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Cardiovascular Events in Rheumatoid Arthritis Patients - 6 Year Follow-up Study

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Abstract

Patients with Rheumatoid Arthritis (RA) have an increased risk of developing cardiovascular disease when compared to the general population. This case-control prospective study investigated whether the atherosclerotic lesions in brachiocephalic vessels, carotid Intima-Media Thickness (cIMT), cerebrovascular, Cardiovascular (CV) risk factors and smoking, as well as level of disease activity and severity, seropositivity are associated with the risk of developing clinical cerebrovascular, cardiovascular events in patients with RA during 6 year follow-up. Therefore a case-control study was performed within the prospective cohort of patients with RA. Cases were patients who developed their first stroke or MI after diagnosis of RA; controls were patients with RA without CVD. Cases and controls had similar RA disease duration. Traditional and disease-specific risk factors for CVD were collected. The data were analyzed using IBM SPSS statistics V.22.0 (IBM, Armonk, New York, USA). Our results showed that cases of CV events were age-dependent. Primary arterial hypertension, severe atherosclerotic plaques and older age of patients, as well as later onset of complaints, were associated with CV cases in RA patients. Other traditional and disease-specific risk factors, as well as seropositivity, RA disease activity and severity, joint replacement surgery was not associated with CV events in RA patients in our study.

Keywords: Rheumatoid arthritis; Cerebrovascular disease; Stroke; MI; Carotid artery intima media thickness

Introduction

Rheumatoid Arthritis (RA) is a chronic inflammatory disease that affects 0.5% to 1% of the adult population [1,2]. RA is associated with joint pain and swelling as well as cardiovascular complications. Inflammation is the driving force known for both diseases atherosclerosis and rheumatoid arthritis. What is more, it is believed that atherosclerosis and RA have common pathophysiology and genetic background [3]. There have been found genotype associated with increased myocardial infarction that is more frequent among patients with RA [4]. Unfortunately, in daily routine practice, genetic tests for stroke and or MI are not available for the majority of RA patients, and we are still in need of further research and innovations that could shed light in this difficult CV risk evaluation process in RA patients. According to EULAR guidelines 2010 disease duration, disease activity, seropositivity affects the risk of CVD in patients with RA [5]. Therefore a case control study was performed in a cohort of patients with RA matched by gender and disease duration to detect Cardiovascular events (CV) and estimate carotid arteries (cIMT) and atherosclerotic changes of brachiocephalic arteries with relation to age, RA disease Intima-Media Thickness activity and severity, joint replacement surgery, seropositivity, traditional CV risk factors and smoking history.

Material and Methods

Patients

This was a case-controlled prospective study of patients with RA that took place from 2012 to 2018. Patients diagnosed according to the criteria of 1987 American College of Rheumatology and or who fulfilled the criteria of 2010 for RA, with disease duration >6 weeks and without prior disease-modifying antirheumatic drug use, were included in the study [6]. All patients gave written consent before any study procedures.

Comprehensive information on comorbidities (including CVD) and the course of the disease were regularly collected and stored in an electronic database. Access to the medical files of each patient was available, which included the periods before and after diagnosis of RA; the registration of comorbidities and medical events, therefore, were complete. Cases for this study were patients who

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developed cerebrovascular events (ischemic stroke and hemorrhagic stroke, as well as unclassified strokes) and cardiovascular events (myocardial infarction and ischemia) after the diagnosis of RA. Cases of cerebrovascular events were selected if the diagnosis was verified by the radiologist in an MRI or CAT scan. Only the first event of a stroke in RA patient was registered in this study.

Cases of cardiovascular events for this study were patients who developed the first MI after the diagnosis of RA. Cases were selected if the diagnosis of MI was made by a cardiologist. The presence of ischemic symptoms, ECG changes and raised cardiac enzyme levels were verified from the patient's medical records. Patients with already known cerebrovascular or cardiovascular diseases as well as atrial fibrillation episodes were not included in this study.

Controls were selected randomly from the cohort of patients with RA, aiming to have similar disease duration (exposition time to inflammation) for cases and controls. The study protocol was approved by the ethics committee of the Riga Stradins University. In this prospective 6-year follow up study of patients with RA we analyzed the baseline levels of several biomarkers known to be associated with atherosclerosis, seropositivity, inflammation in the RA population.

Assessment of disease activity and severity

In the cohort, disease activity was prospectively assessed using the DAS28 [7]. The DAS28 is a measure of disease activity in rheumatoid arthritis. DAS stands for Disease Activity Score and the number 28 refers to the 28 joints that are examined in this assessment. DAS 28 is calculated from the 28-tender joint count, 28-swollen joint count, C-reactive protein and the patient's global assessment of disease-related general health on a visual analogue scale. Disability was assessed using the disability index of the Health Assessment Questionnaire (HAQ) [8]. Disease severity was assessed using X-ray proved erosions in small joints of hands and feet, musculoskeletal sonography of synovial joints, as well as performed joint replacement surgery.

Assessment of seropositivity

Circulating biomarkers Rheumatoid Factor (RF), anti-Cyclic Citrullinated Peptide (anti-CCP) antibodies were analyzed from frozen serum or plasma by ELISAs tests.

Assessment of cardiovascular risk factors

Traditional cardiovascular risk factors were obtained including female gender, metabolic dysfunction, hypertension, diabetes mellitus, and smoking, dyslipidemia with high triglyceride levels, low serum High-Density Lipoprotein (HDL) and high LDL levels. Lipids were assessed from serum samples. The atherogenic index was calculated. It is defined as the base-10 logarithm of the ratio of plasma triglyceride to high-density lipoprotein cholesterol. Body Mass Index (BMI) was calculated from height and weight at baseline. Diabetes mellitus was regarded as present if the diagnosis was made before the event or censoring. Brachial blood pressure was measured according to the European Society of Hypertension guidelines using the OMRON M7 apparatus (Kyoto, Japan) [9]. The average of the last two measurements was reported. Hypertension was defined as a history of hypertension, use of antihypertensive medication before the event or censoring or systolic office blood pressure ≥ 140 mmHg and/or diastolic office blood pressure ≥ 90 mmHg. Information on smoking history and occurrence of clinical cardiovascular disease was assessed at entry visits and obtained from medical records or patients.

Carotid ultrasound imaging

B-mode ultrasonographic examinations of the brachiocephalic vessels were performed with GE Vivid-7 scanner (GE Vingmed Ultrasound) using a 12 (10 to 14) MHz linear matrix array transducer. An experienced sonographer performed all examinations. Intima Media Thickness (IMT) measurements were performed bilaterally in the far wall of the Common Carotid Artery (CCA) over a 5 mm segment, from about 15 mm to 10 mm proximal to the start of the carotid bulb. Before an image was stored for analysis, we ensured that both the near wall and far wall were visualized with sharp edges, indicating an insonation of about 90° to the vessel wall, to avoid overestimation of IMT and plaque size. Atherosclerotic plaques in the CCA, vertebral artery, subclavian artery and the Internal Carotid Artery (ICA) were identified bilaterally in the longitudinal view when both IMT observations of the far wall and near the wall had sharp edges as protrusions into the lumen ≥ 1.5 mm. In cases of doubt about the presence of a plaque, it was verified by a cross-sectional image obtained by rotating the probe 90º. Plaque areas were analyzed only if a sharp delineation of the plaque was obtained.

Statistical analysis

The statistical analyses were undertaken using IBM SPSS statistics V.22.0 (IBM, Armonk, New York, USA). Normally distributed continuous data were expressed as mean and SD and non-normally distributed continuous data as median and IQR. Categorical variables were presented as numbers and percentages. Cases of stroke and controls were compared by disease activity variables and risk factors using the Mann-Whitney U test (for continuous variables) or the Pearson's X^2 test or Fisher's exact test (for dichotomous variables).

Results

There were one hundred twelve (112) patients (females 80.4%) with RA at the moment of the case and control enrolment in this case-control prospective follow-up study. They ranged in age from 21 years to 84 years. Twenty-one patients were selected as cases who had suffered from Cardiovascular (CV) events, 91 controls were randomly selected. Fifteen of RA patients developed a stroke, while twelve developed a myocardial infarction from our case group patients during our follow-up for 6 years. Due to the small number of patients, we further united them in one group. Patients with CV events were mostly females (81%). Study cases and controls were matched by gender Fisher's exact test (p=0.939).

In our study patients, who experienced CV events were significantly older compared to control RA patients respectively, the mean age of case group was 68.78 (± 8.97) *vs.* control 56.14 (± 14.73), (p<0.001). However, not only the age of patients was of importance. Analyzing the onset of joint pain and swelling in both groups we found that the age of onset of RA complaints of case group patients was median 63 years (IQR 52.50 to 72.50) *vs.* control RA patients median 51 years (IQR 42.0 to 72.50), (p<0.005). Therefore late-onset complaints could be an important finding, allowing us to pay additional attention to this particular RA patient group, where traditional CV risk factors together with recent-onset autoimmune inflammatory disease trigger CV events. In our study, the case and control group were matched by disease duration. The median RA disease duration for case group patients was 2 years (IQR 0.4 to 10) *vs.* control group 2 (IQR 1.0 to 6.5), (p=0.431). Analyzing traditional risk factors we found that patients with CV events have suffered from arterial Hypertension (HTN) in 90.5% of cases but the control group

only 54.9% (p=0.002). Body Mass Index (BMI) in all RA patients was evaluated. Obesity is a known driver for hypertension [10]. Moreover, high BMI is associated with poor BP control in RA patients [11].

Mean BMI was 27.41 (± 4.63) for the case group and control group 26.48 (± 5.07), respectively (p=0.247). According to the World Health Organization's (WHO) recommended body weight based on BMI values, our patients were in the overweight category [12]. What is more, a BMI greater than 25 is a negative prognostic factor associated with persistent disease activity and reduced the likelihood of achieving sustained remission [13].

Atherogenic Index of Plasma (AIP) is a strong marker to predict the risk of atherosclerosis of extracranial and intracranial blood vessels and coronary heart disease that is an important risk factor for the development of stroke and MI [14]. Median of Atherogenic Index (AIP) was calculated in case group 0.17 (IQR 0.09 to 0.41) *vs.* control 0.12 (IQR 0.02 to 0.31), (p=0.686). A statistically significant association of CV cases with atherogenic index was not found. However, both groups were classified according to AIP from the medium risk for heart disease and those with more than 0.24 classified as having an elevated risk for CVD.

Diabetes was found equally in both groups 4.8% in the case group and 4.8% in the control group, non-significantly associated with CV cases (p=0.942). Smoking is a well known important risk factor for stroke and MI [15]. In our study patients with CV events mostly were not smokers; neither had a history of smoking before enrolment nor smoked later.

According to our data, only 4.8% of the cases were smokers *vs.* control group 38.5%, (p=0.002). The mean period of smoking for the control group was 22.86 (± 12.596) years *vs.* case group 20 years for one patient, therefore smoking was not attributable to CV events in our study. Observing seropositivity of the patients, there were 85.7% of cases seropositive *vs.* control 87.9%. The difference was not statistically significant (p=0.724), respectively for Anticitrullinated Protein (ACPA) antibodies (p=0.134) and Rheumatoid Factor (RF) (p=0.526).

X-rays of small joints of hands and feet revealed erosions in small joints in 52.4% of case-patients (p=0.544) *vs.* control patient 45.1%. In total 46.4% of RA patients had the erosive disease. The joint replacement surgery was not performed in case group patients *vs.* 11% in the control group (p=0.036) interestingly, 85.7% of RA cases with CV events and 97.8% of controls had detectable synovitis in musculoskeletal ultrasound Fisher's exact test (p=0.016).

RA disease activity evaluated by DAS28 (CRP) score for the case group was the median of 5.19 (IQR 2.83 to 5.99) *vs.* control group median 3.99 (IQR 3.03 to 5.14); (p=0.280). According to our data, both groups were having similar disease activity at the baseline.

Health Assessment Questionnaire (HAQ) for functional status assessment was done. Both of our group patients were moderately disabled according to our data. The median HAQ in case group RA patients was 1.75 (IQR 1.0 to 1.75) *vs.* control 1.25 (IQR 0.47 to 2.0); (p=0.140). It is well known that RA disease activity can be influenced by menarche and menopause onset or delay according to well-known statements. According to previous studies, it was found that menopause status in RA patients is associated with increased RA disease activity, disability, linked to greater joint damage [16]. This risk is doubled for women in early menopause before the age of 45 [17]. In our study, none of the female patients had early menopause neither in case nor control group. Menopause occurrence for case group female patients median 52 years (IQR 50.0 to 53.0) and control group median 50 (IQR 47.0 to 52.0) years, (p=0.106).

What is more, we looked at the data carefully according to the onset of menarche that also can have some impact on RA activity. In some articles, delayed menarche may predispose RA [18]. The onset of menarche for case group was a median of 13 years (IQR 13.0 to 15.0), for control group 14 years (IQR 13.0 to 14.0), (p=0.413). In larger patient group perhaps we could observe some more statistically significant results regarding the age of menarche and or menopause. We visualized subclinical atherosclerosis assessed by cIMT early at the very beginning of patient enrolment. It is important to note that age-related changes of the vessel wall can later lead us to misinterpretation of vessel wall alteration due to atherosclerotic process combined with smoking, cholesterol, arterial hypertension influencing factors [19]. After performing neurosonological examinations no statistically significant difference in cIMT (carotid artery intima-media thickness) dxt et sin between cases and controls have been found. Respectively, IMT (Intima Media-Thickness) of both sides CCA (Common Carotid Artery) dxt et sin did not differ between patients with and without CV events. IMT sin mean 0.90 mm (± 0.22) *vs.* case group IMT sin 0.91 (± 0.26); (p=0.387). IMT dxt mean 0.88 mm (± 0.22) *vs.* case group IMT dxt 0.87 (± 0.27); (p=0.622). It is important to note that our patient carotid artery intima-media thickness correlated with the age of our patients, respectively, Spearman's rho IMT sin=0.448, IMT dxt=0.481. IMT of the RA patients was elevated for those who had hemodynamically relevant stenosis of brachiocephalic vessels, respectively, the median of IMT sin 1.10 (1.0 to 1.20); IMT dx 1.10 (1.0 to 1.10) *vs.* median of IMT sin 0.9 (IQR 0.7 to 1.07); IMT dx 0.9 (IQR 0.7 to 1.0) of patients without severe atherosclerotic lesions, IMT sin (p=0.014), IMT dx (p=0.021). Hemodynamically non-relevant atherosclerotic plaques in brachiocephalic vessels were found in 66.7% of cases *vs.* control 53.8% (p=0.336).

Hemodynamically non-significant atherosclerotic plaques correlated with arterial hypertension 69.6% (p=0.004) but did not have the association with the atherogenic index of plasma (AIP); (p=0.600). Except for atherosclerotic lesions reducing lumen, more than 50% and DAS 28 was of importance, (p=0.032). A difference in DAS 28 score was found between patients with and without severe atherosclerotic changes of vessels. According to our data, the median of DAS 285.35 (IQR 4.94 to 6.41) was higher in patients with severe stenotic plaques than in patients with non-stenotic plaques which do not protrude lumen for more than 50%, the median DAS 283.92 (IQR 2.88 to 5.19).

Atherosclerotic plaques in brachiocephalic, causing >50% lumen obstruction had 23.8% of patients with CV events, *vs.* 2.2% control group patients (p=0.003). We evaluated patients with stroke and MI additionally. From all patients who suffered from MI, just 16.7% had severe hemodynamically relevant atherosclerotic stenoses in their brachiocephalic vessels, (p=0.163). Altogether, 26.7% of patients with stroke had atherosclerotic plaques in brachiocephalic vessels resulting in >50% luminal stenosis (p=0.006).

Discussion

The previous meta-analysis has verified the increased important risk of cardiovascular morbidity especially myocardial infarction, but not stroke in RA patients [20]. According to our prospective study

results patients with RA during 6-year follow-up have suffered from cerebrovascular events stroke (72%), and a lesser extent to MI (55.6%) of cases. The latest cross-sectional study from Israel supports the fact that RA is independently associated with stroke [21]. Especially among young patients under 65 years. It correlates with meta-analysis of Levy et al. [20] data which concludes that the mean age of patients with MI was (60 ± 3.2) years, but with cerebrovascular stroke mean age (60 ± 3.0) years. Our study patient group who experienced a stroke and MI were older, respectively 68.78 (± 8.97) years, revealing CV event risk population aged 60 and older. It correlates with findings in the general population, where subclinical cerebrovascular disease including so called silent infarction identified on brain imaging in ≤ 28% of the population aged >65 years [22].

Regarding our study results, we observed the RA population who suffer the most from CV events. These were patients whose RA symptoms and complaints begin late in their life; the median was 63 years, despite the wide range inclusion category from 21 years to 84 years. Hypertension has been shown as an important risk factor for stroke and MI in our study. Similar results observed in stroke for RA patients in Germany, where data from German biologics register RABBIT (Rheumatoid Arthritis: Observation of Biologic Therapy) were analyzed. According to EULAR 2010 guidelines [23], unfavorable lipid profile is an important prognostic factor for future CV events However, in our study dyslipidemia and diabetes were similarly found in both groups and did not underline any significance for CV events [5].

Neurosonolgy examination revealed that cIMT correlates with patient age and is elevated in patients with severe atherosclerotic changes; however, we could not observe predictive value for stroke and or MI cases. Perhaps in a larger patient cohort, the cIMT would have more important prognostic value. Inflammation has been suggested as a risk factor for stroke both in general population and RA patients. It coincides with our study [23,24], the high disease inflammatory activity described by mean DAS 285.19 (IQR 4.31 to 6.17) was associated with hemodynamically relevant stenosis in the brachiocephalic vessels.

Evidence to date suggests that poor physical function of RA patient physical disability evaluated by HAQ over time do contribute to the risk of stroke events [23]. However, in our study neither disease activity calculated by DAS 28 score, neither HAQ score did not reveal any significance between case and control groups. Disease severity (joint replacement surgery, multiple erosions), according to the results of the present study was not found to have a positive relationship with CV cases ($p>0.05$). Seropositivity, smoking history per years, the beginning of menarche and menopause for female patients, as well as AIP did not have any association with CV events in our study.

Conclusion

To sum up, the results of this 6-year follow-up study non-fatal stroke and MI was observed in older individuals (females), with late complaint onset, suffering from arterial hypertension. Brachiocephalic arterial atherosclerotic plaques, protruding lumen more than 50% were correlating with stroke, but not MI events. Higher RA disease activity calculated as DAS 28 was found in patients with hemodynamically relevant stenosis in the brachiocephalic arteries. Joint erosive disease, joint replacement surgery, seropositivity as well as lipid profile, smoking history were not associated with CV events in RA patients in our study. Additional research is necessary to further investigate the relationship between RA patients and CV disease.

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