Is Silent Ischemic Heart Disease Evident in Rheumatoid Arthritis Patients?

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Abstract: Background: Large number of studies have shown that individuals with rheumatoid arthritis (RA) are at increased risk for morbidity and mortality from ischaemic heart diseases (IHD) which accounts for almost half of all deaths in RA. Half of the RA patients with confirmed IHD had clinically silent disease. Therefore, early detection of Silent IHD can decrease the cardiovascular mortality in patients with rheumatoid arthritis. **Objectives:** To assess the incidence and identify the predictors of silent ischemic heart disease (SIHD) in patients with rheumatoid arthritis. **Methods:** One hundred eighty patients with rheumatoid arthritis with no history of IHD were studied. All patients subjected to full history taking and full clinical examination and investigated to fasting blood glucose, 2 hour post prandial blood glucose, serum creatinine, mean platelet volume, homocysteine level, urinary microalbuminuria, lipid profile RF, ESR, CRP, Resting ECG and stress ECG . **RESULTS:** Prevalence of silent ischemic heart disease in rheumatoid arthritis patients is 10.6%. Significantly increased incidence of SIHD among patients with rheumatoid arthritis with hypertension (27.9%), peripheral neuropathy (21.1%), microalbuminuria (56.7%) and family history of IHD (28.9%) (p value < 0.05). Important predictors for SIHD in RA patients were: increased body mass index, increased duration of rheumatoid arthritis, hypertension, increased mean platelet volume, hyperlipiemia, hyperhomocysteinaemia, and high CRP and RF titre. **Conclusions:** Silent IHD is a rather common incidence in rheumatoid arthritis patients (10.6 %). The predictors for SIHD are prolonged disease duration, hyperlipidemia, increased mean platelet volume, obesity, hypertension, hyperhomocysteinaemia and presence of activity markers. "Targeting these risk factors in RA patients could help in lowering incidence of ischemic heart disease and its complications".

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1. Introduction

Rheumatoid arthritis (RA) is one of the most common chronic inflammatory disorders associated with enhanced cardiovascular morbidity and mortality ***(1).*** The most common cause of death in RA is cardiovascular disease, accounting for more than 50% of the mortality***(2)***. The most likely explanation is that the inflammation associated with RA has an impact on the vasculature***(3).***

The pathogenic mechanisms involved in accelerated cardiovascular complications in rheumatoid arthritis appear to be complex and multifactorial. Both traditional and nontraditional risk factors potentially contribute to the increased cardiovascular risk. There is a need for heightened awareness of the increased risk for silent ischemia, early myocardial infarction, and sudden death. ***(4).*** The underlying cause of ischaemic heart disease (IHD), appears to be accelerated in patients with RA. The reason for this may be related to clustering of classical cardiac risk factors such as dyslipidaemia, a prothrombotic state and other processes**.** However, classical risk factors, although important, do not appear to be sufficient to explain the accelerated atherosclerosis associated with RA***(5).*** This is possibly due to the systemic inflammation associated with RA, which may make RA itself (like diabetes) an independent risk factor for the development of IHD***(6).*** Accumulating evidence suggests that systemic inflammation indeed has an important role in the development of atherosclerosis, ***(7)*** and markers of inflammatory activity such as C reactive protein (CRP) are predictive of cardiovascular risk in the general population***(8).*** A higher risk of sudden cardiac death is associated with particular HLA–DRB1 genotypes that are more frequent in patients with RA. and this can explain in part the higher risk of sudden death in these patients***(9).***

There is evidence that the presentation of coronary heart disease is different in RA patients compared with individuals without RA. Ischemic heart disease may be clinically silent in many RA patients, and there appears to be a higher risk of unrecognized myocardial infarction and sudden cardiac death. RA patients also have a lower likelihood of demonstrating angina symptoms. Furthermore, the increased risk of coronary heart disease in RA precedes the ACR criteria–based diagnosis of RA, and is not due to an increased incidence of traditional risk factors***(10).*** Enhanced inflammatory process may promote the

development of heart dysfunction in inflammatory arthritis***(11).***

In seropositive RA, the extent of inflammation has been shown to predict CV disease and overall mortality***(9)***, so aggressive coronary heart disease prevention strategies should be tested for persons with rheumatoid arthritis to decrease mortality***(12).*** A number of predictors for risk of CV disease are well known for the general population, but identification of new markers is still required to help with better characterization of patients at risk of SIHD. This may be particularly important for patients with disability, who, owing to their reduced exercise capacity, may not elicit symptoms of cardiac ischaemia, or whose symptoms may be wrongly attributed to musculoskeletal causes.***(13)***

2. Subjects and methods:

Two hundred patients (aged 35–76 years) with a diagnosis of RA, attending the Menoufiya University hospitals Internal Medicine Clinic, were recruited into a study investigating the prevalence of silent IHD in RA. All patients fulfilled the 2010 American College of Rheumatology criteria for RA. 180 patients completed the full cardiovascular investigation protocol. The study had local research ethics committee approval.

Inclusion criteria: Include patients with rheumatoid arthritis aged between 35–60 years.

Exclusion criteria: Include patients known to have IHD, DM, severe or malignant hypertension and patients with disabilities which may interfere with stress ECG test as orthopedic or neurological disabilities.

All patients were subjected to full history taking as age, sex, smoking, family history of IHD, family history of Rheumatoid Arthritis or diabetes, RA disease duration and presence of complications. A family history of IHD was defined as a male or female first degree relative sustaining any ischemic cardiovascular disease.

Clinical evaluations Standardized history and examination were performed by a single observer. Cardiovascular symptoms and risk factors were assessed Hypertension was assessed by previous diagnosis, resting systolic and diastolic blood pressure. Height and weight were recorded and body mass index calculated, weight (Kg) divided by the square root of height in meter)..

Cardiovascular investigations: Twelve lead ECG recordings were taken. Detection of cardiac ischaemia was carried out using exercise treadmill stress ECG test.

Exercise treadmill testing:

All patients were subjected to exercise treadmill stress ECG using the modified Bruce protocol. Heart rate, blood pressure, and a 12-lead electrocardiogram were obtained at baseline and at each stage of the exercise protocol (every 3 min) **.** Predicted peak heart rate was calculated as 220 – age ***(14).*** Patients were encouraged to perform a treadmill exercise test until they reached an endpoint. Exercise endpoints included physical exhaustion, significant arrhythmia, severe hypertension (systolic blood pressure >240 mmHg or diastolic blood pressure >110 mmHg), or severe hypotensive response (decrease >20 mmHg in systolic blood pressure from baseline). Ischemic ECG abnormalities during the test were defined as the development of ST-segment deviation of ≥1 mm which was horizontal or down sloping away from the isoelectric line 80 milliseconds after the J point ***(15)***.

Silent ischaemia was defined as ischemia on stress test in the absence of angina and/or ECG changes of either a bundle branch block or ST segment abnormality consistent with IHD ***(14&15)***.

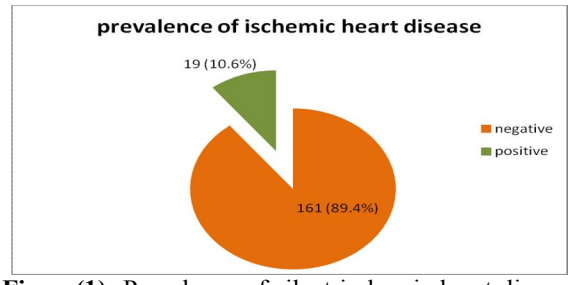
Laboratory investigations including CBC, mean platelet volume, fasting blood glucose, 2 hour post prandial blood glucose, ESR, CRP, RF, homocysteine level, serum creatinine, urinary microalbuminuria and lipid profile.

Statistical analysis:

Data were analyzed using IBM SPSS version 20. Normality of distribution was computed by kolmogrov smirnov test for numerical variables. Categorical data were expressed in frequencies and percentages while numerical data were expressed in means ± SDs . Comparison of quantitative data was performed by Mann Whitney test. Comparison of categorical variables was done using χ^2 test or Fisher exact test where appropriate. Binary logistic regression was performed for variables associated with ischemic heart disease. Statistical significance was set at 0.05 level.

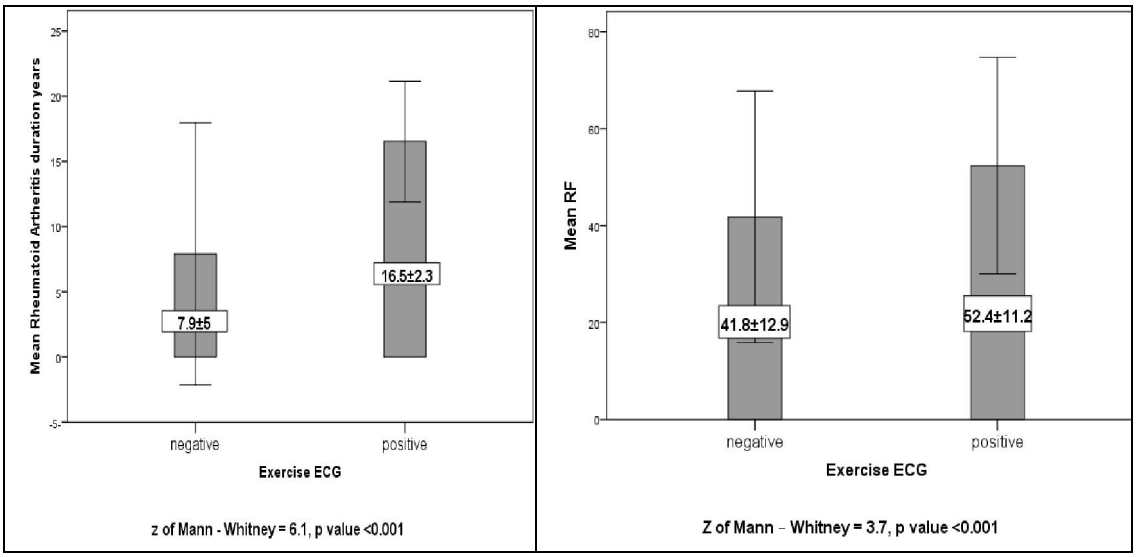
3. Results:

Prevalence of silent ischemic heart disease in rheumatoid arthritis patients in the study is 10.6% as shown in figure (1).



Figure(1): Prevalence of silent ischemic heart disease in rheumatoid arthritis patients:

There is significant Association between both increased duration of rheumatoid arthritis and increased rheumatoid factor titre and occurrence of silent ischemic heart disease in RA patients as shown in figure (2).



Figure(2): Association between rheumatoid factor and rheumatoid arthritis duration and silent ischemic heart disease in rheumatoid arthritis patients:

There is significantly increased incidence of silent ischemic heart disease (p value < 0.05) amongst patients with hypertension (27.9%), peripheral neuropathy (21.1%), presence of microalbuminuria (56.7%) and family history of ischemic heart disease (28.9%) as shown in table (1).

Table (1): Comparison between Ischemic and non-Ischemic group regarding history and laboratory data (categorical variables) in rheumatoid arthritis patients.

History and laboratory data	Exercise ECG(n= 180)				OR (95%CI)	x^2	p-value
	Positive (n=19)		Negative (n= 161)				
	No	(%)	No	(%)			
Gender:							
Male	11	(14.1)	67	(85.9)	0.5 (0.2, 1.4)	1.8	0.176
Female	8	(7.8)	94	(92.2)			
Smoking:							
Yes	6	(19.4)	25	(80.6)	2.5 (0.8, 7.2)	2	0.104
No	13	(8.7)	136	(91.3)			
Hypertension:							
Yes	19	(27.9)	49	(72.1)	--	34.9	< 0.001**
No	0		112	(100)			
Peripheral neuritis:							
Yes	19	(21.1)	71	(78.9)	--	21.2	< 0.001**
No	0		90	(100)			
Microalbuminuria:							
Yes	17	(56.7)	13	(43.3)	96.7 (20, 465.6)	75.3	< 0.001**
No	2	(1.3)	148	(98.7)			
Family history of IHD:							
Yes	11	(28.9)	27	(71.1)	6.8 (2.5, 18.5)	14.9	< 0.001**
No	8	(5.6)	134	(94.4)			

There are significant association between increase in Age, BMI, RA duration, ESR, CRP, mean platelet volume, total cholesterol, LDL, creatinine level, homocysteine level and occurrence of silent ischemic heart disease in RA patients. (p value < 0.05) as shown in table (2).

Table (2): Comparison between Ischemic and non-Ischemic group regarding history, clinical and laboratory data (continuous variables) in rheumatoid arthritis patients.

	Exercise ECG		Z of Mann – Whitney	*p*-value
	Positive (Mean± SD)	negative (Mean± SD)		
Age	61.2±3.7	51.3±8.4	4.9	<0.001**
Body Mass Index (kg/m2)	27.3 ±2.6	25.4 ± 2.1	3.3	<0.001**
Mean platelet volume(fl):	9.9 ± 0.6	8.2 ± 0.4	6.7	<0.001**
RF	52.4±11.2	41.8 ±12.9	3.7	<0.001**
Duration of RA	16.5±2.3	7.9 ± 5	6.1	<0.001**
ESR (1st hour):	67.2 ± 13.3	41.6 ± 13.3	5.5	<0.001**
CRP	31.8 ±5.1	26.8 ± 8.3	3.2	<0.001**
Creatinine	1.9 ± 0.5	0.9 ± 0.3	6.4	<0.001**
Total cholesterol	218.3 ± 37.1	194.5 ± 42.8	2.6	0.010
Triglycerides	168.4 ±25	176.3 ± 40.4	0.8	0.393
LDL	139.7 ± 39.3	112.4 ± 46.3	2.4	0.015*
HDL	43.7± 6.5	45.9 ± 6.5	1.6	0.102
Homocysteine level (µmol/L)	14.9± 1.6	10.9 ± 2.6	5.7	<0.001**

Table (3): Logistic regression for important risk factors for silent ischemic heart disease in rheumatoid arthritis patients:

Variables	Regression coefficient	Wald	OR (95%CI)	*P*-value
Body Mass Index	0.72	8.4	0.5 (0.3, 0.8)	0.004*
Rheumatoid arthritis duration in years	0.26	10.3	1.3 (1.1, 1.5)	0.001**
Rheumatoid factor	0.1	2.7	1.1 (0.9, 1.3)	0.103
Family history of IHD	1.8	3.4	6 (0.8, 40.9)	0.067
Hypertension	4.2	9.1	63.8 (4.3, 949.5)	0.003*
Total cholesterol	0.02	3.9	0.9 (0.9, 1)	0.048*
Mean platelet volume (fl)	1.8	7.8	5.9 (1.7, 20.2)	0.005*
CRP	0.2	3.8	0.8 (0.6, 1)	0.049

Binary logistic regression showed that BMI, hypertension, family history of CAD, duration of RA, total cholesterol, mean platelet volume and inflammatory markers (RF and CRP) are independent predictors for silent ischemic heart disease in rheumatoid arthritis patients.

4. Discussion:

In the current study SIHD was found in 19 patients (representing 10.6 %). ***Maradit-Kremers et al., 2005,(10)*** concluded that Patients with RA have a significantly higher risk of CHD when compared with non-RA subjects. RA patients are less likely to report symptoms of angina and more likely to experience unrecognized MI and sudden cardiac death. RA has a greater burden of coronary atherosclerosis at their first angiogram that is independent of traditional CV risk factors. This may be due, at least in part, to the expansion of no classic $CD4^+$ T cells that have previously been implicated in the pathogenesis of IHD***(16).*** Patients with RA are 30% to 60% more likely to suffer a CV event compared with the general population***(17&18)***, especially myocardial infarction ***(19&20)*** .

In our study age was found to have significant association with SIHD in patients with RA. This is consistent with the results of ***Cecilia et al., 2006. (21)***

We found insignificant correlation between smoking and SIHD in patients with RA in our study. This finding may be because smoking habit is uncommon in female in our people who represent most of our patients. On the other hand

Cecilia et al., 2006, ***(21)*** found significant correlation of smoking with IHD in patients with RA. ***Chung et al., 2005,(22)*** reported that the prevalence and severity of coronary calcification is increased in established rheumatoid arthritis and is related, in part, to smoking.

There was insignificant difference between ischemic and non-ischemic group according to the presence of family history of IHD but this not agree with the results of ***Matty et al., 2004 and Chiharu et al., 2006.(5&23)***

In the present study the frequency of SIHD increased in rheumatoid arthritis patients with prolonged duration and this goes hand to hand with the study of ***Fietta and Delsante 2009***, ***(24)*** who reported that atherosclerosis is an early and common finding in RA patients, positively correlating to the disease duration and severity. On the contrary ***Galiutina and Bychak 2011, (25)*** found that silent myocardial ischemia in patients with RA have no significant correlation with the disease duration..

Our study also showed a significant association between SIHD in patients with RA and the presence of nephropathy which was diagnosed by the presence of microalbuminuria. ***Mpofu and colleagues 2004***, ***(26)***. concluded that microalbuminuria is likely to correlate only poorly with IHD, whether prevalent or silent, in their population of patients with RA ***(Kitas and Erbs, 2004)***[27] agree that, from the practical perspective, it is very important to identify predictive markers of IHD in RA, and microalbuminuria is a very reasonable candidate for the reasons that ***Mpofu and colleagues, (26)*** clearly outline. However, they disagree with the conclusion that 'this simple test cannot be used as a surrogate marker for IHD or IHD risk in patients with RA.

Our study also showed that the occurrence of SIHD is significantly increased in patients with RA in the presence of hypertension. ***Kitas and Erbs 2004, (27)*** have found that more than half (56%) of RA patients with no known cardiovascular co morbidity have hypertension and hypertension should therefore be actively sought and targeted as a risk factor in patients with RA.

Interestingly we found that the occurrence of SIHD is significantly increased in patients with RA in the presence of increased mean platelet volume(MPV) and this agree with ***Kilicli et al., 2005,(28)*** who found that high MPV is an independent risk factor for coronary atherosclerosis and MI. and also agree with ***Gasparyan et al., 2011,(29)*** who found that high MPV associates with a variety of established risk factors, cardio- and cerebrovascular disorders prone to arterial and venous thrombosis.

Our study also showed that the occurrence of SIHD is significantly increased in RA in the presence of increased BMI and this agree with ***Stavropoulos et al., 2009,(30)*** who found that In RA, strong positive associations have been found between high BMI and adverse CVD risk factors. On the contrary ***Kremers et al., 2004*** found that among patients with RA, low BMI is associated with a significantly increased SIHD and risk of cardiovascular death.***(31)*** All traditional CV risk factors, except obesity and physical inactivity, were associated with CV morbidity, and in multivariate models, hypertension, hyperlipidemia, diabetes, and ever-smoking remained independent risk factors ***(32)*** .

It was noticed that the occurrence of SIHD is significantly increased in RA in the presence of hyperhomocysteinaemia. A high prevalence of hyperhomocysteinaemia in Mexican patients with RA who develop high rates of coronary artery diseases.***(33)*** ***Galiutina and Bychak 2011*** also found that silent myocardial ischemia in patients with the RA was associated with hyperhomocysteinaemia.***(25)***

We also found that the occurrence of SIHD is significantly increased in patients with RA in association with the high markers of inflammation and activity as high ESR, increased CRP and high RF titre and this agree with other studies as that of ***Chung et al., 2005***, who reported that the prevalence and severity of coronary calcification is increased in established rheumatoid arthritis and is related, in part, to elevated inflammatory markers.***(22) Maradit-Kremers et al., 2005***,***(10)*** confirmed that markers of systemic inflammation confer a statistically significant additional risk for cardiovascular death among patients with rheumatoid arthritis. Systemic inflammation plays an important role in the development of atherosclerosis, and the extent of inflammation in RA patients has been shown to be predictive of cardiovascular disease and overall mortality.***(34)*** ***Galiutina and Bychak 2011,(25)*** also found that silent myocardial ischemia in patients with the RA was associated with high activity of inflammatory process. CV morbidity and mortality strongly correlate with disease activity, whereas the successful pharmacological control of the chronic inflammation decreases the risk of CV complications.***(24) Myasoedova et al., 2011,(35)*** also reported that their findings underscore the importance of systemic inflammation as a key player in the development of CVD in RA by demonstrating independent associations of ESR

and CRP with cardiovascular outcomes and mortality. This is concordant with the concept of acceleration of cardiovascular risk and mortality with increasing inflammatory burden and suggests the need for minimization of cumulative inflammation in RA.***(36-38)***

Resting ECG has a low sensitivity in detection of SIHD in patients with RA.

Conclusion:

- Silent ischaemic heart disease is a rather common incidence in rheumatoid arthritis patients (10.6 %).
- The predictors for SIHD are hyperlipidemia, obesity, hypertension, hyperhomocysteinaemia, increased mean platelet volume, prolonged disease duration and presence of high activity markers. "Targeting these risk factors in RA patients could help in lowering incidence of ischemic heart disease and its complications".

Recommendation:

Stress ECG is highly recommended as a better screening method for SIHD especially in the presence of its predictors in patients with RA.

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