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The correlation between cardiovascular risk and functional disability and disease activity in patients with rheumatoid arthritis

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Aim: To determine the cardiovascular risk (CVR) in patients with rheumatoid arthritis (RA) and its correlation with disease activity and functional ability by using the Framingham risk score (FRS) and to compare the CVR of the RA patients with the control group with the help of the FRS.

Materials and methods: Seventy-four RA patients, who were in conformity with the criteria of the American College of Rheumatology, were included in this study at Bezmialem Vakıf University Hospital. A total of 39 subjects without inflammatory arthritis were included as the control group. The FRS was calculated by evaluating age, smoking habits, diabetes, cholesterol and blood pressure measurements. The disease activity score-28 (DAS-28) and the health assessment questionnaire (HAQ-DI) were applied to the RA patients.

Results: We could not find any significant difference between the case and control groups in terms of FRS. The means of erythrocyte sedimentation rate (ESR) and blood pressure of participants in the study group were significantly higher than those of the control group. There was not any significant difference in terms of C-reactive protein (CRP) and cholesterol levels between the groups. DAS-28, HAQ-DI, CRP, ESR, and disease duration were not significantly correlated with FRS.

Conclusion: For patients who have inflammatory arthritis, new risk score calculation that consists of other disease-specific risk factors, in addition to traditional ones, is needed.

Key words: Rheumatoid arthritis, cardiovascular risk, functional insufficiency, disease activity

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease associated with increased mortality and decreased life expectancy; it affects approximately 1% of the overall population. Standardized mortality rates vary from 1.28 to 3.0 (1). Increased mortality rates observed in RA result from increased incidences of cerebrovascular atherosclerosis and coronary arterial disease. Indeed, a correlation was demonstrated between the risk for mortality and cardiovascular disease (CVD) in seropositive RA patients. RA is considered an independent risk factor for multiple coronary arterial disease. As well as affecting mortality, CVD also leads to considerable morbidity (2). In the literature, patients with RA were reported to have a higher risk for CVD compared to the overall population (3). In this study we aimed to investigate the correlation between functional disability and disease activity and CVR in patients with RA.

RA is a multisystemic disease with unknown causes. Despite its several systemic symptoms, the most prominent feature of RA is often continuous inflammatory synovitis, which involves the peripheral joints symmetrically. It is approximately 3-fold more common in women compared to men. RA is a disease that is observed throughout the entire world and it can affect any race (4). Microvascular damage and increased number of cells that surround the synovium seem to be the earliest lesions in the rheumatoid synovitis. Mild musculoskeletal symptoms such as insidious lethargy, loss of appetite, widespread weakness, and pain are observed in approximately two-thirds of the patients. In general, specific symptoms appear gradually. Established RA occurs when numerous joints, especially hands, wrists, knees, and feet, are involved symmetrically (4). RA is a systemic disease with several nonarticular symptoms (5). Rheumatoid vasculitis and pleuropulmonary findings are observed in patients with severe RA (6). Heart disease that is related to the rheumatoid process is clinically rare (7,8)

RA is not only a disease that restricts the joint movements by leading to joint damage and permanent pain, but it is also a disease that triggers the formation

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of atherosclerotic plates and results in early ischemic CVD and early death (9). The mortality due to CVD is high in patients with RA (10). In previous studies, it was demonstrated that noncoronary atherosclerosis and coronary calcification were more intensive in patients with RA when compared to age- and sex-matched controls (11). The grade of the inflammation is correlated with the risk for CVD in RA. Therefore, the treatment for inflammatory disease is thought to decrease this excessive risk. The treatment for RA was shown to decrease the inflammation and to regulate all lipid profiles (12).

The Framingham Heart Study was conducted on a large group of patients who neither developed obvious CVD symptoms nor had heart attack or stroke. The group was followed-up with for a long period and the aim was to determine the contribution of common factors or characteristics to the occurrence of CVD. The Framingham risk score (FRS) is a widely studied indicator to determine the CVR in the overall population. It utilizes age, sex, smoking status, blood pressure, and cholesterol levels of the patients. The FRS categorizes 10-year CVR in 3 categories: as low-risk (<10% in 10 years), moderate risk (10%–20%), and high-risk (>20%).

2. Materials and methods

The study was conducted in the Department of Physical Therapy and Rehabilitation of Bezmialem Vakıf University between 2008 and 2009. A total of 74 patients who had been diagnosed with RA, according to 1987 American College of Rheumatology classification criteria, were included in the study. As a control group, we included patients who were diagnosed with mechanical low back pain, lumbar discal hernia, and lumbar spondylosis. Ethics board approval of the study was obtained from the local ethics board committee of our hospital. All patients who participated in the study signed informed consent forms. For all patients, demographics (age, sex, weight, height) were recorded. Body mass index (BMI) of the patients was calculated. Systolic and diastolic arterial blood pressures of the patients were measured after they rested for 15 min. The starting date of the symptoms and the date of RA diagnosis were recorded. The drugs used after the diagnosis and the existing therapies were recorded. For the patients with RA and for the control group, the presence of diabetes, hypertension, dyslipidemia, CVD, and other systemic diseases and the drugs used were recorded. The patients were asked whether their first- and second-degree relatives had hypertension, diabetes, or cerebrovascular and cardiovascular diseases. Information about smoking and exercise habits were obtained from personal interviews with the patients. In all the subjects, the blood samples were drawn in the morning, following a 13-h fasting period. In the blood analyses, complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), total cholesterol, triglyceride (TG), high-density lipoprotein (HDL), and low density lipoprotein (LDL) were investigated. Rheumatoid factor (RF) and anticyclic citrullinated peptide (anti-CCP) values were also investigated in the patients with RA.

The disease activity score-28 (DAS-28) is a scoring system used to evaluate disease activity in patients with RA. The DAS-28 is calculated using a formula that contains the following parameters: ESR (or CRP), visual analogue scale (VAS; the patient grades his/her pain on a scale of 100 mm), the number of swollen joints (determined by the number of the joints involved), and the number of tender joints. For this purpose, in the examination of the joints, tenderness and swelling were evaluated in the right and left shoulders, right and left elbows, right and left wrists, 10 metacarpophalangeal joints (right and left), 10 interphalangeal joints (right and left), and right and left knees. DAS-28 scores below 2.6 were considered as remission, DAS-28 scores between 2.6 and 3.2 as low clinical activity, DAS-28 scores between 3.2 and 5.1 as moderate clinical activity, and DAS-28 score above 5.1 as high clinical activity (10).

In evaluating the daily-life functional status of the patients in rheumatology practice, the most commonly used method is the 'Health Assessment Questionnaire Disability Index' (HAQ-DI). The HAQ-DI evaluates the level of functional ability of the patient. It contains 20 questions within 8 categories, named dressing, lifting off, eating, walking, body care, lying, grasping, and actions. The scores between 0 and 1 are classified as mild and moderate functional disability, the scores between 1 and 2 are classified as moderate and severe functional disability, and the scores between 2 and 3 are classified as very severe functional disability (10).

In the evaluation form for CVR, all the patients were questioned regarding sex, birth date, smoking habits, alcohol consumption, the presence or absence of diabetes, detailed diet habits, familial history of heart disease, and physical activity. Other questions included whether the participants had been previously diagnosed with CVD or whether the patients experienced chest pain at rest or during exercise. Additionally, the subjects were questioned about hypertension and dyslipidemia drugs.

The FRS is one of a number of scoring systems used to determine an individual's chances of developing CVD. The FRS is used to estimate the 10-year CVR of an individual. The FRS is based on data obtained from the Framingham Heart Study. CVR scoring systems give an estimate of the probability that a person will develop cardiovascular disease within the next 10 years. They also indicate who is most likely to benefit from prevention, since they give an indication of who is most likely to develop CVD. For

this reason, CVR scores are used to determine who should be offered preventive drugs, such as drugs to lower blood pressure and drugs to lower cholesterol levels.

In the patients with RA and in the controls, the FRS was calculated on the framinghamstudy.org website using parameters such as hypertension, high cholesterol, smoking, obesity, diabetes, and physical inactivity, as well as other factors such as triglyceride and HDL cholesterol levels, age, sex, and psychosocial problems. The results were divided into 3 categories: low risk (<10% within 10 years), moderate risk (10%–20%), and high risk (>20%). Since 1948, the participants have been periodically evaluated every 2 years based on a detailed medical history, physical examination, and laboratory tests. The participants in the Framingham study were closely evaluated for many years and important data were obtained regarding the effects of important CVR factors.

Statistical analyses were performed using statistical software. While descriptive statistics (frequency, percentage, mean, and standard deviation) were used to evaluate the study results, the Pearson chi-square test was used to compare qualitative data. Quantitative data were compared using the Mann–Whitney U test when there were 2 groups and using the Kruskal–Wallis test in the presence of more than 2 groups. To determine the correlation between the quantitative results, Spearman correlation analysis was used. The results were evaluated as 2-sided, at a 95% confidence interval and at a significance level of $P < 0.05$.

3. Results

While the age of the patients ranged between 28 and 72 years in the patient group, it varied between 40 and 74 years in the control group. Fifty-eight (78.4%) of the patients were women and the remaining 16 (21.6%) were men. For the control group, there were 38 (97.4%) women and there was only 1 man (2.6%) (Table 1). Mean age of the patients was significantly lower than that of the controls ($P < 0.05$). There was not a statistically significant difference between the patients and the controls in terms of weight, height, and BMI ($P > 0.05$).

For the subjects of the case group, the distribution of duration of treatment, duration of disease, and duration of treatment delay is shown in Table 2. FRS findings and their distributions for case and control groups are given in Tables 3 and 4. The difference of FRS was not statistically significant between the case and control groups ($P > 0.05$). The laboratory findings of the case and control groups are given in Table 5.

Of the subjects in the patient group, 41 (55%) were RF-positive and 33 (45%) were RF-negative, whereas 41 (55%) were anti-CCP–positive and 33 (45%) were anti-CCP–negative.

Mean values of ESR, systolic blood pressure, and diastolic blood pressure were significantly higher in the subjects of the case group compared to the controls ($P < 0.05$). The rates of CVD and familial history of CVD are given in Table 6. The familial history of DM, HT, and

Table 1. Demographic characteristics of case and control groups.

	Case	Control	P
Age (mean ± SD)	51.10 ± 10.16	56.05 ± 7.33	0.013
Weight, kg (mean ± SD)	74.29 ± 14.46	74.72 ± 9.60	0.897
Height, cm (mean ± SD)	157.6 ± 06.76	155.39 ± 5.66	0.114
BMI (mean ± SD)	30.03 ± 6.14	30.92 ± 3.37	0.277

Table 2. The distribution of duration of treatment, duration of disease, and duration of treatment delay for the patients.

n = 74	Mean ± SD	Min–max
Duration of treatment (years)	5.95 ± 6.78	0 –29
Duration of disease (years)	8.64 ± 7.76	1–33
Duration of treatment delay (years)	2.69 ± 4.78	0–29

Table 3. FRS findings of the case and control group patients.

	Case	Control	P
FRS (mean ± SD)	0.039 ± 0.051	0.027 ± 0.028	0.741

Table 4. FRS distribution of the case and control groups.

Control, n (%)	Low FRS	22 (57)
	Medium FRS	13 (33)
	High FRS	4 (10)
Case, n (%)	Low FRS	36 (49)
	Medium FRS	22 (30)
	High FRS	16 (21)

Table 5. Laboratory findings of the case and control groups.

(Mean ± SD)	Case	Control	P
CRP	0.59 ± 0.72	0.52 ± 0.42	0.305
ESR	33.54 ± 19.03	17.97 ± 10	0.014
Thrombocytes	283.05 ± 70.30	270.1 ± 65.02	0.428
Total cholesterol	209.3 ± 35.66	215.13 ± 28.93	0.313
HDL	57.04 ± 14.65	61.97 ± 18.03	0.225
VLDL	26.10 ± 11.34	26.21 ± 12.22	0.973
LDL	126.2 ± 34.80	128.79 ± 29.25	0.491
Triglyceride	131.03 ± 56.11	129.71 ± 61.24	0.837
SKB	140.8 ± 25.40	129.23 ± 18.16	0.013
DKB	86.28 ± 14.24	76 ± 9.42	0.012

Table 6. CVD and family history of CVD.

		Case, n (%)	Control, n (%)	P
Angina	Yes	6 (8.1)	5 (12.8)	0.422
	No	68 (91.9)	34 (87.2)	
Prior heart attacks	Yes	2 (2.7)	0 (0)	0.300
	No	72 (97.3)	39 (100)	
Prior angiography	Yes	2 (2.7)	5 (12.8)	0.034
	No	72 (97.3)	34 (87.2)	
Prior stents	Yes	74 (100)	39 (100)	-
Prior bypass	No	1 (1.4)	1 (2.6)	0.642
	No	73 (98.6)	38 (97.4)	
Medication for heart disease	Yes	6 (8.1)	5 (12.8)	0.422
	No	68 (91.9)	34 (87.2)	
A family history of heart disease or heart attacks	Yes	33 (44.6)	21 (53.8)	0.349
	No	33 (44.6)	21 (53.8)	
CVD in the family	Yes	19 (25.7)	17 (43.6)	0.052
	No	55 (74.3)	22 (56.4)	

dyslipidemia for the patient group and the control group can be found in Table 7.

For the subjects in the patient group, the number of the patients who had previously underwent an angiography was significantly lower compared to the controls ($P < 0.05$). For the subjects of patient group and the controls, smoking and exercise habits are seen in Table 8. DAS-28 and HAQ-DI scores of the patient group are given in Table 9.

For the subjects in the case group and the controls, the effect of the use of dyslipidemia therapy on the FRS was not statistically significant ($P > 0.05$). For the patient group, the correlation of the FRS with DAS-28, HAQ-DI, CRP, ESR, treatment duration, disease duration, the correlation of steroid use with FRS, and the correlation of RF positivity and anti-CCP positivity with the FRS were not statistically significant ($P > 0.05$). The correlation of DAS-28 scores with the FRS in the case group is seen in Table 10. The correlation between the FRS and DAS-28 scores observed in the subjects of the case group was not statistically significant ($P > 0.05$). Table 11 shows the HAQ-DI scores of the patient group.

Table 7. DM, hypertension, and dyslipidemia findings and family histories of the case and control groups.

		Case, n (%)	Control, n (%)	P
DM	Yes	8 (10.8)	7 (18)	0.288
	No	66 (89.2)	32 (82)	
Treatment of DM	Yes	7 (9.5)	7 (17.9)	0.193
	No	67 (90.5)	32 (82.1)	
A family history of DM	Yes	37 (50)	14 (35.9)	0.152
	No	37 (50)	25 (64.1)	
HT	Yes	24 (32.4)	14 (35.9)	0.711
	No	50(67.6)	25 (64.1)	
Medication of HT	Yes	20 (27)	14 (35.9)	0.328
	No	54 (73)	25 (64.1)	
Dyslipidemia	Yes	11 (14.9)	7 (17.9)	0.670
	No	63 (85.1)	32 (82.1)	
Medication for dyslipidemia	Yes	5 (6.8)	5 (12.8)	0.281
	No	69 (93.2)	34 (87.2)	

Table 8. Smoking and exercise habits of the case and control groups.

		Case, n (%)	Control, n (%)	P
Smoking habit	Yes	14 (19)	10 (26)	0.406
	No	60 (81)	29 (74)	
		Case, n (%)	Control, n (%)	P
Exercise habit	Yes	23 (31)	11 (28.2)	0.717
	No	51(69)	28 (71.8)	

Table 9. Findings of the DAS-28 and HAQ-DI results for the case group.

n = 74	Mean ± SD	Min–max
DAS-28	3.855 ± 1.224	0.480–6.88
HAQ-DI	0.642 ± 0.705	0.000–2.75

Table 10. DAS-28 findings of the case group and their relationship with the FRS.

FRS		N	Mean ± SD	P
	Inactive (<3.2)	22	0.041 ± 0.038	
DAS-28	Mean (3.2–5.1)	40	0.041 ± 0.061	0.435
	Active (>5.1)	12	0.027 ± 0.032	

Table 11. HAQ-DI values of the case group.

HAQ	n (%)
Light–medium	51 (72.9)
Medium–severe	18 (24.3
Severe	5 (6.7)

4. Discussion

Mean age was significantly lower in the case group compared to the control group. This could be explained by consecutive and randomized selection of the patients who presented to our polyclinic to form the control group. In the study performed on age- and sex-matched control cases, it was demonstrated that the patients with RA had a higher risk for CVDs, such as cardiovascular death, ischemic heart diseases, and heart failure. Smoking is another parameter of the FRS. Due to its inflammatory effect, smoking is more damaging to the vascular wall of patients with RA compared to a normal population (13). In our study, the case group and the control group were not significantly different in terms of smoking, and the smoking rates were lower than in the overall population, with rates of 20% and 26%, respectively.

In the multicenter study performed by Naranjo et al., the prevalence of CVD was investigated in a total of 4363 RA patients from 15 countries (14). In this study, in which mean age was 57 years, the prevalence of smoking was found to be 43%. After an adjustment for age and sex, smoking was shown to be correlated with a more serious coronary arterial classification. In a large study performed on patients who had experienced a myocardial infarction (MI) for the first time and those who had not experienced an MI after the diagnosis of RA, the patients who had experienced MI were shown to exhibit an increased serum level of cholesterol and low HDL cholesterol compared to those who had not experienced an MI (15–17). These undesirable lipid changes were thought to have emerged at least 10 years before the onset of RA. Contrary to this evidence, our study could not find a difference between the 2 groups.

The prevalence of diabetes, one of the traditional risk factors for CVD, was found to be 8% in the study performed by Naranjo et al., which is the same as our result (8%). Systolic blood pressure is also among the traditional risk factors for CVD. The prevalence of hypertension was 32% in the study performed by Naranjo et al. and 24% in our study, being significantly higher compared to control group. The fact that a moderate fall of blood pressure reduces the risk for CVD is a well-known reality (18). In our study, no statistically significant difference of FRS was found between the 2 groups.

Aside from hypertension, there was no difference between the groups regarding the traditional factors used to calculate risk the absolute risk for CVD. As a result, Framingham scores did not show any statistical difference. In this regard, it would be more useful to include healthy volunteers as the control group. In the case group of our study, the prevalence of physical inactivity was not significantly different compared to the control group. Fourteen patients with RA and 10 controls were exercising by walking 3 times per week. In RA, commonly observed functional disability, joint pain, and stiffness may prevent these patients from maintaining a regular exercise routine (19).

BMI is used as to measure the amount of fat in the body. In many previous studies, RA patients and controls did not show a consistency in terms of BMI measurements and it was demonstrated that BMI measurements could be higher than, equal to, or lower than those obtained in the controls (20). In our study, mean BMI value of the subjects with RA and of the controls was 30 (overweight) and, therefore, the difference between the 2 groups was not statistically significant.

When evaluating CVR in patients with RA, it was shown that smoking and physical inactivity were important risk factors (21). Contrary to our study, that study showed that the patients with RA had a high absolute CVD risk, independently from smoking, compared to the control group. On the other hand, another study similar to ours found that the risk for CVD was not different between the patients with RA and those without RA. The magnitude of CVR in patients with RA was reported to be likely equal to that of the patients with type II DM and it was recommended to give RA patients as much attention as diabetics regarding CVR (22).

In our study, no significant correlation could be found between 2 inflammatory markers, ESR and CRP, and the FRS in the patients with RA. In a previous study, 151 patients with RA were examined and CRP levels were found to be above 3 mg/L in 68% and above 10 mg/L in 25% of the patients. At the end of this study, it was reported that CRP levels were correlated with high and very high risk for a CV event. This was the case even in the majority of the patients with RA, in whom the disease activity has been thought to be kept under control. In our study, CRP levels were above 3 mg/L in 35% and above 10 mg/L in 18% of the patients with RA. In our study, ESR levels were significantly higher in the patients with RA compared to the control group. A study showed that ESR levels were higher in RA patients with atherosclerosis compared to RA patients without atherosclerosis. This suggests that both traditional risk factors and inflammation could play a role in the development of CVD (23).

Disease duration and RF or anti-CCP positivity are prognostic markers for the risk for CVD (24). In a prospective study performed by Naz et al., a total of 1098 patients with inflammatory polyarthritis, in whom the disease had begun before the age of 55, were evaluated (25). With 5- and 10-year follow-ups for all reasons and CV mortality, standardized mortality rate (SMR) was calculated. It was detected that CV mortality was higher in those with longer disease duration and in seropositive patients (25). It is clear that long-term follow-up is needed to determine the CV mortality of the case group in our study. In a metaanalysis, SMR was found to be 1.2 in those with a disease duration below 2 years and 1.9 in those with established RA.

In our study, we found that the correlation between therapy duration, disease duration, and FRS was not statistically significant for the patients in the case group. Efficient therapies may lead to an improvement in physical inactivity and, therefore, may be helpful in decreasing the risk for all important conditions such as CVD, hypertension, obesity, and diabetes (26). In a previous study, the effects of long-term disease-modifying antirheumatic drug (DMARD) use on the disease activity and endothelial function were investigated in patients with early RA (ERA). Twenty-five ERA patients who had not experienced any cardiovascular events were evaluated. It was found that DMARDs significantly decreased DAS-28 scores (from 6.0 ± 0.8 to 2.0 ± 0.7) and increased coronary flow reserve (27). In another study, following a 12-week therapy with infliximab, a TNF-α blocker, a significant decrease of DAS-28 scores and lowered ESR and CRP levels were demonstrated (28,29). In our study, the mean DAS-28 score was found to implicate moderate disease activity in the patient group and its correlation with the FRS was not shown to be statistically significant. All of our patients were receiving DMARD therapy and, as the disease activity scores were lower compared to above mentioned studies, its correlation with the FRS was found to be insignificant.

In a study performed by Radovitz et al. (17), the authors investigated whether there was a correlation between DAS-28 results and the occurrence of an MI in the patients who had experienced an MI for the first time after the diagnosis of RA and in the patients who had never experienced an MI. In that study, the patients with RA who had experienced an MI were found to have more classical risk factors, but the 2 groups did not show any significant difference in terms of disease activity.

In another study, blood pressure, arterial thickness, lipids, glucose, ESR, and RF levels were determined and their correlation with HAQ-DI results was investigated in 114 patients with RA, aged between 40 and 65, who had no arterial disease. In that study, a positive correlation was found between arterial thickness and HAQ-DI scores (30). In our study, the mean HAQ-DI score was found to be 0.642 ± 0.705 in the patients with RA and it was not significantly correlated with the FRS.

Although the patients in the RA group had moderate disease activity, their HAQ-DI scores indicated that they were of a good functional status.

In conclusion, we could not find a significant correlation between disease activity and functional disability or CVR in our study. However, the literature contains studies that demonstrated significant correlations in this regard (31–33). To obtain more significant results, long-term prospective studies with a larger sample size are needed.

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