with 0 indicates no pain and 100 indicates the worst intolerable pain and VAS score of 0-25 indicates mild pain, >25-50 indicates moderate pain, >50-75 indicates severe pain and >75 indicates intolerable pain ***(Scott & Huskisson, 1976)***. Functional disability was evaluated using the Swedish version of the Stanford health assessment questionnaire (HAQ) to calculate the Disability Index (DI). The eight categories assessed by DI are 1) dressing and grooming, 2) arising, 3) eating, 4) walking, 5) hygiene, 6) reach, 7) grip, and 8) common daily activities. Difficulty during each of these acts was assessed as follows: 0: without any difficulty, 1: with some difficulty, 2: with much difficulty and 3: unable to do, then the sum of the categories scores is calculated and divided by the number of categories. This gives a score in the 0 to 3 range ***(Ekdahl et al., 1988)***.

All patients underwent trans-thoracic Echocardiography using Vivid 7 dimension GE Medical System GE Vingmed ultrasound ASN-3190 Horten, Norway including the following: M-mode, 2D, pulsed and continuous wave Doppler, and color flow mapping. Through standard echo views (parasternal long and short axis, apical 5,4, and 2 chambers views, and sometimes subcostal view) to asses all cardiac chambers motions and functions and diameters and their contents and assessment of all cardiac layers endocardium, myocardium, and pericardium and assessment of wall motion abnormalities, and assessment of all valves motion, functions and flows.

All patients gave blood samples (fasting samples for 18 hours) for estimation of serum total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), very low-density lipoprotein cholesterol (VLDL) and triglycerides (TG). All estimations were conducted at hospital outpatient lab.

Statistical Analysis

Data are presented as mean±SD, range, numbers and percentages and were analyzed using Wilcoxon's ranked test for unrelated data for measurements comparisons and Chi-square (X^2 test) for numbers and percentages comparisons. Statistical analysis was conducted using SPSS program (Version 15, 2006). *P* value at <0.05 was considered significant.

3. Results

The study included 100 patients; 29 males and 71 females with mean age of 47.9±5.2; range: 41-63 years and mean body mass index of 31.5±2.1; range: 26.6-35.3 kg/m^2. Mean duration of disease was 8±2.3; range: 5-15 years with mean DI index of 1.88±0.7; range: 1-3, mean DAS-28 score of 3.2±1.08; range: 1.5-6.1 and mean pain VAS score of 31.6±17.4; range: 12-69. Lipid profile assessment defined 33 dyslipidemic RA patients (Group A) with dyslipidemia manifested as significantly higher serum levels of total cholesterol, cholesterol, TG and LDL with significantly lower serum HDL levels, (Table 1) compared to the remaining 67 patients who showed near normal lipid profile (Group B).

Dyslipidemic RA patients were found significantly older than non-dyslipidemic and female percentage was significantly higher among them. Moreover, dyslipidemic RA showed significantly longer disease duration with significantly higher DAS-28 and pain VAS scores but with non-significantly higher DI compared to non-dyslipidemic RA patients, (Table 1).

Forty-one RA patients (41%) were free of valvular affection; 32 patients (47.8%) were non-dyslipidemic, while only 9 patients (27.3%) were dyslipidemic RA patients with significantly higher frequency of patients had valvular diseases in dyslipidemic RA patients (X^2=7.796, p<0.01). Forty-seven patients (80%) had only one affected valve; 17 in group A (51.5%) and 30 in group B (44.7%), 9 patients (15.3%) had two affected valves; 4 in group A (12.2%)

and 5 in group B (7.5%), while only 3 patients (9%) in group A had more than two valves affected. Mitral valve was the mainly affected valve in both groups followed by the tricuspid and pulmonary valves, while aortic valve was affected only in dyslipidemic patients, (Table 2, Figs. 1 & 2).

Forty-seven RA patients (47%) were free of myocardial affection; 37 patients (52.2%) were non-dyslipidemic, while 10 patients were dyslipidemic. Fifty-three (53%) patients had myocardial affection in the form of left ventricular diastolic dysfunction, wall motion abnormalities and dilatation of the wall (Figs. 3 & 4). The frequency of myocardial affection in group A was significantly higher compared to its frequency in group B, (X^2=3.856, p<0.05). Sixteen patients showed evidence of pericarditis; 6 in group A (18.2%) and 11 in group B (16.4%) with non-significantly (X^2=1.187, p>0.05) higher frequency in group A (Table 3, Figs. 5 & 6).

Table (1): Patients' enrollment data

		Group A (n=33)	Group B (n=67)	Total
Age (years)		52.1±4.8 (46.2-63)	45.8±4 (41-56)*	47.9±5.2 (41-63)
Gender	Males	15 (45.5%)	14 (20.9%)	29 (29%)
	Females	18 (54.5%)	53 (79.1%)	71 (71%)
BMI data	Weight (kg)	84.9±3.6 (79-92)	84.7±4.3 (74-90)	84.8±4.1 (79-92)
	Height (cm)	162.8±4 (158-181)	164.7±4.7 (156-175)	164.1±4.4 (156-181)
	BMI (kg/m2)	32.1±1.6 (28-35.2)	31.3±2.3 (26.6-35.3)	31.5±2.1 (26.6-35.3)
Disease duration (years)		10.5±1.9 (8-15)	6.8±1.4 (5-9)	8±2.3 (5-15)
DAS-28 score		3.8±0.9 (2.3-6.1)	2.9±1 (1.5-5.6)*	3.2±1.1 (1.5-6.1)
DI		1.94±0.56	1.74±0.66	1.81±0.63
Pain VAS score		46.2±13 (26-69)	22.6±10.7 (12-62)*	30.4±16 (12-69)
Lipid profile	Cholesterol	227±29.3	168±13*	187.5±34.1
	TG	175±38.5	115.9±16.6*	135.4±38
	HDL	27.6±4.4	35.6±6.7*	33±7.1
	LDL	62.6±8.9	58.8±8	60±8.4
	Total cholesterol	492.2±62.1	378.4±25.6*	416±67.6

Data are presented as mean±SD, numbers; ranges & percentages are in parenthesis
*: significant versus group A

Table (2): Echocardiographic data concerning cardiac valves

		Group A (n=33)	Group B (n=67)	Total
Presence	Present	24 (72.7%)	35 (52.2%)	59 (59%)
	Free	9 (27.3%)	32 (47.8%)	41 (41%)
Number of affected valves	One	17 (51.5%)	30 (44.7%)	47 (47%)
	Two	4 (12.2%)	5 (7.5%)	9 (9%)
	>Two	3 (9%)	0	3 (3%)
Valves affected	Mitral	21	28	49
	Tricuspid	6	7	13
	Pulmonary	4	5	9
	Aortic	3	0	3

Data are presented as numbers; percentages are in parenthesis

Table (3): Patients' distribution according to the frequency of pericardial and myocardial affection among studied patients

		Group A (n=33)	Group B (n=67)	Total
Pericarditis	Present	6 (17.9%)	10 (14.9%)	16 (16%)
	Free	27 (82.1%)	56 (85.1%)	84 (84%)
Myocardial affection	Present	23 (69.7%)	30 (44.8%)	53 (53%)
	Free	10 (30.3%)	37 (55.2%)	47 (47%)

Data are presented as numbers; percentages are in parenthesis

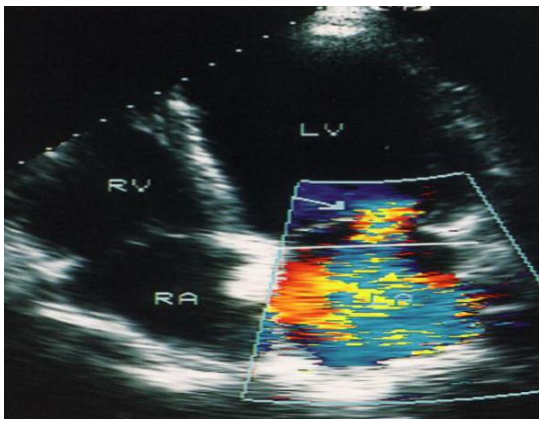

Fig. (1): Shows color Doppler examination showing MR

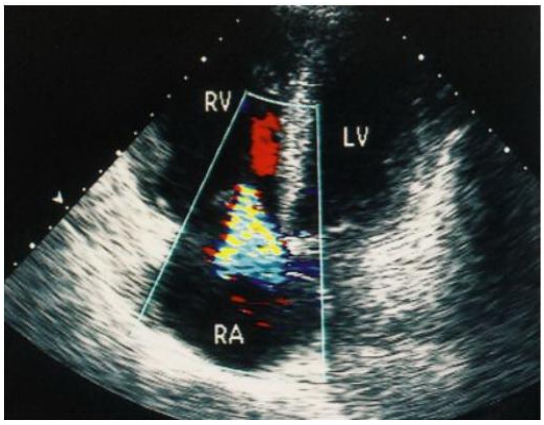

Fig. (2): Shows color Doppler examination showing TR

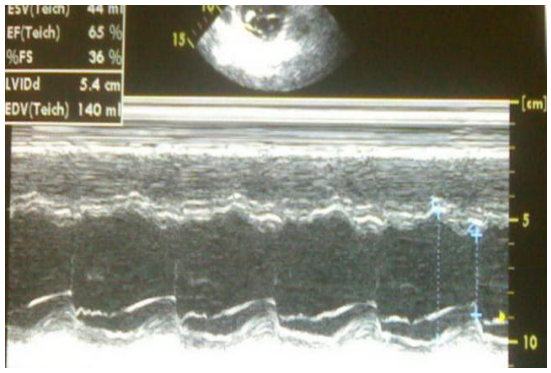

Fig. (3a): Shows normal LV dimension and function by M-mode

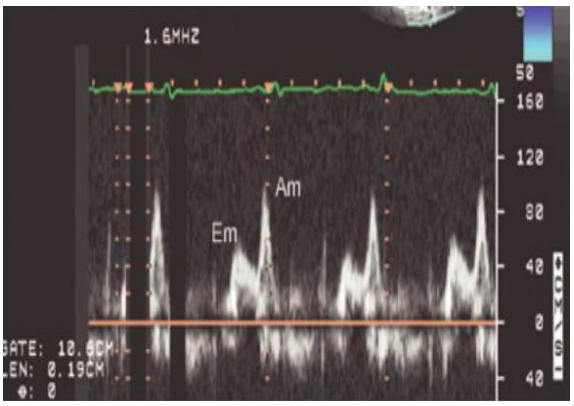

Fig. (3b): Shows LV diastolic dysfunction by M-mode

Fig. (4): Shows LV dilatation

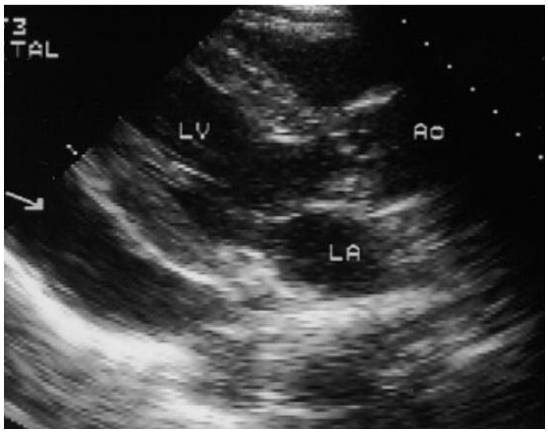

Fig. (5): Shows posterior pericardial effusion (white arrow)

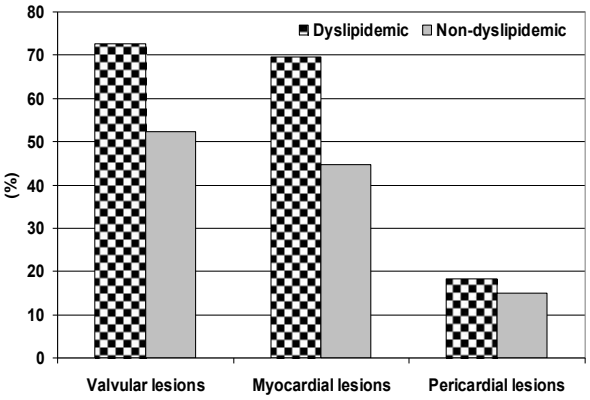

Fig. (6): RA patients' distribution according to cardiac lesions as defined by Echocardiography in both groups

4. Discussion

The current study was relied on survey basis for double-blinded evaluation of 100 RA patients as regards both presence of cardiac involvement as evidenced by echocardiographic examination irrespective of being dyslipidemic or not and the relation between cardiac involvement and RA duration and manifestations. Dyslipidemia in the form of high serum total cholesterol in association with high serum levels of TG and LDL on one side and low serum HDL on the other side was reported in 33 patients while the other 67 patients showed serum lipids within the normal range of used kit at hospital lab.

In hand with these results, ***Rizzo et al. (2009)*** reported that as compared to controls, RA patients had higher plasma triglycerides and lower HDL-cholesterol concentrations, while total- and LDL-cholesterol concentrations were similar and about 1/3 of patients showed the complete "atherogenic-lipoprotein-phenotype". ***Ghosh et al. (2009)*** found LDL-cholesterol was the commonest abnormality seen in 37.2% of RA patients and concluded that lipid abnormalities are common in Indian patients with RA and low HDL-C being the commonest abnormality.

In support of the relationship between dyslipidemia and RA, ***Jick et al. (2009)*** found that statins may be protective against the development of RA in patients with hyperlipidemia. Also, ***Toms et al. (2010 a& b)*** documented that depending on the risk stratification method, 2% to 26% of patients with RA without CVD were dyslipidemic and have sufficiently high risk to require statin therapy, and attributed altered lipid metabolism in RA to systemic inflammation, environmental lifestyle factors, drug therapy and several genetic factors and concluded that these factors may result in changes in overall lipid levels, as well as modifications of lipid/lipoprotein structure and function.

Echocardiographic evaluation of studied patients revealed that about 45% of RA patients without dyslipidemia had echocardiographic evidence of myocardial affection in the form of left ventricular diastolic dysfunction, wall motion abnormalities and dilatation of the wall, while about 70% of RA patients with dyslipidemia had echocardiographic evidence of myocardial affection in the form of left ventricular diastolic dysfunction, wall motion abnormalities and dilatation of the wall. These data indicated an association between RA and myocardial affection that was more aggravated due to the presence of dyslipidemia. ***Mavrogeni et al., (2009)*** [20] evaluated myocardial inflammation in patients with variant autoimmune diseases using cardiovascular MRI and found myocardial inflammation is a common finding in patients with autoimmune diseases and cardiac symptoms. ***Kobayashi et al. (2010)*** reported that myocardial abnormalities, as detected by cardiac MRI, were frequent in RA patients without known cardiac disease and abnormal cardiac MRI findings were associated with higher RA disease activity, suggesting a role for inflammation in the pathogenesis of myocardial involvement in RA.

The present study detected valvular affection in about 73% of RA dyslipidemic patients in comparison to 52% of RA patients; all valves were involved, but with descending order of frequency from mitral, pulmonary, tricuspid to the aortic valves. Valvular affection was in the form of regurgitation. These findings were in hand with ***Beckhauser et al. (2009)*** who studied valvular lesions in RA patients and reported that 15.2% of asymptomatic RA patients had valvular lesions, aortic valve was the most affected and valvular lesions were more common in patients with disease duration longer than 15 years with no association between valvular lesions and sex, age, tobacco exposure, rheumatoid factor positivity, presence of antinuclear antibodies, rheumatoid nodules, anticardiolipin antibodies or functional class. ***Obradović-Tomasević et al. (2009)*** evaluated all parameters of diastolic function (mitral and pulmonary flow) in patients with RA and reported that in RA patients 98.9% had diastolic function disorder, and this parameter had been changed prior to clinical signs of heart failure and decrease of ejection fraction, and indicators of diastolic function, velocities E, A and their ratio V(E)/V(A), as well as velocities S, D and their ratio V(S)/V(D) were lower in patients with positive rheumatoid factor.

Also, pericarditis was detected in 17 patients; 6 dyslipidemic RA and 11 RA patients, these data are in hand with ***Berisha et al. (2010)*** who reported that pericarditis was evidenced in 16.6%, mitral regurgitation in 21.9%, aortal regurgitation in 26%, and pulmonary diffuse fibrosis in 16.6% of RA cases and concluded that cardiac and pulmonary alterations are frequently present and prevalence of elevated CRP levels and positive serologic tests was high in

asymptomatic patients with RA among patients without clinical manifestations

It could be concluded that RA patients free of cardiac complaints are at a definite risk of having hidden or quiescent cardiac affection especially if they were dyslipidemic. The obtained results spotlight on the necessity for cardiac screening programs for RA patients for early detection of cardiac affection prior to be symptomatized and control of both RA activity and dyslipidemia is mandatory for minimizing the cardiac risk in RA patients

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