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Research Article

CARDIOVASCULAR RISK ASSESSMENT IN RHEUMATOID ARTHRITIS

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ABSTRACT

Introduction: There is a significantly higher cardiovascular mortality in Rheumatoid arthritis(RA) compared to general population. Higher cardiovascular mortality is due to an interplay of persistent chronic inflammation of vascular endothelium as a result of high disease activity along with the higher prevalence of traditional cardiovascular risk factors like dyslipidemia, hypertension, obesity and smoking. Another contributing factor could be the widespread use of glucocorticoids in RA, which increases carotid intimal thickening. There are only very few studies in Asian population on the relevance of cardiovascular risk factors in RA patients. Here we highlight the lipid abnormalities in RA patients along with assessment of CV risk score and heart age of RA patients.

Methods: The study was conducted at a Government Medical College in North Kerala, India. RA patients aged between 16 and 80 years who satisfied the ACR-EULAR 2010 criteria attending the Rheumatology clinic during a period of 1 year were studied in comparison with matched controls.

Results: There is statistically significant difference (p value 0.001)in mean total cholesterol level (TC) between the RA group (204.7+42.9 mg/dl) and controls(181.1+40.3 mg/dl). Similar statistically significant difference in the mean LDL cholesterol levels were noted between the RA cases and controls (133.1+39.8 vs 116.7+32) (p value 0.006). RA patients had a higher cardiovascular risk score and heart age compared to general population, demonstrating higher risk for cardiovascular events in such patients.

Conclusions: This study highlights the importance of assessment of CV risk factors in RA patients to improve CVD outcome.

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune inflammatory disease leading to wide ranging articular, extra-articular and systemic manifestations. Most of the extra-articular manifestations are due to persistent uncontrolled inflammation. RA patients roughly have twice the mortality rates compared to general population, and this is mostly attributed to premature atherosclerosis-related cardiovascular disease (CVD). Prompt recognition and management of CVD risk factors will considerably bring down the morbidity and mortality associated with RA. Traditional CVD risk factors (hypertension, smoking, and dyslipidemia) are responsible for around half of all coronary heart disease (CHD) events in the general population. Increased burden of traditional CVD risk factors along with persistent chronic active inflammation of vascular endothelium as a result of poor disease control in RA has been thought to be the reason for higher CVD mortality in RA. Another factor might be wide spread use of glucocorticoids in RA which has been thought to increase the carotid intimal thickening- an independent predictor of cardiovascular mortality in RA.

The CV risk factor profile of RA patients has not been studied in detail in the Indian population. RA patients are expected to die on average 2.5 year earlier than the general population according to few community based studies (Avina-Zubieta *et al* 2012). A meta-analysis by Avina-Zubieta *et al*, which included 14 studies and 41,490 RA patients, showed a 48% increased risk of CVD compared to general population. RA patients in these multiple studies were also noted to have a 68%, 41%, and 87% increase risk of myocardial infarction (MI), cerebrovascular accident (CVA), and CHF respectively. Patients with RA are more prone to recurrent cardiac events and have higher mortality after acute cardiovascular events (Avina-Zubieta *et al* 2012).

Glucocorticoids have been associated with an increase in traditional CV risk factors. Cardiovascular risk (CR) with steroid use in RA is dose dependent (Greenberg *et al* 2011). Prednisone dosages of 1 - 7 mg daily had a CR of 1.78 (95% CI

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1.06- 2.96) compared to aCR of 2.62 (95% CI 1.29-2.96) for dosages above 7.5 mg/day. Separate multivariable models showed that current daily dose, cumulative duration of use, and total cumulative dose were all associated with a significant increased risk of MI (Avina-Zubieta *et al* 2013).

Dyslipidemia is considered to be an important risk factor for atherosclerotic CHD in the general population. In particular, decreased levels of high density lipoprotein (HDL) cholesterol, elevated levels of low-density lipoprotein (LDL) cholesterol, and/or an elevated total cholesterol (TC) or an elevated LDL: HDL ratio predict higher coronary risk, both in established CHD and patients who were initially free of CHD (Wilson PWF *et al* 1998).Several studies have noted low HDL levels in RA patients especially in active or untreated compared to controls (Myasoedova E *et al* 2011). HDL levels in RA patients increases after treatment. There is also a favorable shift in the TC/ HDL ratio in treated RA (Charles-Schoeman C *et al* 2009). Statin therapy in RA has beneficial effects in the primary prevention of CVD and improves all-cause mortality as well (McCarey DW *et al* 2004).

The 10 year CV risk and heart age was calculated for each subject in the RA group and control population using the risk score available at (www.framinghamheartstudy.org/risk /index.html) (D'Agostino *et al* 2008*)*. In this algorithm subjects received a point score based on age, diabetes, smoking, treated and untreated systolic blood pressure, total cholesterol and HDL cholesterol. The Framingham CHD risk assessment tool has been validated among different races in the US and is transportable (with calibration) to culturally diverse population in Europe, the Mediterranean region and Asia.

An individual's heart age was calculated as the age of a person with the same predicted risk but with all other risk factor levels in the normal range. Heart age calculator is meant to be used by individuals 30 to 74 years old who have no history of cardiovascular disease. Heart age is calculated by using simple parameters like age, sex, systolic blood pressure, smoking history, history of diabetes, body mass index and levels of total cholesterol and HDL cholesterol (Groenewegen KA *et al* 2016*)*. Although called heart age for simplicity of risk communication in primary care, the heart age reflects the vascular age.

The impact of traditional CV risk factors on the development of CVD in RA patients is an area of active research. Very few data is available from India regarding conventional cardiovascular risk factors like dyslipidemia in RA.Here we assessed the lipid profile abnormalities, 10 year CV risk and heart age of our RA patients in comparison with age and sex matched controls to determine the CV risk in RA.

MATERIALS AND METHODS

The study was conducted at Government Medical College, Calicut which is the largest tertiary referral hospital in North Kerala, India. RA patients between 16 and 80 years, who satisfied the ACR-EULAR 2010 criteria attending the Rheumatology clinic during a 1 year period were studied. Patients with pre-existing CHD were excluded. The study was approved by the Institutional Ethics Committee, and signed informed consent was taken from all patients. There were 75 patients in the study group and 75 age and sex matched controls.

Baseline values of serum lipids including TC, LDL, HDL and serum triglyceride levels (TG) were recorded. The tests were performed using standard laboratory procedures. Details of the medications including steroids and their dose were recorded.

Patient was considered to have dyslipidemia if TC > 200 mg/dl or HDL-C <40 mg/dl or LDL-C >70 mg/dl. The lower-than-usual cut-off value was used as the revised National Cholesterol Education Program-3 Guidelines recommends an LDL-C ≤70 mg/dl as the cut-off level that should be considered a treatment option for patients at very high-risk for CVD like RA patients (Agarwal D, Malaviya AN 2013).

The 10 year CV risk and heart age were calculated for both patients and controls using the online risk score calculators available at (www.framinghamheartstudy.org/risk/index.html).

RESULTS

80% of the 75 patients in the study group and 77% of age and sex matched controls were females reflecting the female preponderance of the disease in our population.

17.3% patients were below 40 years, 32% were between 40-50 years, 33.3% were 50-60 years and the rest were above 60 years (Fig 1).

35% of RA patients had a disease duration of less than 2 years, while in 33% patients, the duration was between 2-4 years, and in 25% 5-9 years. Only 7% had more than 10 year disease duration.

RA disease activity was assessed using a composite DAS28 score (Disease Activity Score), which included tender joint count, swollen joint count, ESR and patient global assessment of pain (Agarwal D, Malaviya AN 2013). DAS28 score less than 2.4 indicates clinical remission, 2.4-3.2 indicate mild disease activity, 3.3-5.1 moderate disease activity and more than 5.1 severe disease activity.

56% of our RA patients had mild disease activity while 16% had moderate and 9.3% had severe disease activity. 18.6% patients were in clinical remission.

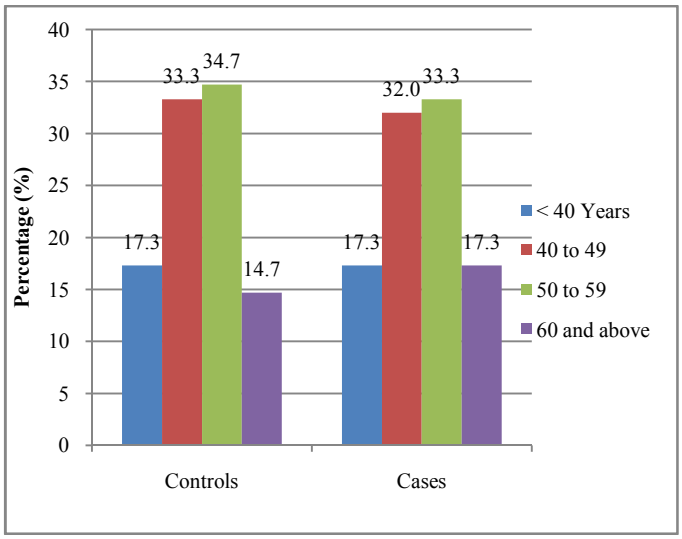

Fig 1 Age distribution of RA patients and controls

22.6% of RA patients were not using steroids while 46.6% of the patients were using very low dose steroids <5mg/day (prednisolone or equivalent) and 25.3% were using low dose steroids (5-10 mg/day). Only 5.3% were using more than 10 mg/day prednisolone or equivalent.

The mean total cholesterol level (TC) in the RA group was 204.7+42.9 mg/dl and in the control group was 181.1+40.3 mg/dl and the difference is statistically significant with p value 0.001 (Table 1). There is statistically significant difference in the mean LDL cholesterol level between the cases and controls (133.1+39.8 vs 116.7+32(p value 0.006). The mean values of TG, HDL, VLDL and TC/HDL ratio did not show any significant difference between cases and controls. However there was no statistically significant difference in dyslipidemia in those who took steroids and who did not (Table 2).

Table 1 Prevalence of dyslipidemia

Lipid profile(mg/dl)	Control		Cases		p value
	Mean	SD	Mean	SD	
Total cholesterol	181.1	40.3	204.7	42.9	0.001
TG	113.3	33.7	118.3	48.3	0.460
HDL	46.8	9.4	45.8	8.5	0.511
LDL	116.7	32.0	133.1	39.8	0.006
VLDL	23.9	9.0	25.5	10.6	0.307
TC/HDL	4.2	0.8	5.5	5.9	0.068

Table 2 Effect of steroid on dyslipidemia

	Steroid	N	Mean	SD	p value
Total cholesterol	Present	49	201.98	46.18	0.447
	Absent	26	209.96	36.17	
LDL	Present	49	129.51	41.00	0.288
	Absent	26	139.85	37.32	

Prevalence of hypertension

27 RA patients (36%) were hypertensive whereas only 11(14.7%) in the control group had systemic hypertension (Fig 2), the difference being statistically significant (p=0.003).There was no statistically significant difference in the development of hypertension among steroid users and non-users (p=0.182) (Table 3).

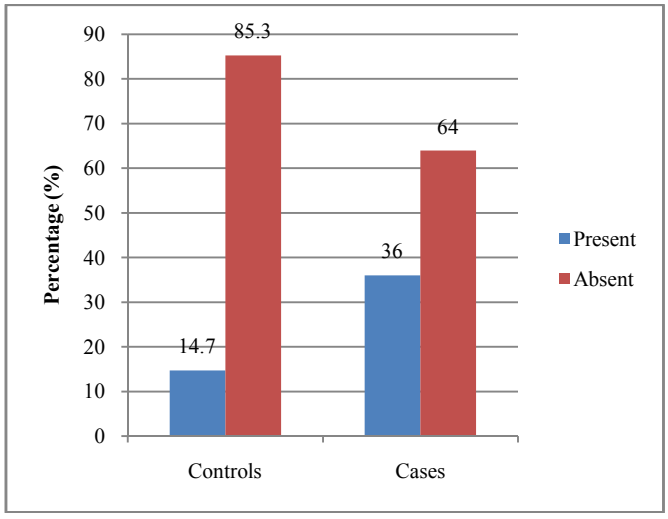

Fig 2 Prevalence of hypertension

Table 3 Effect of steroids use on hypertension

Steroid	Hypertension		p value
	Present n (%)	Absent n (%)	
Present	15 (30.6)	34 (69.4)	0.182
Absent	12 (46.2)	14 (53.8)	

10 year cardiovascular risk

The Framingham 10 year cardiovascular risk was calculated in the RA patients and controls (Table 4). The mean cardiovascular risk in cases was 11.4 +9.2 and in controls was 8.4+6.1. The difference is statistically significant (p 0.024).

Table 4 10 year cardiovascular risk

	Control		Cases		P value
	Mean	SD	Mean	SD	
Cardio Vascular risk	8.4	6.1	11.4	9.2	0.024

Heart age

The heart age was found to be higher in Rheumatoid arthritis patients (Table 5). There is statistically significant difference (p 0.088) in the mean heart age between the RA group (61.7+17.4 years) and control group was (57.3+14.1 years).

Table 5 Heart age of RA patients in comparison with controls

	Control		Cases		p value
	Mean	SD	Mean	SD	
Heart age	57.3	14.1	61.7	17.4	0.088

DISCUSSION

In our observational case control study to assess prevalence of CV risk in RA, 75 RA patients were compared with age and sex matched controls. 80% of our patients were female which is consistent with the results of several studies on RA (Agarwal D, Malaviya AN 2013).

Majority of RA patients (65.3%) were between 40-60 years. The duration of the disease was less than 2 years in 35% and between 2-5 years in 33%. Majority patients (56%) had low disease activity as evidenced by DAAS28 score of 2.4-3.2 and 18.6%were in clinical remission while 9.3% had severe disease.

Regarding prevalence of dyslipidemia, it was found that serum TC and LDL cholesterol were significantly higher in RA patients than controls, which might be related to poor life-style and eating habits of RA patients. Two previous studies have shown increased prevalence of dyslipidemia in RA similar to our study (Charles-Schoeman C *et al* 2009; Myasoedova E *et al* 2011; Agarwal D and Malaviya AN 2013). There was no statistically significant difference in dyslipidemia among those who took steroids and who did not.

The present study showed a significant elevation in two of the standard Framingham CVD risk factors namely, hypertension, and total and LDL-C in RA patients.

The 10 year CVD risk and heart age were higher in the RA patients compared to the normal controls. This is probably due to the increased prevalence of hypertension and dyslipidemia in the RA patients.

CONCLUSION

1. There is a higher prevalence of hypertension and dyslipidemia leading to higher 10 year CV risk and heart age in RA patients compared to normal population which could be contributing to their higher mortality.
2. Medications for RA like corticosteroids did not influence the prevalence of CV risk factors such as dyslipidemia and hypertension.

Identification and correction of the traditional CVD risk factors like dyslipidemia and hypertension along with assessment of 10 year CV risk and heart age in RA is of paramount importance to reduce the excess cardiovascular mortality in RA which is compounded by accelerated atherosclerosis due to chronic inflammation.

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