

Evaluation of risk factors for cardiovascular disease on rheumatoid arthritis patients from outpatient clinic

Abstract

Background: Rheumatoid arthritis (RA) is associated with increased cardiovascular mortality 10 years earlier compared with the general population. Endothelial dysfunction in coronary and cerebrovascular arteries are considered the cause of this premature higher risk. This study focuses on evaluating the risk of developing Cardiovascular Disease (CVD) in a 10 years perspective in patients with RA. Methods: Retrospective data analysis of 78 patients with diagnosis of RA was performed. The risk score of Acute Coronary Disease in 10 years was calculated in accordance to the Framingham Heart Study; Control group (CG) with 21 patients - osteoarthritis and fibromyalgia was also assessed using the same criteria. Age, sex, SBP, total cholesterol, cholesterol HDL, smoking status and diagnosis of diabetes were scored.

Results: RA patients had a mean disease duration of 12.8 years (SD=7.4), aged 58.6 years (SD=10.3); CG 59.3 years (SD=10.0). Total cholesterol, HDL, Higher SBP and being diagnosed with Diabetes Mellitus (DM) showed positive correlations with the higher Cardiovascular Disease (CVD). Global CR in each group were considered low (7,8 points to RA and 9,3 CG).

Conclusion: The RA group did not show a greater risk of CVD when compared to CG. We highlight the fact that the CG higher prevalence of diabetics and under reporting of DM in RA medical records probably impacted the results. Preventive measures should be introduced even in patients with low CVR, and in special for those with chronic inflammatory diseases such as RA.

Keywords: rheumatoid arthritis, cardiovascular diseases, criteria Framingham, fibromyalgia, osteoarthritis

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Abbreviations: SD, standart deviation; BMI, body mass index; FG, fasting glucose; SBP, systolic blood pressure; AC, abdominal circumference; TC, total cholesterol; TG, triglycerides; FB, fibromyalgia; IHD, ischemic heart disease; ASA, acetylsalicylic acid; CG, a control group; BP, blood pressure; FG, fasting glucose; HDL, high density lipoprotein; LDL, low density lipoprotein; FS, framingham score

Introduction

Cardiovascular co morbidities are the leading cause of mortality among inflammatory rheumatological conditions.¹ A closely relation between inflammatory activity, especially in Rheumatoid arthritis (RA), and cardiovascular morbidity and death were stratified in previous studies.² Additionally, non-inflammatory rheumatological conditions, such as Fibromyalgia (FB), has been recently discovered also with a higher risk of Cardiovascular events compared to the general population.^{3,4}

RA are more common in women and is associated with increased mortality.⁵ The accelerated endothelial dysfunction leading to atherosclerosis in coronary and cerebrovascular arteries is a phenomenon that occurs since early RA diagnose.⁵ Clinically, joint destruction on radiographs and rheumatoid factor positivity double

the risk for Cardiovascular Disease (CVD).⁶ It was discovered that CVD occur approximately a decade earlier in RA patients than in the general population, suggesting that RA itself, similarly to diabetes mellitus, is an independent risk factor for premature Ischemic Heart Disease (IHD).⁵⁻⁸

Several causes have been postulated as an explanation to the CVD risk in rheumatological diseases.⁶⁻¹² The increased prevalence of established risk factors (hypertension, diabetes, hypercholesterolemia) and the inflammatory process itself increases 40% of the risk compared to general population.⁹ The use of Acetylsalicylic Acid (ASA) showed high effectiveness in decreasing morbidity and mortality of patients with CVD.¹³ Reduction of inflammation are well defined in protocols for clinical practice as secondary prevention for IHD and Stroke.¹⁴ However, It is uncertain when cardiovascular drugs should be prescribed for RA patients without any clinical symptoms.¹⁴ Giving the interest in quantifying the prevalence of CVD risk, this study focuses on evaluating the risk of developing CVD in a 10 years perspective in patients with RA.

Methods

This is a cross-sectional, descriptive, retrospective and observational study. A total of 99 medical records were analysed

at an outpatient clinic between April and September of 2013; To assess the risk of CVD we assessed the medical records from 78 patients previously diagnosed with RA. Framingham Heart Study Score evaluating the risk of Acute Coronary Disease in 10 years was used. A Control Group (CG) of 21 patients with Osteoarthritis and Fibromyalgia was also assessed using the same criteria. Risk factor for CVD were stratified according to age, sex, smoking habits, diabetes mellitus type 2 (T2DM), hypertension and intake of hypertensives, acetyl salicylic acid (ASA) or Statins. hypertension and T2DM diagnosis followed the recommendation of VI Brazilian Guideline for Hypertension¹⁵ and Standards of Diabetes Care.¹⁶ Antihypertensive, ASA and statins drugs were considered after proper diagnosis and at a least 6 months intake previous the data collection. Patients with previous diagnose (clinically or by ECG) of coronary artery disease, angina pectoris or myocardial Infarction or with less than 6 months of medication intake for hypertension, T2DM or Hypercholesterolemia were excluded from the sample.

Statistical analysis using the IBM SPSS Statistics 25 software was performed. Categorical data was expressed in absolute and relative frequency; numerical variables in mean, standard deviation (SD) and confidence interval of 95% (CI 95%); chi-square test and odds ratio (OR) were used during association analysis between risk factors for CVD between groups. Continuous data such as weight, height, body mass index (BMI), blood pressure (BP), abdominal circumference (AC), fasting glucose (FG), triglycerides (TG), total cholesterol (TC), high density lipoprotein (HDL), low density lipoprotein (LDL), and Framingham score (FS) were compared using the Mann Whitney test; the likelihood ratio test was used for categorical data. The relationship between the dependent variable (CVR) and the independent variables (FS) was estimated by Spearman correlation.

Framingham heart study score

Framingham Heart Study is a cohort study established in Framingham, Massachusetts, USA purpose was to analyze the modifiable risk factors of CVD.^{17,18} Three generation of families and their progressive CVD risks were studied according through periodical assessments of medical history, physical examination, and laboratory tests. Age, Sex, Systolic Blood Pressure (SBP), Smoking, Total Cholesterol (TC) – High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), Diabetes Mellitus (DM), Body Mass Index (BMI) were stratified in accordance to fatal and non-fatal CVD (IHD, Angina, Ischemic and Hemorrhagic Stroke, Cardiac Death) by a 10-year period.^{17,18} To evaluate the risk of developing CVD we used the criteria for Acute Coronary Artery Disease Risk in 10 years where age, sex, SBP, BMI, history of smoking and diabetes diagnosis, were scored. The score is open access and available online.^{17,18}

Results

We studied 99 patients, 78 with AR and 21 with Osteoarthritis and FB. RA mean disease duration was 12.8 years (SD=7.4) and patients were aged 58.6 years (SD=10.3). The CG was aged 59.3 years (SD=10,0). The two groups were similar in terms of mean Age, Weight, BMI and AC (Table 1). RA showed SBP mean levels of 134.4 mmHg (SD = 23) and GC 127,1mmHg (SD=14.1), with no statistically significant difference. TC, HDL and LDL results were very similar (Table 1). TG and FG were different, RA had FG of 95.1 mg/dL (SD=21.8) and TG of 125 mg/dL (SD=62.9). CG the values were FG of 121 mg/dL (SD=68.3) and TG of 180.4 mg/dL (SD=97.8).

Table 1 Descriptive Statistics of Anthropometric features and measures of central tendency and dispersion for variable SBP,TC, LDL, HDL,TG, FG in patients with AR and CG

Variable	Group	n	Mean	SD	Minimum	Maximum	(Median)	(p)
Weight	RA	28	68,9	15,3	45,0	103,0	71,0	0,613
	CG	21	71,1	16,1	42,0	105,0	73,0	
Kg	Total	49	69,9	15,5	42,0	105,0	72,0	
Height	RA	30	158,2	7,4	143,0	172,0	160,0	0,901
	CG	21	158,0	9,9	135,0	177,0	157,0	
cm	Total	51	158,1	8,4	135,0	177,0	160,0	
BMI	RA	26	27,8	6,3	19,5	42,7	27,0	0,669
	CG	21	28,3	5,3	21,3	39,5	26,9	
kg/m ²	Total	47	28,1	5,8	19,5	42,7	26,9	
SBP	RA	59	134,4	23,1	100,0	190,0	130,0	0,432
	CG	21	127,1	14,2	100,0	150,0	130,0	
mmHg	Total	80	132,5	21,3	100,0	190,0	130,0	
AC	RA	18	96,3	11,0	75,0	113,0	98,0	0,280
	CG	19	101,8	13,6	80,0	135,0	101,0	
cm	Total	37	99,1	12,6	75,0	135,0	98,0	
FG	RA	75	95,2	21,8	68,0	208,0	89,0	0,008*
	CG	21	121,0	68,3	67,0	402,0	110,0	
mg/dl	Total	96	100,8	38,3	67,0	402,0	92,0	

Table continued

Variable	Group	n	Mean	SD	Minimum	Maximum	(Median)	(p)
TC mg/dl	RA	76	198,5	45,6	100,0	310,0	195,0	0,658
	CG	21	197,8	62,7	97,0	367,0	186,0	
	Total	97	198,3	49,4	97,0	367,0	195,0	
HDL mg/dl	RA	72	63,7	29,0	28,0	187,0	53,0	0,358
	CG	21	92,5	69,2	30,0	244,0	67,0	
	Total	93	70,2	42,9	28,0	244,0	54,0	
LDL mg/dl	RA	74	118,7	47,0	32,0	356,0	111,5	0,387
	CG	21	107,3	59,5	29,0	256,0	116,0	
	Total	95	116,2	49,9	29,0	356,0	112,0	
TG mg/dl	RA	73	125,1	63,0	45,0	394,0	105,0	0,002*
	CG	20	180,5	97,9	87,0	521,0	174,5	
	Total	93	137,0	74,9	45,0	521,0	119,0	

p* Mann–whitney test

Abbreviations: SD, standart deviation; BMI, body mass index; FG; fasting glucose; SBP, systolic blood pressure; AC, abdominal circumference; TC, total cholesterol; TG, triglycerides

Table 2 shows the results of the analysis of Framingham Cardiovascular risk in 10 years (FCVR). DM was the identified risk factor that scores showed significant difference between groups. This risk was higher in the CG (p=0.013). The risk of CVD was found to be

7.8% and 9.3% in 10 years for RA and CG, respectively

Table 3 describes the results of Categorical Variables. DM was more prevalent among the CG (p <0.001), and obesity in the RA group (p = 0.001).

Table 2 Analysis of cardiovascular risk in 10 years by the framingham score study, in RA and CG

Variable	Group	n	Mean	SD	Mínimum	Maximum	Percentile 25	Percentile 50 (Median)	Percentile 75	(p)
FS Age	RA	78.0	8.1	2.5	2.0	15.0	7.0	9.0	10.0	0,601
	CG	21.0	8.6	2.2	5.0	12.0	7.0	8.0	10.5	
	Total	99.0	8.2	2.4	2.0	15.0	7.0	9.0	10.0	
FS TC	RA	76.0	0.2	1.5	-3.0	3.0	0.0	0.0	1.0	0,914
	CG	21.0	0.2	1.6	-2.0	3.0	-1.0	0.0	1.0	
	Total	97.0	0.2	1.5	-3.0	3.0	0.0	0.0	1.0	
FS HDL	RA	72.0	-0.5	2.2	-3.0	5.0	-3.0	0.0	1.0	0,588
	CG	21.0	-0.8	2.9	-3.0	5.0	-3.0	-3.0	2.0	
	Total	93.0	-0.6	2.3	-3.0	5.0	-3.0	0.0	1.0	
FS SBP	RA	59.0	1.5	2.6	-3.0	7.0	0.0	1.0	4.0	0,899
	CG	21.0	1.2	2.8	-3.0	6.0	-0.5	2.0	3.0	
	Total	80.0	1.4	2.6	-3.0	7.0	0.0	1.0	3.8	
FS smoking	RA	78.0	0.2	0.7	0.0	4.0	0.0	0.0	0.0	0,292
	CG	21.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
	Total	99.0	0.1	0.7	0.0	4.0	0.0	0.0	0.0	
FS DM	RA	78.0	0.4	1.2	0.0	4.0	0.0	0.0	0.0	0,013
	CG	21.0	1.3	1.9	0.0	4.0	0.0	0.0	4.0	
	Total	99.0	0.6	1.4	0.0	4.0	0.0	0.0	0.0	
FSTOTAL	RA	78.0	9.6	4.8	-1.0	20.0	6.0	9.5	13.0	0,44*
	CG	21.0	10.6	5.0	1.0	19.0	7.0	10.0	14.5	
	Total	99.0	9.8	4.9	-1.0	20.0	6.0	10.0	13.0	
FCVR	RA	78.0	7.8	6.3	1.0	30.0	3.3	5.8	10.0	0,461
	CG	21.0	9.4	7.4	1.5	24.8	3.9	6.3	16.1	
	Total	99.0	8.2	6.6	1.0	30.0	3.9	6.3	10.0	

*p Mann–Whitney test

Abbreviations: FS, framingham score (points); TC, total cholesterol; SBP, systolic blood pressure; FCVR, cardiovascular risk in 10 years by the Framingham Score Study (%)

Table 3 Qualitative Variables in AR and CG

Variable	Category	Type		CG		Total		(p)
		RA Freq.	%	Freq.	%	Freq.	%	
SBP	Yes	38	48,7	15	71,4	53	53,54	0,064
	No	40	51,3	6	28,6	46	46,46	
DM	Yes	9	11,5	10	47,6	19	19,19	<0,001*
	No	69	88,5	11	52,4	80	80,81	
Smoking	Yes	4	5,1	3	14,3	7	7,07	0,146
	No	74	94,9	18	85,7	92	92,93	
	Eutrophic	11	14,1	7	33,3	18	18,18	
BMI	Overweight	6	7,7	6	28,6	12	12,12	0,001*
	Obesity	61	78,2	8	38,1	69	69,70	
ASA	Yes	9	11,5	8	38,1	17	17,17	0,004*
	No	69	88,5	13	61,9	82	82,83	

*p Mann whitney test

Abbreviations: SD, standard deviation; BMI, body mass index; DM, diabetes mellitus; SBP, systolic blood pressure; TC, total cholesterol; AAS, acetylsalicylic acid

The multiple linear regression analysis presented an increased correlation between RA and FCVR. Age, TC, HDL, SBP and also a patient with DM showed positive correlations with the FCVR, where in SBP this index was stronger ($r=+0.593$) in RA.

In the CG age, HDL and DM showed positive correlations with the

FCVR, however, in this group, age had the strongest correlation index ($r=+0.702$) (Figure 1).

We had obtained the following final linear regression model to assess the risk factors according to the Framingham score for patients with RA and from the CG (Figure 2).

Figure 1 Multiple linear regression analysis

RA Group: $FCVR=1.205. FS\ TOTAL-0.320. FS\ Age+0.094. FS\ DM.$ Excluding the variable 'FS TOTAL', we had obtained the following regression model conformed:

$FCVR = 0.590. FS\ Age+0.333. FS\ SBP+0.240. FS\ DM+0.238. FS\ HDL+0.188. FS\ TC+0.088. FRA\ smoke.$

Control Group: Considering the variable 'FS TOTAL', we have the following model conformed regression:

$FCVR = 1,363. FS\ TOTAL-0.424. FS\ Age.$

When we disregard the variable 'FRA TOTAL', we had obtained the following regression model conformed:

$FCVR = 0.600. FS\ Age+0.298. FS\ SBP+0.313. FS\ DM + 0.334. FS\ HDL+0.183. FS\ TC.$

Figure 2 Final linear regression analyses

Group RA:

$FCVR = 0,590, FS\ Age + 0,333, FS\ SBP + 0,240, FS\ DM + 0,238, FS\ HDL + 0,188, FS\ TC + 0,088, FS\ Smoke$

Control Group:

$FCVR = 0,600, FS\ Age + 0,298, FS\ SBP + 0,313, FS\ DM + 0,334, FS\ HDL + 0,183, FS\ TC$

Discussion

According to the known association between RA and atherosclerosis,⁶ we wondered the relationship between coronary risk factors and RA. The Framingham Study score uses data of daily screening during clinical care. This index allows us to assess prospectively the probability of a major coronary event in 10 years.

Our results have shown that the group of patients with RA lies within the classification values for overweight. These results are consistent with literature, where weight gain and metabolic syndrome have greater correlation.^{19,20} The functional limitation of these patients due to the disease itself, with decreased physical activity certainly also contributed to the increase in weight. Central obesity in RA had a higher prevalence in our sample, condition is also a predictor for CVD.^{21,22}

RA group found average BP levels that matches pre-hypertension classification (data not shown) according to the Joint Report National Committee, which is a further association with risk CVD.²³ Surely this fact is a relevant clinical information, since the elevation of 5-6 mmHg in diastolic pressure increases cardiovascular risk by 15%.²⁴

For DM, our results were consistent with those previously described, which do not show a greater prevalence of DM in patients with RA.²⁵ It is important to notice that in literature insulin resistance among systemic inflammatory diseases, such as RA is common, which contradicts our results.^{26,27} We believe a lack of proper reporting in the Medical Records may have impacted in the prevalence of DM among the RA group. Independently, patients in this group were overweighted, which probably may also contribute to insulin resistance even though when no reported hypoglycaemia or DM is performed. As expected, the TC, HDL, SBP and DM showed positive correlations with the FCVR in patients with RA. It is worth remembering that the SBP rate had a stronger correlation.

The average score of the overall risk assessment under Framingham was 7.8 for the RA group, lower than the CG. It is important to notice that being a female with DM increases the CVR in the FCVR score in 2.4%. As that being said, the lower prevalence of DM may have contributed to the lower score in the RA group. Since the CG prevalence of patients with DM was higher is also expected a higher FCVR score and so forth a higher CVR.

Early assessment using FCVR can lead to identification of CVR in RA patients, fact that could guide changes in lifestyle and use of drugs to decrease atherosclerosis and inflammation. The use of regulatory drug lipids for example, is a fairly simple alternative.¹³

Conclusion

The RA group did not show a greater risk of CVD when compared to CG. We highlight the fact that the CG group higher prevalence of diabetics and under reporting of DM in RA medical records probably impacted the results. Preventive measures should be introduced even in patients with low CVR, and in special for those with chronic inflammatory diseases such as RA.

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Conflict of interests

Authors declare that there is no conflict of interest

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