Rheumatoid Arthritis: Cardiovascular Diseases and Dyslipidaemia

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Abstract: The cardiovascular diseases (CVDs) such as myocardial infarction and stroke associated with rheumatoid arthritis (RA) are an increased in the past years. Cardiovascular risks factors, such as hypertension and dyslipidaemia are important but not explain all of the excess risk. Systemic inflammation with classic risk factors may also contribute. The aim of this study to investigate CVDs and lipid profile in RA patients and to determine the correlation between lipids and CVDs. One hundred patients with RA diagnosed according to American Collage of Rheumatology (ACR1987) and ACR/EULAR 2010 criteria were included in this study. The patients subjected to clinical evaluation, lipid profile & Apo lipoprotein A-I, radiological (plain x ray hand and chest), Echocardiography (Echo), stress electrocardiography (ECG) and Carotid Duplex. This study was showed that, the most common cardiovascular diseases (CVDs) among the studied cases were Carotid atherosclerosis, heart failure, ischemic heart disease and valvular diseases (59.0%, 34%, 30% and 30.0 % respectively). Most studded cases of RA that complicated with CVDs, had normal level of total cholesterol (TC), low density lipoprotein (LDL) and triglyceride(TG) (86.36 %, 78.40% and 62.5% respectively), with no significant differences with RA patients that not complicated with CVDs. high density lipoprotein (HDL) and Apo lipoprotein A-I were low in most cases of RA that complicated with CVDs (96.59% and 92.05 % respectively), with no significant differences with RA patients that not complicated with CVDs. From this result we found that in spite of TC, LDL, and TG were normal in most our cases of RA, but the incidence of CVDs was high (88.00%) and the incidence of atherosclerosis also was high (59.00%). But HDL and Apo lipoprotein A-I were low in most our cases of RA that complicated with CVDs. So this dyslipidaemia may explain the risk of CVDs in RA patients.. So we recommend that cardiovascular assessment are important to RA patients and dyslipidaemia may correlate with CVDs in RA patients.
[Saad M. Elzokm, Mahmud farag, Mohamed Adel and Ali Mansur. **Rheumatoid Arthritis: Cardiovascular Diseases and Dyslipidaemia.** *Nat Sci* 2017;15(1):135-142]. ISSN 1545-0740 (print); ISSN 2375-7167 (online). http://www.sciencepub.net/nature. 18. doi:10.7537/marsnsj150117.18.

Keywords: Rheumatoid Arthritis, Dyslipidaemia and Cardiovascular diseases

1. Introduction

The cardiovascular diseases (CVDs) in RA patients are common including pericarditis, cardiomyopathy/myocarditis, cardiac amyloidosis, coronary vasculitis, arrhythmia, valve diseases, congestive heart failure and ischemic heart disease and are associated with an increased mortality compared with the general population (**Turesson *et al.*, 2007).**

Traditional risk factors of CVDs as smoking, hypertension, diabetes and hyperlipidaemia, are important, but do not fully explain the increased risk of CVDs in RA (**Solomon *et al.*, 2004**). Systemic inflammation with traditional CV risk factors had direct and indirect effects on the vasculature (**George and Sherine, 2011**).

Semb *et al.* (2010), found that hyperlipidaemia (high total cholesterol (TC) or low-density lipoprotein (LDL) less common in RA than in non-RA patients**, but Toms *et al.* (2010)**, described that dyslipidaemia may affect up to 50 % of all patients with RA.

Myasoedova *et al.* (2009), described that lipids appear to have a paradoxical effect on CV risk in people with RA, for example, decreased lipid levels are associated with increased CV risk. Also ***Myasoedova et al. (2010),*** described that serum levels of total cholesterol and LDL cholesterol decline during the 3–5-year period before RA incidence.

Apo lipoprotein A-I, has a specific role in lipid metabolism. Apo lipoprotein A-I is the major protein component of high density lipoprotein (HDL) in plasma.. The protein promotes cholesterol efflux from tissues to the liver for excretion. It is a cofactor for lecithin cholesterol acyl transferase which is responsible for the formation of most plasma cholesterol esters (**Wasan *et al.*, 2008)**.

The aim of this study to investigate CVDs and lipid profile in RA patients and to determine the correlation between lipids and CVDs.

2. Patients and Methods

Patients:

One hundred patients (7.0 males and 93.0 females) of different age ranged from 21 to 58 years old with RA diagnosed according to American Collage of Rheumatology (ACR1987) and

ACR/EULAR 2010 criteria, were studied, with informed consent. All patients recruited from rheumatology clinic in Al- Azhar University hospital at Damietta. All patients had been treated with one or more of disease modifying anti rheumatic drugs (DMARDs) including methotrexate, leflunamide and hydroxychloroquine, with short course of steroid. Patients having diabetes mellitus, hypertension, morbid obesity, chronic liver disease, chronic renal disease, hepatitis C virus (HCV), hepatitis B virus (HBV) and chronic pulmonary disease were excluded from this study.

Methods:

The patients were subjected to:-

1-**Clinical methods**:

.All patients were examined personally at presentation by full medical history taking and medical examination (general, cardiac and joint examination).

2- **Laboratory investigations**

The following investigations were performed:-

A)- Routine laboratory investigations: Complete blood count (CBC), C reactive protein "CRP" and, Erythrocyte sedimentation rate (ESR), fasting and postprandial blood sugar, liver function test, kidney function test, HCV, HBV antibodies to help in exclusion of chronic disease.

B) Lipid profiles including, total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL) and high density lipoprotein (HDL).

C) Serum Apo lipoproteins A-1.

The normal values of lipid profiles and Apo lipoprotein A1 are:-

1-Cholestrol: - less than 200 mg/dl, borderline 200-239 mg/dl and high 240 mg/dl or above.

2-Triglycride: - less than 150 mg/dls) is considered normal, while 200 to 499 mg/dl is considered high. In between the ranges is considered borderline.

3-LDL: - less than 100 mg/dl is considered optimal and up to 129 mg/dl is near optimal. Borderline high LDL ranges from 130 to 159 mg/dl and 160 to 189 mg/dl is considered high. Above that level is categorized as very high.

4-HDL:-Normal HDL levels above 40 mg/dl for men and above 50 mg/dl for women.

5-Apolipoprotein A1:-Male1 109-184 mg/dl and female 106-228 mg/dl.

3-Cardiovascular assessment methods:

Cardiovascular affection assessed by

1- Stress ECG: -

Stress ECG using QRS-CARD apparatus was performed for all patients for manifestations of ischemia including (ST-T wave changes, new onset bundle branch and / or dysrhythmia).

2-Echocardiography (ECHO):-

Resting Transthoracic Echocardiography (M-mode, 2D echocardiography, pulsed wave, continuous wave and color Doppler) were performed for all patients using Esaote Biomedica apparatus, for the following parameters:- {LV internal dimensions, LV ejection fraction, percentage of Fraction shortening, Resting segmental and / or regional wall motion **(Lang *et al.*, 2006),** Cardiac diseases (as pericardial effusion, cardiomyopathy, sclerocalcific valves, pulmonary hypertension), optimal diastolic flow of the mitral valve (peak early rapid filling E velocity, peak atrial contraction A velocity was measured)}.

3-Carotid duplex:

The degree of atherosclerosis by carotid duplex, classified into mild, moderate and sever atherosclerosis according to the diameter of lumen of the vessels, intima media thickens and the presence of atheromatous plaques or not. Using carotid artery intima media thickness (CIMT) as a marker for atherosclerotic burden and cardiovascular risk. CIMT measurement is a noninvasive and economical test which is quite reliable and sensitive for assessment of atherosclerosis (**Lorenz *et al.*, 2007**). Increased atherosclerosis in carotid arteries holds true to atherosclerosis for multiple vascular beds including coronaries, and so measurement of carotid IMT is an important surrogate marker for increased cardiovascular risk including acute coronary syndrome (Del **RI, *et al.*, 2005).**

4- Statistical methods: -

The collected data were organized, tabulated and statistically analyzed, using Statistical Package for Social Science (SPSS) version 19 (SPSS Inc, Chicago, USA), running on IBM compatible computer with Microsoft ® Windows 7 Operating System. Mean, standard deviation, number and percent of each observed category was calculated and Fisher exact test was used for qualitative data and t student test for quantitative data to test the significance differences between studied patients. The level of significance was adopted at $p < 0.05\%$.

3. Results

A)* - Demographic data onto patients*:

One hundred RA patients were included in this study. Majority of patients 47.0% aged from 30 to 50 years, and 93.0% were females and most of them 43.0 % having disease duration less than 5 years with 53.0% having moderate disease activity. Most of the RA patients 88% having CVDs (Table 1).

B) - frequency of cardiovascular complications to RA patients according to ECHO, stress ECG and carotid duplex results:

This study showed that, the most common cardiovascular complications from the studied cases were carotid atherosclerosis, heart failure, ischemic

heart disease and valvular affection (59.0%, 34%,30% and 30.0 % respectively (Table 2).

C) Correlation between lipid profile and ApoA-1 with CVDs in RA patients:-

This study showed that most RA cases that having CVDs having normal level of TC, LDL and TG (86.36 %, 78.40% and 62.5% respectively), with no significant differences with RA patients that not complicated with CVD. But HDL and Apo lipoprotein A-I, were low in most cases of RA that having CVDs (96.59 % and 92.05 % respectively), with no significant differences with RA patients that not complicated with CVDs (Table 3).

D) Lipid profile and Apo lipoprotein A-I in RA patients complicated with carotid atherosclerosis and ischemic heart disease

This study showed, most studded cases of RA that complicated with carotid atherosclerosis and ischemic heart disease have normal level of TC, LDL and TG. But HDL and Apo lipoprotein A-I were low in most cases (Table 4).

Table (1): Demographic data onto RA patients

characteristics	No = 100	%
Age		
Less than 30 years	16	16.0
From 30-50 years	47	47.0
More than 50 years	37	37.0
Mean(SD) = 46.62±11.67		
Sex		
Male	7.0	7.0
Female	93	93.0
Duration of RA		
Less than 5 years	43	43.0
From 5-10 years	37	37.0
More than 10 years	20	20.0
Mean(SD) =5.94±4.86		
Severity of RA		
Mild	27	27.0
Moderate	53	53.0
Severe	20	20.0
RA patients with CVD	88	88.0
RA patients without CVD	12	12.0

Table (2): Frequency of cardiovascular complications to RA patients:-

Cardiovascular complications	No	%
Carotid atherosclerosis	59	59.0
Heart failure	34	34.0
Valvular affection(mitral and aortic)	30	30.0
Ischemic heart disease	30	30.0
pericardial effusion	13	13.0
pulmonary hypertension	6	6.0
Cardiomyopathy	5	5.0

Table (3): Correlation between lipid profile and Apo lipoprotein A-I with CVD in RA patients:-

Lipid profile	**RA with CVD N= 88**		**RA without CVD N= 12**		***P* Value**
TC	N	%	N	%	
Normal	76	86.36	10	83.33	0.78 NS
Low	0	0.00	0	0.00	
High	12	13.63	2	16.66	
Mean level (SD) mg/dl	**158.75**±6.02		152.76±47.13		0.67 NS
LDL	N	%	N	%	
Normal	69	78.40	9	75.00	0.72 NS
Low	6	6.81	0	0.00	
High	13	14.77	3	25.00	
Mean level (SD) mg/dl	**107.85± 11.1**		**101.78±37.97**		0. 59 NS
TG	N	%	N	%	
Normal	55	62.5	7	58.33	0.76 NS
Low	15	17.04	3	25.00	
High	18	20.45	2	16.66	
Mean level (SD) mg/dl	**148.17±68.79**		143.75± 29.53		0.70 NS
HDL	**N**	**%**	N	%	0.41 NS
Normal	**3**	**3.40**	1	8.33	
Low	**85**	**96.59**	11	91.66	
High	**0**	**0.00**	0	0.00	
Mean level (SD) mg/dl	**39.18±62.71**		**42.12±42.11**		0.83 NS
Apo lipoprotein A-I	N	%	N	%	0.29 NS
Normal	7	7.95	2	16.66	
Low	81	92.05	10	83.33	
High	0	0.00	0	0.00	
Mean level (SD) mg/dl	99**.92 ± 43.1**		101.50±16.54		0.81 NS

Table (4): Lipid profile and Apo lipoprotein A-I in RA patients complicated with carotid atherosclerosis and ischemic heart disease

Lipid profile	**Carotid atherosclerosis N=59**		**Ischemic heart disease N=30**	
TC	N	%	N	%
Normal	51	86.44	28	93.33
Low	0	0.00	0	0.00
High	8	13.55	2	6.66
LDL				
Normal	49	83.05	28	93.33
Low	0	0.00	0	0.00
High	10	16.94	2	6.66
TG				
Normal	43	72.88	27	90.00
Low	6	6.81	0	0.00
High	10	16.94	3	10.00
HDL				
Normal	3	5.08	2	6.66
Low	56	94.91	28	93.33
High	0	0.00	0	0.00
Apo lipoprotein A-I				
Normal	7	11.86	3	10.00
Low	52	88.13	27	90.00
High	0	0.00	0	0.00

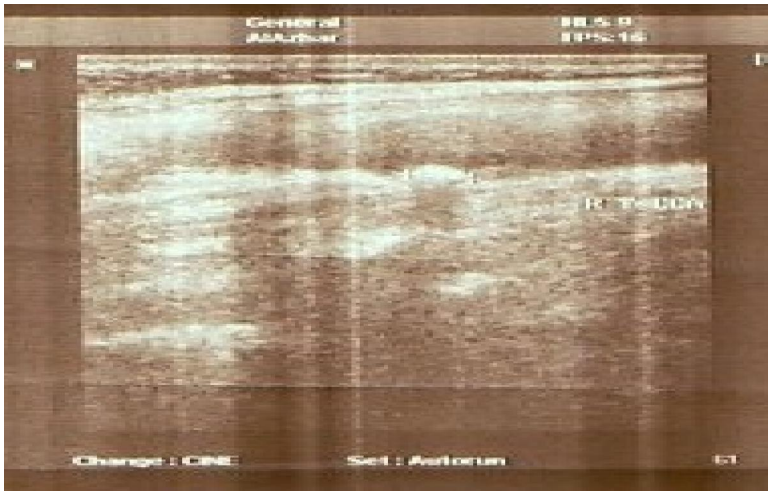

Figure (1): Carotid duplex fore female patient 58 years with rheumatoid arthritis since 8 years, show fixed atheromatous plague 8 mm at the posterior wall of the right common carotid artery.

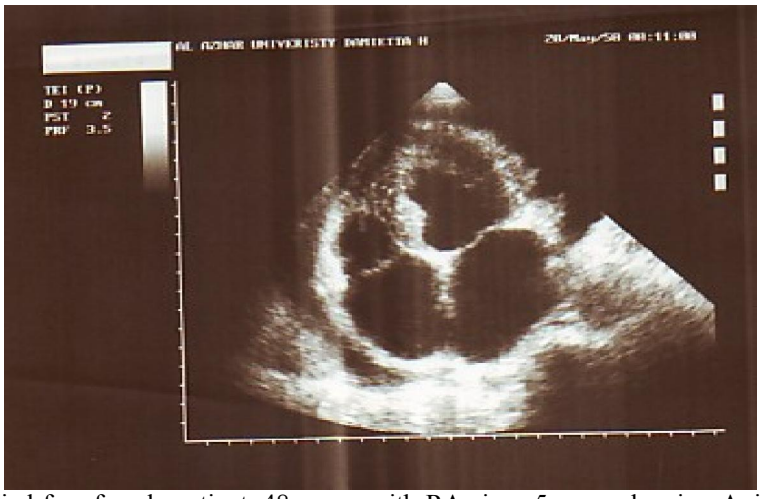

Figure (2) ECHO studied fore female patient, 48 years, with RA since 5 years showing Apical four chamber view with pericardial effusion.

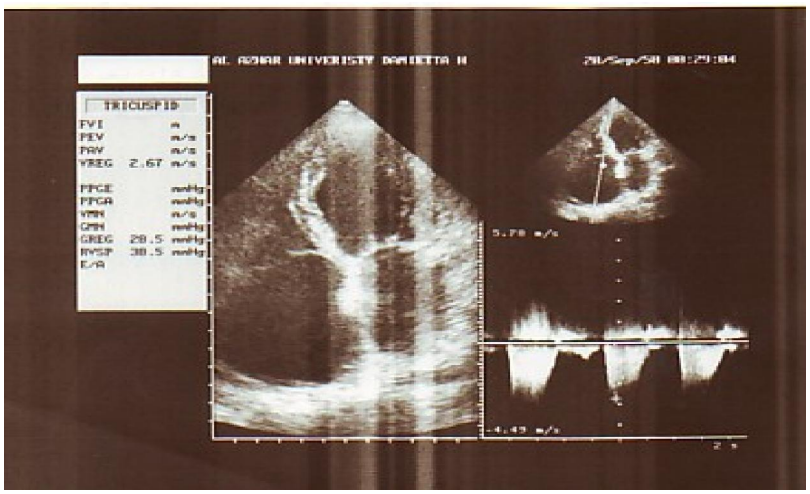

Figure (3) ECHO studied fore female patient, 50 years, with RA since 7years showing Apical four chamber view showing pulmonary hypertension (50 mmHg).

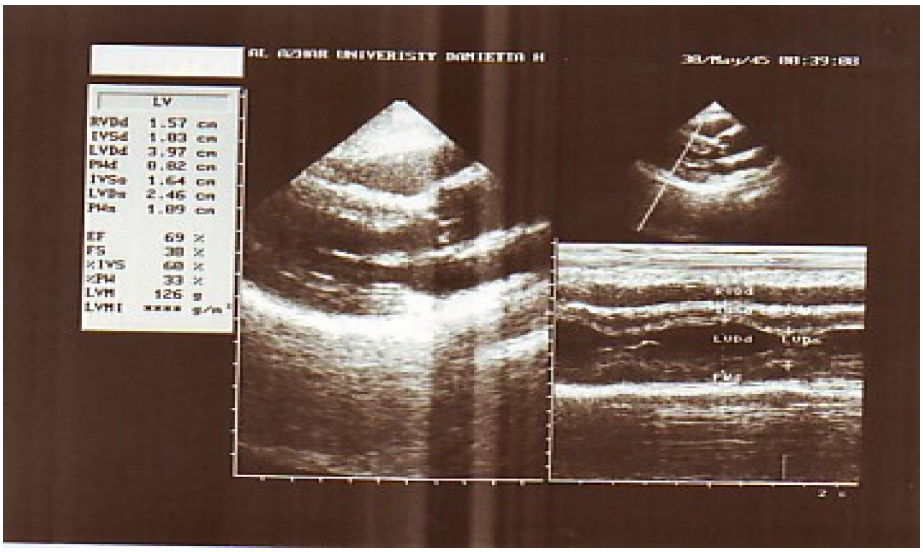

Figure (4) ECHO studied fore female patient, 43 years, with RA since 6 years, showing left parasternal long axis view and M mode showing asymmetrical hypertrophy of the left ventricle (hypertrophic cardiomyopathy (HCM**).**

4. Discussion

Rheumatoid arthritis is associated with an increased mortality. The majority of which is originating from cardiovascular diseases. The main objectives of our study were to investigate the lipid profile and Apo A-1 in RA patients and to determine the correlation between lipid profile and Apo A-1 with CVDs in RA patients.

Our study showed that in most studded cases (88.0 %) had one or more of CVDs and the most CVDs in our patients were; carotid atherosclerosis, heart failure, ischemic heart and valvular affection (59.0%, 34%, 30% and 30.0 % respectively), but **Roman *et al.* (2006) and Voskuyl (2006)**, reported that the commonest CVD in RA patients were pericarditis (50.0%) then cardiomyopathy (30.0%) but coronary vasculitis represents (20.0%). This difference is probably due to, **Voskuyl** study not include carotid duplex in his study and also my be due to the difference in nature of diet and atmosphere between Egypt and Amsterdam.

Our study showed pericardial effusion in 13 patients (13.0%) of RA patients, although usually clinically silent, and this result is supported by **(Guedes *et al.*, 2001)**. Other cardiac complications from our study were; pulmonary hypertension and cardiomyopathy representing 6.0% and 5.0% respectively and this result is supported by **(Ankur and Barry, 2009)**.

The mean (SD) levels of TC in RA with CVD was 98.75±6.02 mg/dl, while in RA without CVD was 102.76±47.13 mg/dl, with no significant difference between them(*P*=0.05), and the mean(SD) levels of LDL in RA with CVD was **87.85± 11.1**mg/dl, while in RA without CVD was 90.78±37.97 mg/dl with no significant difference between them(P=0. 25). The mean (SD) levels of TG in RA with CVD was **108.17±68.79** mg/dl, while in RA without CVD was111.75± 29.53 mg/dl, with no significant difference between them (P=0.006). The mean (SD) levels of HDL in RA with CVD was **39.18± 62.71** mg/dl, while in RA without CVD was **42.12± 42.11** mg/dl, with no significant difference between them (*P*=.0.05).

The mean (SD) levels of Apo A-I in RA with CVD was99**.92 ± 43.1** mg/dl, while in RA without CVD was101.50±16.54mg/dl, with no significant difference between them (*P*=.0.05).

So from this result we founded that no difference between lipid profile among the studied patients, so we can say that lipids are not responsible directly as a risk factor of CVDs in RA patients and this results in agreement with **Holme *et al.* (2009)** and **Semb *et al.* (2010)**. So using lipid lowering agents in patients with RA have less effective than in people without RA.

Our study, described that TC, LDL and TG were normal in most patients with RA either complicated with CVD or not. **Semb *et al.* (2010)**, reported that TC, LDL and TG were low in most cases of RA patients, other studies reported that TC, LDL and TG were high and others reported that they similar with non RA people. These inconstant results from various studies my are explained by **Peters *et al.* (2010)**, that he explained that these inconstant results may be related to difference in populations studied, disease severity or disease duration**.**

In spite of TC, LDL, and TG were normal in most our cases of RA, but the incidence of CVD was high (88.00%) and the incidence of atherosclerosis also was high (59.00%), but HDL and apoA-1 were lower in most our cases of RA and as known that HDL and Apo A-1 having anti atherogenic with anti-oxidative and anti-inflammatory capacity, so this dyslipidaemia may be has a role in the pathogenesis of CVDs in RA patients. This result in agreement with **Hurt-Camejo *et al.* (2001) and Semb *et al.* (2010).** Also **Tanimoto *et al.* (2003)** have shown that the properties of HDL are altered in RA, becoming less anti atherogenic with a lower anti-oxidative and anti-inflammatory capacity.

Also, Choi *et al.* (l 2002) and **Krishnan *et al.* (2004)**, have shown that chronic inflammation is primarily responsible for accelerated atherosclerosis in RA patients, so that therapy with methotrexate reduces risk of cardiovascular disease in RA. Also, use of anti TNF in RA patients had lower rates of cardiovascular events and death during follow-up.

Jacobsson *et al.* (2007), suggested that aggressive anti-inflammatory therapy in RA patients, might additionally reduce clinical manifestations of cardiovascular disease.

from our study and other studies we recommend that, CVDs in RA are common, so cardiovascular assessment for all patients with RA by using carotid duplex and echocardiography mast be done annually. Using lipid-lowering agents as statins in RA have a little value to prevent CVDs. Adequate control of inflammatory disease activity of RA by using of disease-modifying ant rheumatic drugs and biological therapy reduce the risk of CVDs morbidity and mortality.

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1/25/2017