MAK HILL Publications Research Journal of Medical Sciences

Research Article
doi: 10.59218/makrjms.2023.10.72.77

Correlation Between Anti-CCP Levels and Carotid Intima Media Thickness in Rheumatoid Arthritis: A Cross-sectional Observational Study

[1]Akhila Bhandarkar, [2]Rajnish Singh, [3]Anoosha Bhandarkar, [4]Nandini Duggal, [5]Akhilandeshwari Prasad, [6]Pranav Mallya and [7]Sughosh Kulkarni

[1]Department of Endocrinology, K S Hegde Medical Academy, Nitte University, Deralakatte, Mangalore Karnataka, India
[2]Department of General Medicine, ABVIMS and Dr Ram Manohar Lohia Hospital, New Delhi, India
[3]Department of Pharmacology, SDM College of Medical Sciences and Hospital, Shri Dharmasthala Manjunatheshwara (SDM) University, Dharwad, India
[4]Department of Microbiology, ABVIMS and Dr Ram Manohar Lohia Hospital, New Delhi, India
[5]Department of Radiology, ABVIMS and Dr Ram Manohar Lohia Hospital, New Delhi, India
[6]Department of Radiology, Aster Medcity, Kochi, Kerala, India
[7]Department of Microbiology, SDM College of Medical Sciences and Hospital Shri Dharmasthala Manjunatheshwara (SDM) University Dharwad-580009, India

ABSTRACT

Rheumatoid Arthritis (RA), a chronic inflammatory joint disorder, is marked by increased morbidity and mortality, largely attributed to cardiovascular disease (CVD). Despite advancements, the underlying mechanisms driving heightened CVD risk in RA remain incompletely elucidated, with chronic inflammation emerging as a key contributor. Recently, attention has turned to biomarkers such as Anti-cyclic citrullinated peptide (Anti-CCP), linked not only to RA disease activity but also to endothelial dysfunction. To address this knowledge gap, we conducted a cross-sectional observational study to investigate the relationship between anti-CCP levels and carotid intima-media thickness (CIMT), a surrogate measure of subclinical atherosclerosis, in RA patients. In this cross-sectional observational study, we enrolled 79 consecutive Anti-CCP positive RA patients, assessing their clinical and disease characteristics and cardiovascular risk factors and conducting carotid artery Doppler assessments for CIMT. Serum anti-CCP levels were measured using ELISA. Notably, patients exhibiting abnormal CIMT (>0.6mm) displayed higher Disease Activity Score 28 (DAS 28) scores (mean 4.44±0.63) compared to those with normal CIMT (≤0.6mm; mean DAS 28 score 3.45±0.81), linking increased disease activity to CIMT changes. Significantly elevated Anti-CCP levels were observed in patients with abnormal CIMT (mean 290.45±22.74 U mL^{-1}) compared to those with normal CIMT (mean 111.72±92.63 U mL^{-1}; p = 0.0004). Univariate regression analysis identified several factors linked to CIMT, including anti-CCP (p = 0.0004), LDL cholesterol (p = 0.026), DAS 28 score (p = 0.0002) and erythrocyte sedimentation rate (ESR) (p = 0.001). Importantly, anti-CCP maintained a robust, independent association with CIMT in multivariate regression analysis (r^2 = 0.812, p = 0.007). Our study establishes a compelling, direct correlation between anti-CCP levels and CIMT in RA patients. Even after accounting for potential confounders, the association remains pronounced. This underscores the potential utility of anti-CCP as a predictive tool for CVD risk in RA patients.

OPEN ACCESS

Key Words
Rheumatoid arthritis, cardiovascular disease, anti-CCP levels, carotid intima-media thickness

Corresponding Author
Sughosh Kulkarni,
Department of Microbiology, SDM College of Medical Sciences and Hospital, Shri Dharmasthala Manjunatheshwara (SDM) University, Dharwad-580009, India
dr.sughosh86@gmail.com

Author Designation
[1]Consultant Endocrinologist
[2,5]Professor
[3,7]Assistant Professor
[4]Professor and Head
[6]Consultant Radiologist

Received: 22 September 2023
Accepted: 7 October 2023
Published: 8 October 2023

Citation: Akhila Bhandarkar, Rajnish Singh, Anoosha Bhandarkar, Nandini Duggal, Akhilandeshwari Prasad, Pranav Mallya and Sughosh Kulkarni, 2023. Correlation Between Anti-CCP Levels and Carotid Intima Media Thickness in Rheumatoid Arthritis: A Cross-sectional Observational Study. Res. J. Med. Sci., 17: 72-77, doi: 10.59218/makrjms.2023. 10.72.77

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology that manifests as symmetric peripheral polyarthritis. It is the most common form of chronic inflammatory arthritis, affecting approximately 0.5-1% of the adult population worldwide and often leads to stiffness, joint destruction and long-term physical disabilities[1]. RA though most commonly presents with joint pain and deformities; is a systemic disease marked by a variety of extra-articular manifestations[2-4]. The incidence of carotid atherosclerosis and coronary artery disease is higher in patients with RA than in the general population, irrespective of the presence or absence of traditional cardiac risk factors such as hypertension, diabetes, obesity and smoking. Patients with RA are at a twofold increased risk for myocardial infarction and stroke, with risk increasing to nearly threefold in patients who have had the disease for 10 years or more, making cardiovascular disease the most common cause of death in RA patients[5]. Studies have shown that the increase in inflammatory markers in RA could explain the increased risk of cardiovascular mortality in these patients. Mediators such as interleukin-6 and tumor necrosis factor-alpha seem to be mediators of inflammation in RA[6]. Anti-anti-cyclic citrullinated peptide (anti-CCP) is an independent predictor of radiological damage and progression in patients with RA[1,4]. These antibodies have been associated with the pathogenesis, clinical expression and cardiovascular risk in RA. Patients positive for anti-CCP, have shown endothelial dysfunction and it might reflect an early reversible stage of the atherosclerotic process possibly indicating an increased risk of cardiovascular disease (CVD)[7]. Ultrasonic assessment of carotid intima-media thickness (CIMT) is a reliable and valid method for both population studies and clinical trials of atherosclerosis progression and regression. CIMT is a mirror image of CVD risk and clinical coronary events[8,9]. It is a strong predictor of future cardiovascular events and is associated with conventional markers of cardiovascular risk, such as age, diabetes and serum cholesterol. Statistically significant correlations were observed between CIMT and atherosclerosis have been noted. As a noninvasive method for the risk assessment of CVD, CIMT has therefore become a valuable research tool in clinical trials for the assessment of interventions directed against atherosclerosis[8,10]. Few observational studies have suggested that anti-CCP antibody positivity is associated with increased CIMT. However, many of these studies have only considered the presence or absence of anti-CCP antibodies[4]. Studies evaluating the impact of anti-CCP titers on atherosclerosis or CIMT are limited[3,11,12]. There is a paucity of Indian studies on CVD risk in patients with RA despite the high disease burden of both CVD and RA in India. This study aimed to determine the correlation between anti-CCP antibody levels and CIMT in RA patients.

MATERIAL AND METHODS

This cross-sectional observational study was conducted at a tertiary care government hospital in India. Consecutive patients attending the rheumatology clinic of the department during the study period who were diagnosed with RA according to the ACR EULAR-2010 criteria 13 and found to be anti-CCP positive were included in the study. Patients were excluded from the study in case of the presence of confounding variables like obesity (BMI$\geq$30 kg m^{-1}), diabetes mellitus, hypertension, CVD (old myocardial infarction, CABG/PTCA, typical angina, stroke, peripheral vascular disease, etc.), renal insufficiency (GFR <60 mL min^{-1}), taking biologicals or statins, history of previous or current smoking as these factors are known to influence CIMT and inflammation. After applying the exclusion criteria, 79 patients were included in the study. Written informed consent was obtained from all patients. The study was approved by the Institutional Review Board and Ethics Committee of the Atal Bihari Vajpayee Institute of Medical Sciences (Formerly PGIMER) and Dr. Ram Manohar Lohia Hospital, New Delhi.

A detailed history, including the history of medications for each subject, was noted. Each subject was clinically examined in detail, with a focus on the musculoskeletal system. The patients were evaluated for the presence of obesity, hypertension, diabetes mellitus and renal dysfunction. The disease activity status of RA was estimated using the Disease Activity Score-28 for Rheumatoid Arthritis with ESR (DAS 28-ESR) score. The patients then underwent investigations such as blood sugar, lipid profile, kidney function tests, ECG, markers of inflammation (ESR, CRP), anti-CCP levels and rheumatoid factor. Anti-CCP antibodies of IgG class were measured using second-generation enzyme-linked immunosorbent assay (ELISA) using Hycor Biomedical AUTOSTATTM Anti-Cyclic Citrullinated Peptide (Anti-CCP)' kit as per manufacturer's instructions and a value >5 IU mL^{-1} was considered as positive for anti-CCP. CIMT in the study participants was estimated by ultrasound Doppler examination of carotids using Philips HD 11 by transducer L12-3 MH following standard methods 9 by an experienced radiologist blinded to the patient characteristics and the ongoing study protocol. Statistical analysis of the data was performed using Statistical Package for Social Sciences (SPSS) software version 21.0. Continuous variables are presented as mean±SD while categorical variables are presented as numbers with percentages. Quantitative variables were compared between the two groups using an unpaired t-test. Qualitative variables were compared using the chi-squared test. Univariate and multivariate

linear regression analyses were performed to assess the significance of the correlation between anti-CCP antibody levels and CIMT. Statistical significance was set at p-value <0.05.

RESULTS

The study group included a minimum age of 21 years and a maximum age of 70 years. The mean age was 42.85±9.65 years. The proportion of females was higher (78.48%) than expected in RA patients. Disease duration of RA in patients ranged from 6 months to 8 years. Patients showed a high percentage of seropositivity with 96.2% (n = 76) of the patients having positive RF. The mean DAS 28 score in our study population was 3.71±0.88 with the majority of patients having moderate disease activity. For statistical analysis, patients were divided into 2 groups, group 1 consisting of patients with normal CIMT (≤0.6 mm) and group 2 consisting of patients with abnormal CIMT (>0.6 mm). The two groups were comparable for age, sex, SBP, DBP, FBS, BMI, eGFR, serum HDL, Triglycerides and Total cholesterol, CRP and Disease Duration. However, the mean values for LDL, Anti-CCP, DAS 28 score and ESR were all higher in group 2 compared to group 1(Table 1). The mean Anti-CCP value was 290.45±22.74 U mL^{-1} in group 2 (CIMT>0.6) patients whereas it was 111.72±92.63 U mL^{-1} in group 1. The DAS 28 score was higher in patients in group 2 (CIMT>0.6) with a value of 4.44±0.63. The patients with CIMT ≤0.6 had a DAS 28 score of 3.45±0.81.

For statistical analysis, a regression model was applied to find whether the increase in CIMT, which represented a cardiovascular risk, was associated with traditional and other risk factors present in RA patients. The association of individual risk factors or independent variables with increased CIMT as a dependent variable was initially assessed by univariate regression analysis. Further, variables found to have an association with CIMT on univariate analysis were subjected to multivariate regression analysis to determine the independent association of the variable with CIMT. On univariate analysis, Anti-CCP was found to have a significant association with CIMT (r^2 = 0.744, p = 0.0004) (Table 2).

A scatter plot drawn between Anti-CCP and CIMT showed a positive linear relationship between the two (Fig. 1). Other variables that were also associated with CIMT were LDL (p = 0.026), DAS 28 score (p = 0.0002) and ESR (p = 0.001). Total cholesterol (p = 0.158), Disease duration (p = 0.150) and eGFR (p = 0.125) also showed an association with CIMT but it was not significant. All of these variables were considered for multivariate analysis by relaxing the p<0.2. On multivariate analysis, it was found that Anti-CCP showed an independent significant association with increased CIMT (B = 0.47, p = 0.007, r^2 = 0.812). This association was found even after adjusting for confounding variables like LDL, DAS 28 score, ESR, Total cholesterol, Disease duration and eGFR, proving the independent direct relationship between CIMT and anti-CCP. This regression model accounted for 81.2% of the total variance (Table 3).

Table 1: Patient characteristics according to CIMT status

Characteristic	Group 1 (CIMT≤0.6 mm) (n = 58)	Group 2 (CIMT >0.6 mm) (n = 21)
Age (years)	43.05±10.15	42.29±8.31
Male	11 (18.9%)	6 (28%)
Female	47 (81%)	15 (71.4%)
SBP (mm of Hg)	111.17±8.1	109.62±9.37
DBP (mm of Hg)	77.97±5.79	77.81±8.22
BMI (kg m^{-2})	22.5±2.11	22.48±1.89
FBS (mg dL^{-1})	87.64±11.61	86.48±9.03
Triglycerides (mg dL^{-1})	100.22±10.27	102.13±11.77
HDL (mg dL^{-1})	51.53±7.48	52.19±7.78
LDL (mg dL^{-1})	92.74±8.96	100.48±20.17
Total Cholesterol (mg dL^{-1})	144.71±31.95	155.54±29.37
eGFR (mL/min/1.73 m^2)	110.71±10.9	106.67±7.73
Anti-CCP (U mL^{-1})	111.72±92.63	290.45±22.74
CIMT (mm)	0.4±0.08	0.76±0.08
Disease Duration (years)	2.06±1.27	1.55±1.58
DAS 28 Score	3.45±0.81	4.44±0.63
CRP (mg dL^{-1})	10.9±7.43	13.1±8.19
ESR (mm/hr)	42.76±0.81	61.38±0.63

Table 2: Univariate regression analysis to find variables showing association with CIMT

Independent variable	B	S.E.	P value	Odds ratio	95% C.I. for odds ratio Lower	Upper	R^2
AGE	-0.008	0.027	0.754	0.992	0.941	1.045	0.002
SBP	-0.022	0.030	0.468	0.978	0.922	1.038	0.01
DBP	-0.004	0.040	0.924	0.996	0.922	1.077	0
BMI	-0.006	0.125	0.963	0.994	0.778	1.271	0
FBS	-0.010	0.024	0.675	0.990	0.945	1.037	0.003
Triglycerides	-0.028	0.015	0.342	0.972	0.945	1.001	0.08
HDL	0.012	0.034	0.730	1.012	0.947	1.081	0.002
LDL	0.044	0.020	0.026	1.045	1.005	1.085	0.092
Total cholesterol	-0.012	0.009	0.158	0.988	0.971	1.005	0.037
Anti-CCP	0.041	0.012	0.0004	1.042	1.019	1.066	0.744
Disease duration (years)	-0.359	0.250	0.150	0.698	0.428	1.139	0.047
DAS 28 score	1.997	0.531	0.0002	7.366	2.602	20.855	0.387
CRP	0.037	0.033	0.261	1.037	.973	1.106	0.023
ESR	0.068	0.020	0.001	1.070	1.030	1.112	0.284
eGFR	-0.041	0.027	0.125	.959	.910	1.012	0.046
SEX							
M				1.000			0.015
F	-0.536	0.588	0.362	0.585	0.185	1.852	
RF (+)	0.997	1.764	0.572	2.711	0.085	86.087919	0.107

Table 3: Multivariate regression analysis to find the variables showing independent association with CIMT

					95% C.I. for odds ratio	
Independent variable	B	S.E.	p-value	Odds ratio	Lower	Upper
LDL	0.022	0.038	0.556	1.023	0.949	1.102
Anti-CCP	0.047	0.018	0.007	1.048	1.012	1.084
DAS 28 score	1.493	1.043	0.152	4.448	0.576	34.364
ESR	-.010	0.046	0.810	0.990	0.905	1.084
eGFR	-.040	0.073	0.566	0.961	0.833	1.108
Total Cholesterol	-0.002	0.019	0.877	0.998	0.962	1.035
Disease Duration (years)	0.397	0.370	0.254	1.487	0.720	3.071

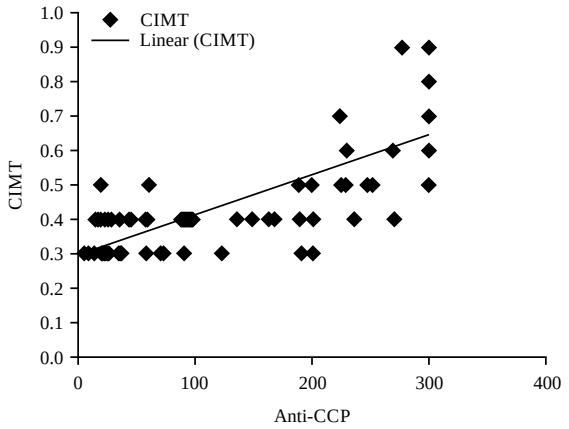

Fig. 1: Scatter plot showing a positive linear relationship between Anti-CCP titers and CIMT

DISCUSSION

RA patients are known to have an increased risk of CVD which in turn accounts for nearly 40% mortality in these patients and reduced life expectancy by 3 years. The exact cause for this increased prevalence of CVD in RA patients is not known. Many studies have highlighted that traditional cardiovascular risk factors are no different in RA patients compared to non-RA patients[13-15]. There is increasing evidence that ongoing chronic inflammatory process and immune dysregulation contributes to accelerated atherosclerosis in these patients. There are some reports implicating biomarkers like RF and anti-CCP as the cause of increased cardiovascular events in RA patients. We hence aimed to find the correlation between anti-CCP levels; a biomarker of RA and CIMT; a marker of subclinical atherosclerosis.

According to the CIMT, patients were divided into two groups: Group 1 with CIMT ≤0.6 mm and Group 2 with CIMT >0.6 mm. Patient characteristics were compared between the two groups. The age group >50 years had a maximum percentage of patients (33.33%) with increased CIMT. Thus, the age of patients could be an additive risk factor for subclinical atherosclerosis. Group 2 was seen to have a higher percentage of male patients. In group 2 anti-CCP had a mean value of 290.45±22.74 U mL^{-1} compared to group 1 which had mean anti-CCP as 111.72±92.63 U mL^{-1}. This difference in anti-CCP between the two groups was assessed statistically by an unpaired t-test, which showed that anti-CCP was significantly higher in patients with CIMT >0.6 mm (p = 0.0004). Thus, in this study, we were able to demonstrate an association between higher anti-CCP levels in patients with increased CIMT. A scatter plot drawn between Anti-CCP and CIMT also showed a linear relationship (Fig. 1). Other factors that showed significant association were LDL (p = 0.026), DAS 28 score (p = 0.0002) and ESR (p = 0.001). The DAS 28 score was higher in patients with CIMT >0.6 mm with a value of 4.44±0.63 in comparison to patients with CIMT ≤0.6 mm who had a DAS 28 score of 3.45±0.81, reflecting that the patients with higher disease activity had increased CIMT. Only 4 patients in the study had DAS28 scores in the high disease activity range and all these patients had their CIMT values >0.6 mm. Other patient characteristics were comparable between these two groups. A multiple logistic regression analysis was performed using anti-CCP, LDL, DAS28 score, ESR, total cholesterol, disease duration and eGFR after relaxing p<0.2 to include other significant variables. It was found that anti-CCP was strongly associated with increased CIMT (B = 0.47, p = 0.007, r^2 = 0.812). This association was found even after adjusting for confounding variables like LDL, DAS 28 score, ESR, Total cholesterol, Disease duration and eGFR, proving an independent direct relationship between CIMT and anti-CCP (Table 3). The study showed that there is a strong, direct, statistically significant correlation between anti-CCP levels and CIMT in RA patients. Considering the high prevalence of RA in India, the result of this study is of immense importance for the detection of subclinical atherosclerosis in RA patients. This could be of great value in the prediction of and hence prevention of the development of CVD in RA patients.

In a study from Mexico, Mercado *et al.*[11] studied the relationship between serum anti-CCP levels and increased CIMT in RA patients. In this study, 45 anti-CCP positive and 37 anti-CCP negative RA patients and 62 healthy controls were studied. Along with anti-CCP, other biomarkers of RA i.e., CRP, TNF-alfa and Interleukin-6 were measured. Conventional risk factors for atherosclerosis which can influence CIMT were measured and considered while drawing results. In addition to the exclusion criteria mentioned in our study, this study also excluded patients who were previously treated with high doses of steroids

(>10 mg day^{-1} prednisone, including intravenous administration). They found that among RA patients, levels of anti-CCP antibodies were associated with increased CIMT (r = 0.37, p<0.009) Result obtained in the present study is similar and rather association is even stronger. The average age of patients in anti-CCP-positive patients in this study was comparable to the mean age of patients in our study. The duration of RA in these patients was higher and their DAS28 score was in the low disease activity range. Mean LDL and total cholesterol levels were higher and HDL mean was lower than our study. Among the inflammatory markers studied, mean CRP was comparable though ESR was found to be higher in our study. In Mercado *et al*.[11] study, in a multivariate linear regression analysis using CIMT as a dependent variable, anti-CCP level was independently and directly associated with CIMT after adjusting for various variables including age, disease duration, CRP, RF, DAS 28 score, TNF-alfa, Interleukin-6. These results are in concurrence with our study. In addition, higher levels of CRP were also seen to be associated with increased CIMT in the study. CRP levels in our study did not have a statistically significant relationship with CIMT, possibly because serum CRP level determined by conventional assay often fluctuates in patients with chronic inflammatory diseases[16]. Since atherosclerosis may be dependent on the median of serial measurements of CRP levels, measurement of CRP at a single point failed to be associated with increased CIMT.

In a similar study from India, Banerjee *et al*.[4] carried out a cross-sectional and observational study and evaluated the association between anti-CCP antibody and atherosclerotic changes as well as CV manifestations in established RA patients. RA patients with both anti-CCP positive and negative status were included in the study. Conventional risk factors for atherosclerosis which can influence CIMT were measured. The baseline characteristics of patients used were comparable to those used in the present study. They found significantly increased average CIMT among anti-CCP positive individuals (p = 0.029) as compared to the age, sex-matched anti-CCP negative RA population. In addition to CIMT measurement, ECG and transthoracic echocardiography were also done in all cases to assess CVD. Disease duration was greater in this study (6.24±3.76 years) in comparison to our study, as RA patients having a disease duration of at least 3 years since diagnosis were considered in the study. Anti-CCP positive group had relatively increased disease activity and higher ESR (p = 0.007). This was consistent with the findings in our study. This study underscores the significant link between subclinical atherosclerosis, as represented by CIMT and specific risk factors in RA patients. The findings suggest that the autoimmune component of RA, indicated by anti-CCP levels, plays a pivotal role in the development of atherosclerosis, even when accounting for other traditional cardiovascular risk factors and disease-related parameters. These results shed light on the complex interplay between inflammation, autoimmune activity and cardiovascular risk in the context of RA. Further research is warranted to elucidate the underlying mechanisms driving this relationship, with the potential to guide more effective preventive and management strategies for cardiovascular complications in RA patients.

CONCLUSION

There is a strongly independent and direct correlation between anti-CCP levels and CIMT, even after adjusting for confounding variables, as evidenced by the present study and supported by other studies. This suggests that anti-CCP might be an emerging and useful biomarker for the prediction of CVD in RA patients. Considering the high prevalence of RA in India, the results of this study could be of help in early detection of subclinical atherosclerosis in RA patients and measures to prevent CVD could be undertaken. This might prove to be a very cost-effective way of reducing the prevalence of CVD in RA patients. Larger multicentric prospective studies should be done to further establish this association.

REFERENCES

1. Alamanos, Y. and A. Drosos, 2005. Epidemiology of adult rheumatoid arthritis. Autoimmunity Rev., 4: 130-136.
2. Cimmino, M.A., C. Salvarani, P. Macchioni, C. Montecucco and V. Fossaluzza *et al*., 2000. Extra-articular manifestations in 587 Italian patients with rheumatoid arthritis. Rheumatol. Int., 19: 213-217.
3. Sahatçiu-Meka, V., S. Rexhepi, S. Manxhuka-Kërliu and M. Rexhepi, 2010. Extra-articular manifestations of seronegative and seropositive rheumatoid arthritis. Bosnian J. Basic Med. Sci., 10: 26-31.
4. Arnab, B., G. Biswadip, P. Arindam, M. Shyamash, G. Anirban and P. Rajan, 2013. Anti-ccp antibody in patients with established rheumatoid arthritis: Does it predict adverse cardiovascular profile? J. Cardiovasc. Dis. Res., 4: 102-106.
5. Dhawan, S.S. and A.A. Quyyumi, 2008. Rheumatoid arthritis and cardiovascular disease. Curr. Atherosclerosis Rep., 10: 128-133.
6. Wei, S.T., Y.H. Sun, S.H. Zong and Y.B. Xiang, 2015. Serum levels of il-6 and tnf-α may correlate with activity and severity of rheumatoid arthritis. Med. Sci. Monit., 21: 4030-4038.

7. Hjeltnes, G., I. Hollan, Ø. Førre, A. Wiik, K. Mikkelsen and S. Agewall, 2011. Anti-ccp and rf igm: Predictors of impaired endothelial function in rheumatoid arthritis patients. Scand. J. Rheumatol., 40: 422-427.
8. Nambi, V., L. Chambless, A.R. Folsom, M. He and Y. Hu *et al*., 2010. Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk. J. Am. Coll. Cardiol., 55: 1600-1607.
9. Paul, J., K. Shaw, S. Dasgupta and M.K. Ghosh, 2012. Measurement of intima media thickness of carotid artery by b-mode ultrasound in healthy people of India and Bangladesh and relation of age and sex with carotid artery intima media thickness: An observational study. J. Cardiovasc. Dis. Res., 3: 128-131.
10. Sibal, L., S.C. Agarwal and P.D. Home, 2011. Carotid intima-media thickness as a surrogate marker of cardiovascular disease in diabetes. Diabetes Metab Syndr Obes., 4: 23-34.
11. Mercado, M.V.D., L. Nuñez-Atahualpa, M. Figueroa-Sánchez, E. Gómez-Bañuelos and A.D. Rocha-Muñoz *et al*., 2015. Serum levels of anticyclic citrullinated peptide antibodies, interleukin-6, tumor necrosis factor-*α* and c-reactive protein are associated with increased carotid intima-media thickness: A cross-sectional analysis of a cohort of rheumatoid arthritis patients without cardiovascular risk factors. BioMed Res. Int., 2015: 1-10.
12. Barbarroja, N., C. Pérez-Sanchez, P. Ruiz-Limon, C. Castro-Villegas and M.A. Aguirre *et al*., 2014. Anticyclic citrullinated protein antibodies are implicated in the development of cardiovascular disease in rheumatoid arthritis. Arteriosclerosis, Thrombosis, Vasc. Biol., 34: 2706-2716.
13. Kang, S., K. Han, J.H. Jung, Y. Eun and I.Y. Kim *et al*., 2022. Associations between cardiovascular outcomes and rheumatoid arthritis: A nationwide population-based cohort study. J. Clin. Med., Vol. 11, No. 22 .10.3390/jcm11226812
14. Avina-Zubieta, J.A., J. Thomas, M. Sadatsafavi, A.J. Lehman and D. Lacaille, 2012. Risk of incident cardiovascular events in patients with rheumatoid arthritis: A meta-analysis of observational studies. Ann. Rheumatic Dis., 71: 1524-1529.
15. Nikiphorou, E., S. de Lusignan, C.D. Mallen, K. Khavandi and G. Bedarida *et al*., 2020. Cardiovascular risk factors and outcomes in early rheumatoid arthritis: A population-based study. Heart, 106: 1566-1572.
16. Pope, J.E. and E.H. Choy, 2021. C-reactive protein and implications in rheumatoid arthritis and associated comorbidities. Seminars Arthritis Rheumatism, 51: 219-229.