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Original article

Anti-CCP antibody in patients with established rheumatoid arthritis: Does it predict adverse cardiovascular profile?

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ABSTRACT

Background: Rheumatoid arthritis (RA) is an independent risk factor for adverse cardiovascular (CV) events that accounts for a significant proportion of mortality among these patients. Anti-CCP antibodies are associated with higher frequency of extra-articular manifestations and poorer outcomes in RA.
Aims: To determine the role of anti-cyclic citrullinated peptide (CCP) antibody as an independent risk factor for developing CV complications as documented by carotid intima medial thickness and abnormal echocardiography in established RA patients.
Materials and methods: Eighty patients of RA having disease duration of at least 3 years participated in this hospital-based, cross-sectional, and observational study. Forty patients were anti-CCP antibody positive. Patients of established RA having known CV risk factors, known heart disease, or family history of premature ischemic heart disease were excluded.
Results: Anti-CCP positive group had early morning stiffness, tender and swollen joint count, and c-reactive protein (CRP) level significantly higher than those in anti-CCP negative group. Average intima-medial thicknesses of common carotid arteries were also significantly higher among anti-CCP positive group ($P = 0.029$) and were positively correlated with patients' age and disease duration. Lower left ventricular ejection fraction and left ventricular diastolic dysfunction were more commonly dispersed among the anti-CCP positive patients with P values of 0.01 and 0.034, respectively. Mild pericardial thickening was documented among 12.5% patients of anti-CCP positive group, while none of the anti-CCP negative patients had similar findings in echocardiography.
Conclusion: This study stressed on the important role of anti-CCP antibody in myocardial dysfunction due to inflammation in RA patients. Both atherosclerotic vascular involvement and cardiac abnormalities including pericardial, myocardial, and endocardial involvements were higher among anti-CCP positive RA patients. Hence, patients with high titer of anti-CCP antibody associated with prolonged disease duration and increased disease activity should be evaluated for CV morbidity more meticulously.

1. Introduction

Rheumatoid arthritis (RA) is an independent risk factor for cardiovascular (CV) events such as ischemic heart disease or congestive cardiac failure,[1] which causes up to 40% of deaths in these patients.[2] In RA patients, severe extra-articular manifestations are associated with higher risk of development of CV complications.[3] Traditional and nontraditional CV risk factors have yet not been reported to contribute to the development of their CV morbidity.[4] Inflammatory activity is important for the development of CV diseases in RA, even after the adjustment for traditional CV risk factors.[5] The consistent association of carotid intima-medial thickness (IMT) with inflammatory markers supports the evidence that CV outcome in RA patients is associated with inflammation. Anti-cyclic citrullinated peptide (CCP) antibodies (one of the antibodies used to detect anti-citrullinated peptide antibodies, ACPA) are potentially important surrogate marker for diagnosis and prognosis in RA. It is an independent predictor of radiological

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damage and progression in patients suffering from RA.[6] Anti-CCP antibody is also found to be associated with numerous extra-articular manifestations in RA.[7] The present study was aimed to evaluate the association between anti-CCP antibody and atherosclerotic changes as well as CV manifestations in established RA patients.

2. Materials and methods

This was a hospital-based, cross-sectional, and observational study. Study population included RA patients, based on 1988 – Revised American Rheumatism Association Criteria for Classification of Rheumatoid Arthritis, having a disease duration of at least 3 years since diagnosis, aged 20–55 years, attending rheumatology outpatient department (OPD) of a tertiary care hospital. Patients having diabetes (fasting blood sugar ≥126 mg/dl or random blood sugar ≥200 mg/dl plus symptoms of diabetes or post-prandial blood sugar ≥200 mg/dl), hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or on anti-hypertensive medication), body mass index ≥25 kg/m^2, history of heart disease, renal compromise, smoking, or family history of premature atherosclerosis in 1st degree relative were excluded. Informed consent was taken in all cases. Relevant Institutional Ethical Committee clearance was obtained before commencing the study.

Sample population was divided into two groups:

Group I – Patients of rheumatoid arthritis (RA) with anti-CCP antibody positive status and
Group II – RA patients with anti-CCP antibody negative status

Patients were included in the study by strict adherence to the inclusion and exclusion criteria. On an average, the number of newly established RA patients of >3 years of disease duration in our clinic was observed as 3 per week. We proposed to include two of them in the study. Therefore, to complete the recruitment in 1 year and also keeping in mind that anti-CCP negative patients are fewer in number, we arbitrarily fixed the sample size as 80. Consecutive consenting participants were chosen for both the groups. When the desired sample size was reached, further inclusion in the respective group was stopped. A total of 80 patients were incorporated, divided equally into study (Group 1) and control (Group 2) arm on account of anti-CCP positivity.

Information regarding age, sex, smoking status, body mass index, family history, menstrual history, history of additional/other associated disease, and history of oral contraceptive pill (OCP) intake were obtained in all the cases. The cases then underwent thorough general and systemic examination. Disease activity score (DAS) for measurement of disease activity; multi-dimensional health assessment questionnaire (HAQ), and visual analog scale (VAS) for pain (VAS-Pain) for assessment of functional status were documented in all cases.

Anti-CCP antibodies were measured by second generation enzyme-linked immunosorbent assay (ELISA) test i.e., CCP-2 test [AESKULISA RA/CP-Detect, solid phase enzyme immunoassay for the quantitative and qualitative detection of human immunoglobulin G (IgG) antibodies to specific synthetic citrullinated peptides of IgG in human serum] with a cut-off of 15 U/ml. Rheumatoid factor (RF) was estimated by using ELISA. All the investigations were performed in the hospital laboratory. There were no missing data as every participant underwent clinical examination and investigations on the same day. Reports of investigations were collected by the author only.

Intima-media thickness (IMT) of the carotid artery bifurcation was measured with Ultrasonogram Doppler using a 7.5 MHz linear transducer in *hp Agilant* machine (Netherlands). Transthoracic echocardiographic examination was performed with two-dimensional, M-mode, and pulsed wave Doppler measurement using Vivid-7 machine by the same observer.

Following values of DAS were taken as reference; high >5.1, low <3.2, and remission <2.6. The HAQ or modified HAQ (mHAQ)[8] are patient self-reported functional questionnaire. It correlates significantly with disease activity. The PROMIS HAQ developed by Stanford University, USA was used in the study, downloaded from URL: http://aramis.stanford.edu/. The questions were slightly modified with respect to Indian lifestyle context. A score of 0–100 was obtained. VAS for Global Health assessment by patient (VAS-GH patient) and VAS for Global Health assessment by physician (VAS-GH physician) are validated measure of quality of life. A 15-cm, double-anchored horizontal VAS that starts at 0 (very well) to 100 (very poor) was used in the study.

In this study, categorical variables are expressed as the number of patients and compared across groups using Chi-square test for independence of attributes. Continuous variables have been expressed as mean ± standard deviation as compared across the two groups using unpaired *t*-test. Spearman's correlation coefficient has been used to capture the extent of association between continuous variables. The statistical software SPSS version 16 has been used for the analysis. $P < 0.05$ has been considered as significant.

3. Results

Female patients constituted 90% ($n = 72$) of the study population. Mean age of the anti-CCP antibody positive RA group was 39 ± 10.6 years with a mean disease duration of 6.24 ± 3.76 years. While the anti-CCP test negative RA group had a mean age of 41.35 ± 8.24 years with a mean disease duration of 4.18 ± 2.05 years. Anti-CCP antibody positive population appeared to have statistically significant increased disease duration ($P = 0.003$) and early morning stiffness ($P = 0.004$) as compared to anti-CCP negative population. Both the groups were matched for baseline variables [Table 1]. Anti-CCP positive group had relatively increased disease activity, having increased tender joint count ($P < 0.001$), swollen joint count ($P = 0.002$), erythrocyte sedimentation rate

Table 1
Demographic and clinical data of anti-CCP positive and negative RA patients.

Parameter	Anti-CCP positive RA ($n = 40$)	Anti-CCP negative RA ($n = 40$)	*P* value
Female patients	34 (85%)	38 (95%)	0.136
Age (years)	39 ± 10.6	41.35 ± 8.24	0.272
Disease duration (years)	6.24 ± 3.76	4.18 ± 2.05	**0.003***
Early morning stiffness (h)	1.18 ± 0.98	0.60 ± 0.72	**0.004***
Menstrual history (Normal/Menopause)	21/13	20/18	0.243
OCP use	5 (12.5%)	0 (0%)	**0.021***
Deformity (yes/no)	7 (17.5)	2 (5%)	0.077
BMI (Kg/m^2)	21.27 ± 2.35	22.74 ± 2.28	**0.06**
Body surface area (m^2)	1.47 ± 0.14	1.47 ± 0.12	0.886
Systolic BP (mm of Hg)	127.65 ± 7.21	128.3 ± 6.21	0.667
Diastolic BP (mm of Hg)	79.3 ± 4.97	78.95 ± 5.24	0.760
Steroid use (years)	0.51 ± 0.76	2.4 ± 1.59	**<0.001***
Methotrexate use (years)	1.05 ± 1.76	2.13 ± 1.68	**0.006***
Sulphasalazine use (years)	1.02 ± 1.77	1.6 ± 1.59	0.128
Hydroxychloroquin use (years)	0.7 ± 1.01	0.2 ± 0.52	**0.007***
Leflunamide use (years)	0.03 ± 0.16	0.00 ± 0.00	0.226
Tender joint count	12.38 ± 7.07	5.45 ± 5.79	**<0.001***
Swollen joint count	8.73 ± 6.72	4.3 ± 5.25	**0.002***

*P value was statistically significant. Anti-CCP – Anti-cyclic citrullinated peptide; RA – Rheumatoid arthritis; OCP – Oral contraceptive pill; BMI – Body mass index; BP – Blood pressure.

(ESR; $P = 0.007$), c-reactive protein (CRP; $P < 0.001$) as well as significant joint space reduction, erosion, peri-articular osteopenia in hand X-ray as compared to the anti-CCP negative group [Table 2]. Interestingly, anti-CCP negative group was found to have increased duration of steroid (2.4 ± 1.59 years vs. 0.51 ± 0.76 years) and methotrexate use (2.13 ± 1.68 years vs. 1.05 ± 1.76 years) that were statistically significant.

All the RA patients were subjected to carotid artery Doppler test that revealed that anti-CCP antibody positive group had a significantly increased common carotid artery average IMT (0.65 ± 0.102 mm vs. 0.59 ± 0.130 mm with $P = 0.029$) as compared to the anti-CCP negative group. But none of the examined patients had any evidence of carotid plaque. Table 3 shows the carotid artery IMT parameters in both the groups.

Resting electrocardiograph (ECG) was almost normal except for sinus tachycardia in a single patient. All the participants were subjected to transthoracic echocardiography with special emphasis on assessment of diastolic dysfunction, pericardial pathology, and valve involvement. Table 4 shows the ECG parameters in both the groups. Cusp opening appeared to be greater in anti-CCP negative population (17.30 ± 3.34 mm vs. 15.38 ± 2.66 mm). Interventricular septal thickness was significantly greater among anti-CCP positive group (10.05 ± 2.10 mm) as compared to anti-CCP negative group (8.73 ± 1.22 mm with $P = 0.001$). Ejection fraction (EF) also appeared to be diminished in anti-CCP positive population (64.55 ± 12.01 mm vs. 69.73 ± 3.22 mm with $P = 0.01$). Left atrial diameter, aortic root diameter, left ventricular (LV) posterior wall thickness, and LV internal diameter during systole and diastole were not significantly different in the two groups. Both LV mass and LV mass corrected for body surface area (LVMI) were significantly increased in anti-CCP positive group. For LV mass P value was 0.003 and for LV mass index P value was 0.002. Assessment of transmitral flow parameters yielded a significantly low E velocity (84.95 ± 16.88 cm/s vs. 96.68 ± 15.68 cm/s) with P value of 0.002. But there was no significant difference in the velocity among the two groups. E/A ratio was 1.33 ± 0.40 in anti-CCP positive group and 1.57 ± 0.29 in the anti-CCP negative group with $P = 0.002$, hence, it was significantly reduced. E/A ratio of <1 was present in 10 anti-CCP positive patients (i.e., 25%) as compared to 3 patients in anti-CCP negative group (7.5%), and this difference was statistically significant. Isovolumetric relaxation time (IVRT) was significantly increased among anti-CCP positive population (83.93 ± 18.25 vs., 74.25 ± 17.45, $P = 0.018$). Considering the values of E/A, MV Dec. Time and IVRT, we found diastolic dysfunction among 10 anti-CCP positive (25%) and 3 anti-CCP negative patients (7.5%), this difference was statistically significant with $P = 0.034$. Thus, anti-CCP positive patients had significantly more diastolic dysfunction than anti-CCP negative patients.

Mild pericardial effusion was found in 4 anti-CCP positive and in 1 anti-CCP negative patient. Mild pericardial thickening was present in 5 anti-CCP positive patients, but no such thickening was found in any of the anti-CCP negative patients; this difference was significant with $P = 0.021$. Among the valvular pathology, trivial mitral regurgitation was found in 6 anti-CCP positive patients and 1 anti-CCP negative patient; this difference was statistically significant. No other valvular abnormality could be detected.

Disease activity, as assessed by DAS-28 ESR score, was significantly more among anti-CCP positive group ($P < 0.001$). Regarding the assessment of quality of life, both VAS pt GA and VAS ph GA were significantly more among anti-CCP positive group (P values being 0.010 and 0.008, respectively). Table 5 shows the parameters.

Table 2
Imaging and laboratory data in anti-CCP positive and anti-CCP negative RA patients.

Parameter	Anti-CCP positive RA ($n = 40$)	Anti-CCP negative RA ($n = 40$)	P value
HXR-JSR	6 (15%)	0 (0%)	**0.011***
HXR-E	8 (20%)	0 (0%)	**0.003***
HXR-PO	10 (25%)	0 (0%)	**0.001***
HXR-D	4 (10%)	2 (5%)	0.336
ESR (1st h)	59.55 ± 32.99	41.18 ± 25.95	**0.007***
CRP (mg/dl)	21.23 ± 17.06	6.83 ± 7.42	**<0.001***
FBS (mg/dl)	83.35 ± 7.93	80.37 ± 8.05	0.100
PPBS (mg/dl)	121.25 ± 10.004	110.9 ± 13.34	**<0.001***
Total Cholesterol (mg/dl)	150.82 ± 19.47	157.3 ± 13.7	0.089
Triglyceride (mg/dl)	123.07 ± 27.31	115.27 ± 25.91	0.194
LDL (mg/dl)	83.45 ± 17.3	90.8 ± 9.56	**0.022***
HDL (mg/dl)	41.92 ± 7.80	44.37 ± 7.95	0.168
VLDL (mg/dl)	24.6 ± 5.46	23.01 ± 5.18	0.187
Rheumatoid factor reactive	37 (92.5%)	16 (40%)	**<0.001***

*P value was statistically significant. HXR-JSR – Hand X-ray-Joint space reduction; HXR-E – Hand X-ray–erosion; HXR-PO – Hand X-ray-peri-articular osteopenia; HXR-D – Hand X-ray-deformity; ESR – Erythrocyte sedimentation rate; CRP – C-reactive protein; FBS – Fasting blood sugar; PPBS – Post-prandial blood sugar; LDL – Low density lipoprotein; HDL – High density lipoprotein; VLDL – Very low density lipoprotein.

Table 3
Carotid artery Doppler study and ECG data in anti-CCP positive and anti-CCP negative rheumatoid arthritis patients.

Parameter	Anti-CCP positive RA ($n = 40$)	Anti-CCP negative RA ($n = 40$)	P value
ECG (Resting) abnormality	1 (2.5%)	0 (0%)	0.314
RCC-IMT (mm)	0.83 ± 1.16	0.59 ± 0.13	0.199
LCC-IMT (mm)	0.65 ± 0.112	0.60 ± 0.134	0.07
CC-IMT average (mm)	0.65 ± 0.102	0.59 ± 0.130	**0.029***

*P value statistically significant. ECG – Electrocardiograph; RCC-IMT–Right carotid intima-medial thickness; LCC-IMT – Left carotid intima-medial thickness; CC-IMT – Carotid intima-medial thickness.

Table 4
Echo-Doppler measurement in anti-CCP positive and anti-CCP negative RA patients.

Echo-Doppler parameter	Anti-CCP positive RA ($n = 40$)	Anti-CCP negative RA ($n = 40$)	P value
LAD (mm)	27.55 ± 6.44	28.93 ± 4.01	0.255
Aortic root diameter (mm)	23.05 ± 5.4	24.95 ± 4.18	0.082
Cusp opening (mm)	15.38 ± 2.66	17.30 ± 3.34	**0.006***
RVID (mm)	15.13 ± 3.41	15.00 ± 2.55	0.85
IVSD (mm)	10.05 ± 2.10	8.73 ± 1.22	**0.001***
LVPW (mm)	10.05 ± 1.60	9.5 ± 0.93	0.064
LVIDD (mm)	41.60 ± 3.59	40.83 ± 3.38	0.323
LVIDS (mm)	26.25 ± 4.83	24.78 ± 2.53	0.091
LVEF %	64.55 ± 12.01	69.73 ± 3.22	**0.01***
MV E velocity (cm/s)	84.95 ± 16.88	96.68 ± 15.68	**0.002***
MV A velocity (cm/s)	67.25 ± 14.14	62.63 ± 11.07	0.107
E/A ratio	1.33 ± 0.40	1.57 ± 0.29	**0.002***
E/A ratio <1	10 (25%)	3 (7.5%)	**0.034***
MV Dec Time (ms)	211.3 ± 29.51	197.13 ± 24.72	**0.022***
LVM (g)	1.39 ± 4.45	1.16 ± 2.02	**0.003***
LVMI (g/m^2)	9.51 ± 3.01	7.86 ± 1.20	**0.002***
IVRT (ms)	83.93 ± 18.25	74.25 ± 17.45	**0.018***
Diastolic dysfunction	10 (25%)	3 (7.5%)	**0.034***
Pericardial effusion	4 (10%)	1 (2.5%)	0.166
Pericardial thickening	5 (12.5%)	0 (0%)	**0.021***
MR	6 (15%)	1 (2.5%)	**0.048***

*P value statistically significant. LAD – Left atrial diameter; RVID – Right ventricular internal diameter; IVSD – Interventricular septal diameter; LVPW – Left ventricular posterior wall; LVIDD – Left ventricular internal diameter in diastole; LVIDS – Left ventricular internal diameter in systole; LVEF % – Left ventricular ejection fraction; MV E velocity – Mitral valve E velocity; MV A velocity – Mitral valve A velocity; MV Dec Time – Mitral valve deceleration time; LVM – Left ventricular mass; LVMI – Left ventricular mass indexed to body surface area; IVRT – Isovolumetric relaxation time; MR – Mitral regurgitation.

Table 5
Disease activity among anti-CCP positive and anti-CCP negative RA patients.

Parameter	Anti-CCP positive RA ($n = 40$)	Anti-CCP negative RA ($n = 40$)	*P* value
DAS-28	5.95 ± 1.43	4.56 ± 1.46	**<0.001***
VAS Pt GA	48.5 ± 16.26	38.5 ± 17.77	**0.010***
VAS Ph GA	43.75 ± 14.62	33.5 ± 18.89	**0.008***

**P* value is statistically significant. DAS-28 – Disease activity score-28; VAS Pt GA – Visual Analog Scale for Global Health assessment by patient; VAS Ph GA – Visual Analog Scale for Global Health assessment by physician.

Co-relation coefficient among demographic, inflammatory, and disease activity parameters and carotid IMT and ECG variables were assessed [Table 6]. Age showed a positive co-relation with left common carotid IMT and average IMT of carotid arteries. Disease duration was positively co-related with average IMT of carotid arteries and MV Dec. Time, and it was negatively co-related with *E*/*A* ratio. There was a negative co-relation between anti-CCP antibody titer and *E*/*A* ratio. ESR appeared to have a negative co-relation with *E*/*A* ratio and EF, but a positive co-relation with LVMI. CRP was negatively co-related with EF. DAS-28 ESR value had a negative co-relation with EF. IVRT could not be co-related with any of the parameters.

4. Discussion

In RA patients, anti-CCP antibodies are associated with greater inflammatory activity, poorer radiologic outcome, and higher frequency of extra-articular manifestations. The anti-CCP response may also be involved in the pathogenesis of RA because of both the presence of antibodies directed against citrullinated proteins in the target tissue and the association between anti-CCP antibodies and severe RA.[3,9]

In RA patients, CV disease has not been associated with traditional CV risk factors such as smoking, hypertension, diabetes mellitus, being overweight, and dyslipidemia.[1] The lack of association among the traditional CV risk factors and CV disease suggests the presence of alternate mechanisms or, more likely, additive mechanisms[4] such as chronic inflammation, RF status. In our patients, anti-CCP antibodies were associated with high ESR and positive RF.

Subclinical vascular disease may be linked to the presence of anti-CCP antibodies,[10] and the presence of circulating anti-CCP antibodies has recently been associated with stronger evidence of subclinical atherosclerosis in RA patients.[11] They are also independently associated with the development of ischemic heart disease.[12] In our study, the significantly increased average IMT of carotid arteries among anti-CCP positive individuals as compared to the age, sex-matched anti-CCP negative RA population. Although few studies have documented increased carotid IMT among RA patients as compared to the non-RA population,[13,14] there are not many studies that could document this feature among anti-CCP positive RA patients as compared to the anti-CCP negative RA patients. All the participants had normal lipid profile, and other CV risk factors were also absent; this could account for the absence of carotid plaque in any of our study population.

During transthoracic echocardiography pericardial, myocardial, and endocardial involvement was sought. We found significant diastolic dysfunction in the form of E/A ratio <1, prolongation of MV Dec. Time, and IVRT prolongation among anti-CCP positive group as compared to the anti-CCP negative group. Although systolic function was preserved in both the groups, the EF was lower among anti-CCP positive patients as compared to the anti-CCP negative group. Trivial mitral regurgitation (MR) and mild pericardial thickening were found among anti-CCP positive patients, that were significantly higher as compared to that in the anti-CCP negative group. In our study, diastolic dysfunction was studied by Doppler echocardiography, which yielded significant negative correlation between anti-CCP antibody and *E*/*A* ratio. The negative correlation of *E*/*A* with anti-CCP antibody level, obtained by Spearman's correlation test, suggests that anti-CCP antibody might be an indicator of initial myocardial damage in active RA. Anti-CCP antibody may be independently associated with impaired LV relaxation.[15] According to our knowledge, the role of the anti-CCP antibodies in cardiac involvement requires in-depth research. These antibodies share some similarities with anti-vimentin and anti-fibronectin antibodies, which are considered to be responsible for inflammatory myocarditis and cardiac transplant rejection in animals.[16] Citrullination of the peptides is present in several inflammatory tissues. It was also detected on the skeletal muscle in autoimmune arthritis.[17] However, data on citrullination in RA myocardium or the possible activity of the anti-CCP antibodies against it are still lacking. If these antibodies are destructive to the synovial process, it could only be speculated that they may exert similar action on the myocardial tissue as well. The possible role of anti-CCP antibodies in the pathogenesis of impaired cardiac relaxation was beyond the scope of the present study design, as the aim was to identify which of the parameters easily obtained in daily routine is most suitable to predict cardiac involvement in RA.

We found preserved LV systolic function among our RA patients of both the groups, that was consistent with the observation of

Table 6
Co-relation coefficient between demographic, inflammatory and disease activity parameters and carotid Doppler and echocardiography variables (Spearman's correlation test).

Parameters		RCC-IMT	LCC-IMT	CC-IMT avg	E/A	MV Dec time	IVRT	EF%	LVMI
Age (years)	Correlation coefficient	0.078	0.430	0.421	−0.158	0.193	0.148	0.127	−0.114
	P value	0.493	**0.000***	**0.000***	0.161	0.086	0.191	0.261	0.316
Disease duration	Correlation coefficient	0.003	0.203	0.266	−0.374	0.299	0.118	0.120	0.114
	P value	0.977	0.072	**0.017***	**0.001***	**0.007***	0.298	0.288	0.315
ESR	Correlation coefficient	−0.095	0.136	0.121	−0.313	0.197	−0.095	−0.316	0.284
	P value	0.404	0.229	0.286	**0.005***	0.080	0.404	**0.004***	**0.011***
CRP	Correlation coefficient	−0.022	0.059	0.058	−0.217	0.201	0.074	−0.228	0.043
	P value	0.846	0.606	0.611	0.053	0.074	0.515	**0.042***	0.703
Anti-CCP	Correlation coefficient	0.070	0.161	0.162	−0.247	0.130	0.112	−0.128	0.115
	P value	0.536	0.154	0.151	**0.027***	0.251	0.321	0.257	0.311
DAS-28	Correlation coefficient	0.037	0.184	0.168	−0.215	−0.048	−0.021	−0.261	0.131
	P value	0.743	0.103	0.137	0.055	0.674	0.857	**0.020***	0.246

**P* value statistically significant. RCC-IMT – Right carotid intima-medial thickness; LCC-IMT – Left carotid intima-medial thickness; CC-IMT – Carotid intima-medial thickness; E/A velocity – Mitral valve E velocity/mitral valve A velocity; MV Dec Time – Mitral valve deceleration time; IVRT – Isovolumetric relaxation time; EF % – Left ventricular ejection fraction; LVMI – Left ventricular mass indexed to body surface area; ESR – Erythrocyte sedimentation rate; CRP – C-reactive protein; DAS-28 – Disease activity score-28.

Alpaslan et al.[18] Few studies have observed significant difference in *E*/*A* ratio and MV Dec. Time between RA patient and the control group.[19,20] We found that this observation is true even when anti-CCP positive RA patient are being compared with anti-CCP negative RA patients. In contrast to the observation of Wislowska et al,[21] we found no correlation between *E*/*A* ratio and the patient's age, but there was significant negative correlation with disease duration and ESR level. Higher average IMT of carotid arteries was found to be positively correlated with patient's age and disease duration, an observation substantiated by many previous studies.[22,23]

5. Conclusion

From our study, it was concluded that both atherosclerotic vascular involvement and cardiac abnormalities including pericardial involvement in the form of pericardial thickening and effusion, myocardial involvement in the form of lower LV EF, LV diastolic dysfunction, and endocardial involvement in the form of valvular regurgitation were relatively higher among anti-CCP positive patients than in anti-CCP negative established RA patients. Age and disease duration were also closely associated with these adverse CV outcomes. Hence, we propose that all RA patients with high titer of anti-CCP antibody associated with prolonged disease duration and increased disease activity should be routinely evaluated with carotid artery Doppler study and a thorough echocardiography to assess their CV status.

6. Limitations

One limitation of the study was the relatively small numbers of patients recruited in a single center. The patients with the anti-CCP positive group had prolonged disease duration and more severe disease (DAS-28 suggestive of severe disease as compared to moderate disease activity in anti-CCP negative group). Prolonged uncontrolled RA itself is an independent risk factor for atherosclerosis, which may affect the CV profile of the patients. The patients in anti-CCP positive group received lesser steroids and disease modifying drugs and this might have resulted in poor control of disease activity, which again would be an independent risk factor for atherosclerosis. These factors may be taken care of in a multicenter prospective study looking for adverse CV outcomes incorporating larger patient population.

Conflicts of interest

All authors have none to declare.

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