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Silent Coronary Artery Disease in Patients with Rheumatoid Arthritis in Kurdistan, Iraq: A Cross-sectional Study

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ABSTRACT
Objectives: This study attempts to determine the silent coronary artery disease (CAD) in a sample of Iraqi Kurdish patients diagnosed with rheumatoid arthritis (RA).
Methods: A total of 50 such patients from Duhok, Kurdistan region of Iraq, underwent multi slices computed tomography (MSCT) coronary angiography 64 slices to determine coronary artery calcium (CAC) scores and coronary stenoses.
Results: 62% of cases had a (CAC) score > zero on non-contrast MSCT scans. Coronary angiograms showed that 26 (52%) of the cases had variable coronary artery stenosis; 17(34%) of them were obstructive (>50% luminal narrowing). The study demonstrated that Inflammatory markers (rheumatoid factor, Anti-cyclic citrullinated peptides, and some cardiovascular risk factors, namely (hypertension and type 2 diabetes mellitus) were significantly related to the presence of CAD in these patients.
Conclusions: Patients with rheumatoid arthritis are at increased risk of CAD. This risk is higher in the presence of inflammatory and cardiovascular risk factors.
Keywords: Coronary artery disease, arthritis, rheumatoid, coronary vessels

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown aetiology with prominent joint manifestations.[1] Compared to the general population, patients with RA have a reduced life expectancy due to comorbidities such as hypertension and other cardiovascular diseases. Those patients with the established RA have an average of two or more comorbidities.[2-4] The RA cases are known to have a higher prevalence of cardiovascular morbidity and mortality compared to the general population.[5,6]

Cardiovascular diseases, particularly CAD, constitute the leading cause of premature mortality in patients with RA.[7,8] The underlying mechanism of CAD tends to be complex and multifactorial, with the additive association of non-traditional risk factors to atherosclerosis.[9,10] Rheumatoid factor, anti-cyclic citrullinated peptide antibody, long duration of RA, and thrombogenic factors are among the non-traditional risk factors contributing to morbidity and mortality of CAD in RA[9-12]

Given the fact that RA patients are less likely to experience symptoms of CAD and somewhat likely to develop unrecognized events and unforeseen death, the clinical presentation of CAD in such patients is different, apparently earlier, silent, and sudden.[13,14] RA patients were twice as likely to experience sudden death than non-RA subjects.[5,14,15] Despite the incomplete data to fully explain the relationship between RA and CAD, patients with RA increasingly reported a higher atherosclerotic burden and coronary artery calcification. Consequently, atherosclerosis accelerated, and the cardiovascular outcomes worsened.[5,16,17]

The European Alliance of Associations for Rheumatology (EULAR) recommended the prevention, detection, and management of comorbidities associated with RA to improve the long-term outcomes of patients.[18] Such outcomes can be improved by the identification of the new markers for the silent CAD. Hence, this study aimed to assess the presence of silent CAD in patients with RA in Duhok, Iraq.

Material and Methods

Study Design

This cross-sectional study was conducted at the Rheumatology Center and Azadi Heart Center in Duhok, Iraq. A total of 50 patients (47 females and 3 males) aged 18-70 years were involved in the study.

Patients

All cases were already diagnosed with RA according to the American college of rheumatology 2010 criteria for RA. Included patients in this study did not have a prior history of CAD or ischemic stroke. Detailed clinical history and examination of RA cases were taken. Patients were checked for cardiovascular risk factors namely, hypertension, type 2 diabetes mellitus, dyslipidemia, smoking, and family history of CAD. Drug history, including the use of disease-modifying anti-rheumatic drugs and steroids, was also recorded.

Methods and Investigations

Serologic markers, including the rheumatoid factor (RF), antibodies to cyclic citrullinated peptides (Anti-CCP), erythrocyte sedimentation rates (ESR), and C-reactive protein (CRP) were measured. A cardiac assessment was performed by basic resting electrocardiography and echocardiography. Multi-slices CT (MSCT) scan of coronary arteries was performed for the cases according to standard protocols. The degree of coronary artery calcification was calculated based on the method described by Agatston et al.[19]

The sum of the scores for all coronary artery lesions represented the overall Agatston calcium score for each individual was graded as [0 for non, 1 for mild (1–100 HU), 2 for moderate (101–399 HU), 3 for severe (> 400 HU)] coronary artery calcification. Coronary artery stenosis severity was scored from 0–4 based on grades (G0–4) of luminal restriction as following: [grade 0 (G0): normal coronary lumen, grade 1 (G1) represented 1-29% stenosis, G2: 30–49%, G3: 50–69% stenosis, G4: > 70% stenosis]. Lesions rendering > 50% stenosis were considered obstructive.

Inclusion/Exclusion Criteria

All adult patients diagnosed with rheumatoid arthritis were included in the study. Whereas, patients with overlapping rheumatoid arthritis, childhood rheumatoid arthritis, history of coronary artery disease, and patients with incomplete information or missing data were excluded from the study.

Statistical Analysis

Continuous variables were calculated as mean ± (SD), and categorical variables were presented as counts and percentages. A chi-square test was used for the comparison of categorical variables. The continuous variables were assessed by Students *t*-test. A probability value of $P \leq 0.05$ was considered statistically significant. Formal consent was obtained from all the cases orally upon enrollment. The ethical approval of this study was obtained from the Iraqi national board of medical specializations in Baghdad, Iraq.

Results

Clinical Characteristics of Participants

The mean age of patients is 52.78 ± 12.4 years, 47(94%) of them were females. The mean duration of RA was 9.88 years. 26 cases (52%) were early cases of RA (< 5 years duration from diagnosis of disease) and 24 (48%) were established cases (≥ 5 years duration). 18 (36%) out of 50 cases were hypertensive, 12 (24%) were T2DM, and 17 (34%) had dyslipidemia. Only 8 (16%) had a positive family history of CAD. RF was positive in 31 (62%) cases. Erythrocyte sedimentation rate (ESR) and c- reactive protein (CRP) were raised in 33 (66%) and 14 (28%), respectively. The Anti-CCP test was positive in 27 (54%) of patients, as in Table 1.

Patients with hypertension and T2DM had more CAC scores with statistical significance (P = 0.04, 0.009), respectively. Dyslipidemia did not achieve a significant statistical association with CAC (P = 0.06). Patients with the early duration of RA had lower CAC scores compared to those with established RA (P = 0.01). The presence of RF and anti-CCP were significantly related to higher CAC scores (P = 0.009, 0.006), respectively. However, ESR and CRP were found to be statistically non-significant in their association with CAC scores, as seen in Table 2.

The grades of coronary artery stenoses among RA were significantly higher in patients with hypertension and

Table 1. **Characteristics of the study's participants *N* = 50**

Clinical characteristics	No. of patients	Percentage
Age (mean) year	52.78 ± 12.4	–
Female %	47	94%
Early RA	26	52%
Established RA	24	48%
Smoking	12	24%
Hypertension	18	36%
Diabetes Mellitus	12	24%
Dyslipidemia	17	34%
Positive RF	31	62%
ESR >21 mm/1st h	33	66%
CRP > 10	14	28%
Positive Anti-CCP	27	54%

RA: Rheumatoid arthritis; RF: Rheumatoid factor; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; CCP: Cyclic citrullinated peptides.

Table 2 **Coronary Artery Calcium score according to the patient's clinical characteristics**

Variables	0	1–100	101–399	>400	Total	*P* value
Age	48.78 ± 10.02	51.23 ± 7.5	52.7 ± 13.4	58.23 ± 15.6	52.78 + 12.4	0.18
Sex (female)	17(34%)	4(8%)	8(16%)	18(36%)	47(94%)	0.1
Early RA	13(26%)	3(6%)	6(12%)	4(8%)	26(52%)	0.03*
Established RA	7(14%)	1(2%)	3(6%)	13(26%)	24(48%)	0.01*
Hypertension	4(8%)	0	3(6%)	11(22%)	18(36%)	0.04*
T2DM	0	0	4(8%)	8(16%)	12(24%)	0.009*
Dyslipidemia	4(8%)	1(2%)	2(4%)	10(20%)	17(34%)	0.06
Positive Family history of CAD	2(4%)	1(2%)	1(2%)	4(8%)	8(16%)	0.2
Current active smoking	2(4%)	0	1(2%)	1(2%)	4(8%)	0.3
Positive RF	16(32%)	2(4%)	5(10%)	8(16%)	31(62%)	0.009*
Raised ESR	15(30%)	2(4%)	6(12%)	10(20%)	33(66%)	0.06
Positive CRP	4(8%)	2(4%)	1(2%)	7(14%)	14(28%)	0.1
Positive Anti-CCP	6(12%)	2(4%)	6(12%)	13(26%)	27(54%)	0.006*

*P-value ≤ 0.05 is considered statistically significant. RA: rheumatoid arthritis; T2DM: Type 2 diabetes mellitus; RF: Rheumatoid factor; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; CCP: cyclic citrullinated peptides.

Table 3. **Grading of coronary CT-angiography according to patient's clinical characteristics**

Variables	G0	G1	G2	G3	G4	Total	*P*-value
Age (years)	49.16 ± 14.2	49 ± 7.6	57.5 ± 3.4	56.57 ± 5.4	59.4 ± 12.6	52.78 + 12.4	0.07
Sex (female)	23(46%)	5(10%)	4(8%)	5(10%)	10(20%)	47(94%)	0.3
Early RA	16(32%)	3(6%)	3(6%)	2(4%)	2(4%)	26(52%)	0.02*
Established RA	8(16%)	2(4%)	1(2%)	5(10%)	8(16%)	24(48%)	0.003*
Hypertension	5(10%)	2(4%)	2(4%)	3(6%)	6(12%)	18(22%)	0.01*
T2DM	2(4%)	0	2(4%)	2(4%)	6(12%)	12(24%)	0.06
Dyslipidemia	5(10%)	2(4%)	0	4(8%)	6(12%)	17(34%)	0.02*
Positive family history of CAD	3(6%)	0	1(2%)	1(2%)	3(6%)	8(%16)	0.2
Current active smoking	2(4%)	0	1(2%)	1(2%)	0	4(8%)	0.4
Positive RF	19(38%)	3(6%)	1(2%)	3(6%)	5(10%)	31(62%)	0.08
Raised ESR	17(34%)	2(4%)	2(4%)	5(10%)	5(10%)	33(66%)	0.2
Positive CRP	5(10%)	2(4%)	0	1(2%)	6(12%)	14(28%)	0.1
Positive anti-CCP	9(18%)	5(10%)	1(2%)	5(10%)	7(14%)	27(54%)	0.01*

*P-value ≤ 0.05 is considered statistically significant. RA: rheumatoid arthritis; T2DM: Type 2 diabetes mellitus; RF: Rheumatoid factor; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; CCP: cyclic citrullinated peptides.

dyslipidemia with (P = 0.01, 0.02), respectively. Among T2DM, such grades were also high but didn't reach a significant level (P = 0.06). The cases with established RA and those with anti-CCP were significantly had higher coronary stenoses, as shown in Table 3.

Discussion

The excess mortality associated with RA is mainly due to cardiovascular diseases, particularly CAD.[5,16-18] Recent observational studies suggested that the hidden CAD risk in RA is not related only to traditional atherosclerosis risk factors.[10,20] Given the importance of chronic inflammation in atherogenesis, the presence of RA only may be of primary importance in terms of cardiovascular comorbidities and burden.

This cross-sectional study was conducted in patients with RA lacking a prior history of CAD or ischemic stroke to assess the relationship between silent coronary artery disease and RA. Its main findings were as follows; 31 (62%) of them had a coronary artery calcium score > zero on non-contrast MSCT, and 26 (52%) cases had a variable coronary luminal lesion on MSCT angiograms. The mechanism underlying the observed increase in CAC in RA is likely complex and multifactorial. Following an inflammatory event, interleukin-6 induce the production of acute phase reactant (CRP), which is a key marker of systemic inflammation in RA and has a direct role in the development and progression of atherosclerosis.[21] In multiple population-based studies,[20,22-25] individuals with the highest concentrations of circulating inflammatory markers were at the greatest risk of cardiovascular events and mortality and tended to demonstrate an increased burden of subclinical atherosclerosis like MSCT-measured CAC burden.[25]

Recent reports suggest that the mechanism and management of cardiovascular risk in RA are challenging. Apart from the fact that several risk factors are involved in this mechanism, the presenting features of CAD might be silent and differ from those in the general population. RA patients may experience cardiovascular events in the presence of minimal atherosclerosis. Maradit-Kremers et al.[16] reported an increased risk for CAD among RA patients not only from the disease onset but even before meeting the criteria of the American college of rheumatology for RA. Nevertheless, in early RA, the extent of coronary atherosclerosis is not increased.[26]

The RA patients reportedly experienced sustained unrecognized myocardial infarction and faced sudden death more often than non-RA subjects.[16,25,26] The frequencies of multi-vessel coronary disease, recurrent ischemic events, and death after an acute coronary syndrome are increased in RA.[27] The CAC obtained by MSCT in RA might improve the prediction of cardiac events among RA. The MSCT evaluates the severity of stenosis and the burden of the coronary plaques, thus improving the predictive value of CAC for future events.[27-29]

Regarding traditional risk factors for CAD, hypertension and T2DM were significantly correlated with CAC. Among the non-traditional risk factors assessed in this study, 62% of the patients were RF positive, and 54% had a positive anti-CCP. The anti-CCP autoantibodies and RF autoantibodies have a synergistic effect in mediating RA-associated inflammation and disease activity, and their presence was associated with a higher rate of CAC and CAD in patients with RA.[30-32]

Choi and colleagues demonstrated in their study that methotrexate-treated patients had a 70% reduction in cardiac events compared with those not receiving the same therapy regularly.[33] Other disease-modifying drugs such as sulfasalazine, penicillamine, hydroxychloroquine, and gold did not confer this protection. Thus, the RA disease process itself likely contributes to accelerated CAD.[31,33]

Limitations of this study include the relatively small sample size, dominance of female cases and disease activity by DAS 28-ESR and DAS 28-CRP were not measured. Its strengths lie in the screening design of silent CAD in the RA, the use of MSCT-coronary angiography modality, and the novelty of the study at the national and Middle East levels.

Conclusion

This study concludes that RA patients remain at increased risk of CAD even regardless of traditional cardiovascular risk

factors. MSCT coronary angiography is a good option for the evaluation and screening of RA patients at risk of silent CAD. The awareness of silent CAD among patients with RA and their doctors is of paramount importance for the initiation of lifestyle changes and necessary medication to decrease the progression of coronary atherosclerosis early in the disease course. Further studies are indicated to thoroughly understand the mechanisms of increased atherogenesis in RA.

List of Abbreviations

Anti-CCP: Antibodies to cyclic citrullinated peptides; CAC: Coronary artery calcium; CAD: Coronary artery disease; CRP: C-reactive protein; DAS 28: Disease activity score-28; ESR: Erythrocyte sedimentation rates; EULAR: European Alliance of Associations for Rheumatology; MSCT: Multi-slices computed tomography; RA: Rheumatoid arthritis; RF: Rheumatoid factor; T2DM: Type 2 Diabetes Mellitus.

Ethics Approval

The Iraqi national board of medical specializations in Baghdad, Iraq approved the study protocol.

Informed Consent

Informed consent was obtained from all the cases upon enrollment.

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Conflict of Interests

The authors declare that they have no conflict of interest.

Sources of Funding

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Data Availability

The data sets used in this study are available from the corresponding author upon request.

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