Correlation of Carotid Intima Media Thickness with Disease Duration and Activity of Rheumatoid Arthritis

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Abstract: *Context*: Rheumatoid Arthritis (RA) patients have a higher chance of adverse cardiovascular events due to accelerated atherosclerosis. The objective of this study was to assess if there is any correlation of duration and disease activity of Rheumatoid Arthritis with carotid intima media thickness (CIMT), an efficient marker of atherosclerosis and predictor of future adverse cardiovascular events.

Aims: To look for any correlation between CIMT and disease duration and activity of Rheumatoid Arthritis.

Settings and Design: Cross-sectional observational study.

Methods and Material: Sixty patients of Rheumatoid Arthritis, diagnosed as per 2010 ACR/EULAR guideline, were divided in three groups depending on disease duration and then disease activity was measured by DAS28 scoring. Carotid intima medial thickness was measured using USG and correlation was calculated by statistical measures.

Statistical Analysis Used: Correlations between the variables were measured using Chi Square test and Pearson Correlation test.

Results: Significant statistical correlation with the haematological parameters and inflammatory parameters were found to the disease activity of RA. Disease activity of RA was also strongly correlated with dyslipidemia. Also thickened Carotid IMT was associated with older age and it was strongly associated with Rheumatoid Factor and Anti CCP positivity. Disease duration was found to be strongly correlated with thickened carotid intima media and carotid plaque in this study. Disease activity also showed similar strong correlation with carotid intima media thickness and carotid plaque.

Conclusions: Both disease duration and disease activity were strongly associated with increased CIMT and carotid plaque, marker of accelerated atherosclerosis, in RA patients.

Keywords: Carotid intima media thickness, Atherosclerosis, Duration of RA, Activity of RA.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory autoimmune disease characterized by chronic and erosive polyarthritis and causes irreversible joint deformity, disability along with extra-articular involvement of other organs like lungs, heart, eye and skin.

Patients with RA have almost two fold increased risk of developing coronary artery disease (CAD) compared to the normal healthy population [1, 2] which is almost same as diabetes mellitus [3]. Even prior to the diagnosis, individuals with RA have three times higher risk to have had a prior myocardial infarction (MI) than subjects without RA [2]. An expert committee of the European League against Rheumatism (EULAR) has recommended to multiply Cardiovascular risk scores (e.g., Framingham) by 1.5 in some patients with RA to establish their actual risk of heart disease augmented by the disease process of RA [4].

Cardiovascular mortality is increased among patients with RA [5-9]. The incidence of coronary artery disease and carotid atherosclerosis is higher in RA patients than in general population even when controlling for traditional cardiovascular risk factors, such as hypertension, obesity, hypercholesterolemia, diabetes and cigarette smoking [10]. Untreated RA is associated with an adverse lipid profile that is conventionally accepted as a risk factor for cardiovascular disease (CVD) [11]. It has also been proved that the adverse lipid profile can be improved to an extent that is clinically meaningful by effectively treating RA without using a lipid-lowering agent [12].

The magnitude and chronicity of the inflammatory response, as measured by C-Reactive Protein (CRP), correlates with carotid atherosclerosis development in RA [13]. As increased carotid intima–media thickness (IMT) and carotid plaques have been proved to predict the development of CV events in RA.

Though many studies have already been done on the prevalence of atherosclerosis in Rheumatoid Arthritis and its association with increased mortality, only a very few studies are available regarding correlation of atherosclerosis with disease activity and disease duration of Rheumatoid Arthritis. This study is taken up to look for any correlation between

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accelerated atherosclerosis and disease duration and activity of Rheumatoid Arthritis using Carotid Intima Medial Thickness and Disease Activity Score-28 (DAS-28).

SUBJECTS AND METHODS

It is a Cross-sectional observational study done on diagnosed or newly diagnosed patients of rheumatoid arthritis, as per 2010 ACR/EULAR classification criteria, attending the Rheumatology clinic and medical Out-patient department of a tertiary care hospital in eastern India.

Sixty cases diagnosed as Rheumatoid Arthritis divided in three groups based on duration of disease, Group one: those subjects who had RA of less than two years, Group two: those subjects who had RA between two to five years, Group three: those subjects having RA for more than five years [14].

Inclusion Criteria

Patients who are older than 16 years and diagnosed or newly diagnosed with RA as per 2010 ACR/EULAR criteria were included in the study after taking an informed consent about participating in the study.

Exclusion Criteria

Patients with burnt out cases of RA were excluded from the study. Patients with known cases of Ischemic Heart Disease, past history of cerebrovascular events, evidence of renal/liver/lung failure, history of tobacco chewing, smoking were also excluded from the study. Persons who were not willing to take part in the study were excluded from the study.

Written well-informed consents were obtained from the participants of the study group. This study was in accordance with the declaration of Helsinki and was approved by the institutional ethical committee.

Laboratory Investigations

Blood samples were collected from patients and evaluated for complete hemogram, ESR, C-reactive protein, Fasting and Postprandial Blood Sugar, HbA1c, Blood Urea, Serum Creatinine, Lipid profile, RA Factor & Anti-cyclic Citrullinated Peptide Antibodies (Anti-CCP).

All subjects included in the study were evaluated for their disease activity using simplified DAS 28.

DAS 28 = $0.56\sqrt{TJC} + 0.28\sqrt{SJC} + 0.70$ (log ESR) + 1.08 +0.16.

TJC=tender joint count

SJC=swollen joint count

Carotid Intima Media Thickness Measurement

All subjects underwent carotid sonography using 7.5MHz transducer. The common carotid arteries (CCA) were examined bilaterally up to the bifurcation including proximal part of internal carotid artery (ICA) and external carotid artery (ECA). The intima media thickness, plaque characterization (including echo texture, calcification, and cavitations) were assessed – initially by gray scale USG and then followed by colour flow imaging. Three readings were taken and then the average was used as the mean carotid IMT of the subject.

The normal intima-medial thickness of common carotid artery as evaluated by B-mode ultrasound imaging was 0.70 ± 0.14 mm [15]. For the present study carotid IMT value of 0.7 mm was considered as the higher limit of normal value. Typically, carotid plaques were defined as a local IMT of 1.5 mm. (range between 1.2 –1.9 mm in different studies) or as a focal thickening of greater than 50% of the surrounding area [16].

Statistical Methods

The statistical software Statistical Package for Social Sciences (SPSS, Chicago, IL, USA), version 20 has been used for the analysis. An alpha level of 5% has been taken, i.e. p value less than 0.05 been considered as statistically significant. Correlations between the variables were measured using Chi Square test for categorical variables and Pearson Correlation test for continuous variables.

RESULTS

Majority of the study population (89%) belonged to the age group of 31-60 years and most of them were female (70%). Majority (73.33%) of the study population had disease duration of more than two years and a significant (35%) no of patients had severe disease activity. Rheumatoid factor was positive in 80% of the study population and 72% were positive for Anti-CCP. 81.67% patients had IMT thickness more than normal (>=0.07), but only 8 (13.33%) patients had carotid plaque on Ultrasonography.

Relation of Different Parameters with Disease Activity

Haematological abnormalities were more common in patients with higher disease activity. Anaemia (P Value- 0.042), Increased Total Count (P Value- 0.045), Higher Neutrophil Count (P Value- 0.002) all were more common in the study population with severe disease activity. Patients with higher disease activity also had higher levels of ESR (>40) with P Value of <0.001. Patients with severe disease activity also had elevated values of CRP (>6) with P Value of 0.011.

Though Hypertension and Diabetes were not associated but Dyslipidemia was more common in the study population with severe disease activity (P Value- 0.037).

Relationship of Different Parameters with Increased Carotid IMT

Carotid IMT were significantly increased in relatively older population (P Value- 0.001). Carotid IMT were comparatively increased in female patients but the correlation was not statistically significant (P Value- 0.719).

In the present study, increased Carotid IMT was associated with haematological parameters like Anaemia, Raised TLC, Raised Neutrophil Count and high level of inflammatory markers like ESR and CRP which was statistically significant. Increased Carotid IMT was statistically very strongly correlated with Rheumatoid Factor positivity (P Value- 0.019) and Anti-CCP positivity (P Value- 0.00001).

Table **1** suggests more than 50% patients with disease for less than two years had thickened carotid IMT and 100% of the patients who had disease for more than 5 years had thickened CIMT. This correlation of thickening of carotid IMT with duration of RA was statistically significant (P Value of 0.003).

Table **2** suggests Most (95.24%) of the patients with severe disease activity had thickened Carotid IMT and nearly three fourth (74.36 %) of the study population with Moderate disease activity had thickened CIMT & the correlation of Disease activity with Carotid IMT was statistically significant (P Value- 0.046).

Table **3** suggests Patients with longer duration of RA (>5 years) had more incidence of Carotid Plaque

Table 1: Correlation of Disease Duration with Carotid IMT

		Duration			Total	p Value	Significance
		1	2	3			
Carotid IMT	<0.07	7(43.75)	4(16.67)	0(00)	11(18.33)	**0.003**	**Significant**
	>=0.07	9(56.25)	20(83.33)	20(100)	49(81.67)		
Total		16(100)	24(100)	20(100)	60(100)		

Table 2: Correlation of Disease Activity with Carotid IMT

		Disease Activity		Total	p Value	Significance
		Moderate	Severe			
Carotid IMT	<0.07	10(25.64)	1(4.76)	11(18.33)	**0.046**	**Significant**
	>=0.07	29(74.36)	20(95.24)	49(81.67)		
Total		39(100)	21(100)	60(100)		

Table 3: Correlation of Disease Duration with Carotid Plaque

		Duration			Total	p Value	Significance
		1	2	3			
Carotid Plaque	Absent	15(93.75)	23(95.83)	14(70)	52(86.67)	**0.026**	**Significant**
	Present	1(6.25)	1(4.17)	6(30)	8(13.33)		
Total		16	24	20	60(100)		

Table 4: Correlation of Disease Activity with Carotid Plaque

		Disease Activity		Total	p Value	Significance
		Moderate	Severe			
Carotid Plaque	Absent	37(94.87)	15(71.43)	52(86.67)	**0.018**	**Significant**
	Present	2(5.13)	6(28.57)	8(13.33)		
Total		39(100)	21(100)	60(100)		

(30%) and the correlation was significant statistically (P Value- 0.026).

Table **4** suggests Out of eight patients with carotid plaque six patients had severe disease activity which was statistically significant (P Value- 0.018).

DISCUSSION

This is a cross-sectional observational study on "Correlation of Carotid Intima Medial Thickness with Disease Duration and Activity of Rheumatoid Arthritis" conducted with patients attending Rheumatology and Medical outpatient departments of a tertiary hospital in eastern India.

A total of 60 patients of proven RA with various disease duration and activity, were recruited as per study protocol, out of which majority (70%) were female with male to female ratio of 1:2.33. This correlates with the incidence of RA among the general populations as documented by Cojocaru *et al*. [17] and study done by Singh H *et al*. [14].

In the present study majority of the study population belonged to 41-50 years of age group (37%), followed by 51-60 years of age group (30%) & the mean age was 46.68 years. The mean age at presentation of RA was 42.69 years in a study done by Mandal SK *et al*. [18] whereas in study done by Myasoedova *et al.,* mean age of the study population was 58.42 [19].

In present study the patients were divided in three groups according to the duration of their disease, patients with RA for six months to two years were labeled as group 1 (27%), patients with RA for two years to five years were in group 2 (40%) & patients with disease for more than five years were in group 3 (33%), as done in previous studies [14].

Disease activity was measured according to DAS 28 calculator with the help of website address www.dasscore.nl/das28/DAS calculators/dasculators. Disease activity was stratified into mild (score<3.2); moderate (score 3.2-5.1); severe was (score>5.1). In the current study 65% of patients had moderate disease activity and 35% of patients had severe disease activity. None of the patients had mild disease activity or disease in remission. In study done by Singh H *et al.,* 15.55% patients had mild disease activity, 51.11% patients had moderate disease activity and 33.33% patients had severe disease activity [14].

In the present study, severe disease activity was more common in the age group of 41-50 years (40.91%), though not statistically significant (p value-0.796). Most of the patients with severe disease activity belonged to age> 40 years (80.95%), corroborative with study done by Pawlowska *et al*. [20].

In the present study severe disease activity was more among female patients (P Value- 0.443), corroborative with study done by Jawaheer *et al*. [21].

In this study 5% of the patients had anemia of chronic diseases which is similar to the study done by Mariana Costa *et al.* (4.5%) [22] Anemia was more evident in patients with severe disease activity (41.67%) which was statistically significant (P Value-0.042).

In the present study 11.67% of patients had leukocytosis compared to 27% found in study done by Syed KM *et al*. [23]. Severe disease activity was also associated with higher total leukocyte count (P Value-0.045) and higher neutrophil count (P Value- 0.002) significantly showing similar findings as study done by Syed KM *et al*. [23].

Higher levels of inflammatory mediators like ESR and CRP were also proved to be important predictor of severe disease activity in RA patients (P Values of <0.0001 and 0.011 respectively), similar findings were also seen in the studies done by Silva *et al*. [24].

In the present study 25% patients had hypertension, 8% patients had diabetes and 26.66% patients had dyslipidemia compared to 15% hypertensive, 3.77% diabetic in the study done by Park *et al*. [25]. Though hypertension (P Value-0.274) and diabetes (P Value -

0.807) were not significantly correlated with disease activity. Dyslipidemia was related with disease activity (P Value- 0.037) suggesting ongoing chronic inflammation may be the cause behind this, corroborating with study done by Mandal *et al*. [18].

In 80% patients of the study group, Rheumatoid Factor (RF) was positive which was in correlation with other study [26], correlation of RF with disease activity showed no statistical significance (P Value- 0.185).

71.67% of patients were positive for Anti CCP antibody in this study whereas study done by Del amo *et al.* showed Anti CCP positivity in 64% patients [27]. Correlation of Anti CCP antibody and disease activity is non-significant statistically with P Value of 0.076, not corroborating with study done by Del amo *et al.* (P Value < 0.0001) [27].

Only 8.33% of the study population was positive for ANA, whereas ANA positivity was as high as 60% in RA patients in study done by Aitcheson *et al*. [28] and correlation of ANA with disease activity was not statistically significant (P Value- 0.807).

Carotid Doppler was performed with 7.5 MHz ultrasound probe transducer and observed carotid IMT and carotid plaque.

Carotid IMT was significantly higher (>=0.7 mm) in 48 cases (80%) of the study population, Sarker RN, *et al*. [29] also showed similar findings in their study. The study also showed that carotid IMT was thicker among older patients (P Value- 0.001) corroborating with Mandal SK *et al*. [18] and Singh H *et al*. [14].

Thickened IMT was more common among female population (83.33%) compared to male population (77.78%), though the correlation was not statistically significant (P Value- 0.719).

Carotid IMT was not associated with anemia (P Value- 0.435) but increased total count (P Value- 0.768) & increased neutrophil count (P Value- 0.455) was associated with carotid IMT.

Both inflammatory markers ESR and CRP were higher in study subjects with carotid atherosclerosis and thicker IMT though no statistical correlations were present (P Value- 0.094 & P Value- 0.259 respectively).

Both Rheumatoid factor positivity (P Value- 0.019) and Anti-CCP antibody positivity (P Value- <0.001) are correlated statistically with thicker IMT but ANA positivity (P Value- 0.920) shows no correlation.

Hypertension (P Value- 0.192), diabetes (P Value- 0.268) & dyslipidemia (P Value- 0.959) though common in study subjects with thicker IMT but correlations were not statistically significant, corroborating with findings of Singh H *et al*. [14].

Carotid plaque was present in 8 patients (13.3%) of the study population which is corroborative with the study done by Sarker R N *et al.* (13.3%, p<0.0001) [29]. On the other hand, Park *et al.* showed only 1 out of 53 study subjects having carotid plaque [25].

Carotid plaque was more in the age group of 51-60 (22.22%) and in male patients (16.67%) which was corroborative with the study done by Roman *et al*. [30], Singh H *et al*. [14] and Mandal SK *et al*. [18] but these variables were not statistically significant (P Value- 0.817 & P Value- 0.686 respectively).

Carotid plaque was more common in patient with anemia (P value- 0.493), high total leukocyte count (P Value- 0.937) and high neutrophil count (P Value- 0.61) which were not corroborating with that of Mandal SK *et al*. [18].

Carotid plaque was more common with increased values of ESR (P Value- 0.225) and CRP (P Vlue- 0.416). Similar findings were also present in study done by Mandal SK *et al.* (P Value- 0.282 & P Value- 0.28) [18]. It was also more common in patient with RF (P Value- 0.683), Anti-CCP (P Value- 0.286) and ANA (P Value- 0.524) positivity, though statistically not significant.

Plaque was also more common in hypertension (P Value- 0.400), Diabetes (P Value- 0.603) and dyslipidemia (P Value- 0.192) corroborating with previous studies done by Pope *et al*. [31] and Mandal SK *et al*. [18].

The present study showed Carotid IMT was strongly correlated with disease activity (P Value- 0.046) and disease duration (P Value- 0.003), similar finding was found in study done by Singh H *et al*. [14]. Gonzales *et al.* in their study had found disease duration as one of the best predictor for the development of severe morphologic expression of atherosclerotic disease [32], Del Rincon *et al*. [33] and Mahajan *et al*. [34] also had similar observations.

In this study it was also found that that carotid plaque had statistically significant association with disease activity (P Value- 0.018) and disease duration (P Value- 0.026) which was corroborative with the

study done by Singh H *et al*. [14] and other studies [32, 34].

Thus, the present study suggested that patients with RA having higher incidence and early onset of atherosclerosis and prone to adverse cardiovascular events due to chronic inflammatory disease process. The progression of atherosclerosis, as measured by thickening of Carotid IMT and carotid plaques depends on the disease duration of RA and activity of the disease in that particular patient. Also thickened Carotid IMT was more common in older population and it was strongly associated with Rheumatoid Factor and Anti CCP positivity. Patients with RA having severe disease activity also showed strong correlation with hematological parameters like anemia, increased total leukocyte count, increased neutrophil count and inflammatory parameters like ESR and CRP. Dyslipidemia among RA patients was also more common in patients with severe disease activity.

CONCLUSION

Prevention of cardiovascular disease in RA requires a combined approach incorporating cardiovascular risk factors screening and management, effective and sustained control of RA disease activity, a high index of suspicion and prompt investigation of suspected cardiac disease. The treatment of the underlying disease process, i.e., atherosclerosis, and preventing its acute complications present an enormous challenge and opportunity simultaneously.

But our study was done on a small group of hospital based population so it may not reflect the proper correlation of the whole population. A bigger study with larger patient size may be needed to reflect the proper picture.

REFERENCES

[1] Solomon DH, Goodson NJ, Katz JN, *et al*. Patterns of cardiovascular risk in rheumatoid arthritis. Ann Rheum Dis 2006; 65: 1608-1612. https://doi.org/10.1136/ard.2005.050377

[2] Maradit-Kremers H, Crowson CS, Nicola PJ, *et al*. Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population-based cohort study. Arthritis Rheum 2005; 52: 402-411. https://doi.org/10.1002/art.20853

[3] Peters MJ, van Halm VP, Voskuyl AE, *et al*. Does rheumatoid arthritis equal diabetes mellitus as an independent risk factor for cardiovascular disease? A prospective study. Arthritis Rheum 2009; 61: 1571-1579. https://doi.org/10.1002/art.24836

[4] Peters MJ, Symmons DP, McCarey D, *et al*. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Ann Rheum Dis 2010; 69: 325-331. https://doi.org/10.1136/ard.2009.113696

[5] Symmons DP, Jones MA, Scott DL, Prior P. Longterm mortality outcome in patients with rheumatoid arthritis: early presenters continue to do well. J Rheumatol 1998; 25: 1072-7.

[6] Wallberg-Jonsson S, Ohman ML, Dahlqvist SR. Cardiovascular morbidity and mortality in patients with seropositive rheumatoid arthritis in Northern Sweden. J Rheumatol 1997; 24: 445-51.

[7] Mutru O, Laakso M, Isomaki H, Koota K. Ten year mortality and causes of death in patients with rheumatoid arthritis. BMJ 1985; 290: 1797-9. https://doi.org/10.1136/bmj.290.6484.1797

[8] Isomaki HA, Mutru O, Koota K. Death rate and causes of death in patients with rheumatoid arthritis. Scand J Rheumatol 1975; 4: 205-8. https://doi.org/10.3109/03009747509165257

[9] Erhardt CC, Mumford PA, Venables PJ, Maini RN. Factors predicting a poor life prognosis in rheumatoid arthritis: an eight year prospective study. Ann Rheum Dis 1989; 48: 7-13. https://doi.org/10.1136/ard.48.1.7

[10] Kobayashi H, Giles JT, Polak JF, Blumenthal RS, Leffell MS, Szklo M, Petri M, Gelber AC, Post W, Bathon JM. Increased prevalence of carotid artery atherosclerosis in rheumatoid arthritis is artery-specific. J Rheumatol 2010; 37(4): 730-9. https://doi.org/10.3899/jrheum.090670

[11] Park YB, Lee SK, Lee WK, Suh CH, Lee CW, Lee CH, *et al*. Lipid profiles in untreated patients with rheumatoid arthritis. J Rheumatol 1999; 26: 1701-4. https://doi.org/10.1016/S0002-9343(02)01186-5

[12] Park Y-B, Choi HK, Kim M-Y, Lee W-K, Song J, Kim D-K, *et al*. Effects of antirheumatic therapy on serum lipid levels in patients with rheumatoid arthritis: a prospective study. Am J Med 2002. In press.

[13] Kaplan MJ. Cardiovascular disease in rheumatoid arthritis. Curr Opin Rheumatol 2006; 18(3): 289-97. https://doi.org/10.1097/01.bor.0000218951.65601.bf

[14] Singh H, Goyal M, Sen J, *et al*. Correlation of Intima Media Thickness (as a Marker of Atherosclerosis) with Activity and Duration of Rheumatoid Arthritis using Carotid Ultrasound JIACM 2011; 12(1): 15-20.

[15] Mohan V, Ravikumar R, Shanthi Rani S, Deepa R. Intimal medial thickness of the carotid artery in South Indian diabetic and non-diabetic subjects: The Chennai Urban Population Study. Diabetologia 2000; 43: 494-9. https://doi.org/10.1007/s001250051334

[16] Casadei A, Floreani M, Catalini R, Serra C, Assanti AP, Concif P. Sonographic characteristics of carotid artery plaques: Implications for follow-up planning? J Ultrasound 2012; 15(3): 151-157. https://doi.org/10.1016/j.jus.2012.06.002

[17] Cojocaru M, Cojocaru IM, Silosi I, Vrabie CD, Tanasescu R. Extra-articular Manifestations in Rheumatoid Arthritis. Maedica 2010; 5(4): 286-91.

[18] Mandal SK, Sarkar P, Sarkar RN, *et al*. Assessment of carotid atherosclerosis in rheumatoid arthritis in Asian Indian cohort: a cross-sectional study. JEMDS 2016; 5(65): 4666-72. https://doi.org/10.14260/jemds/2016/1063

[19] Myasoedova E, Crowson CS, Kremers HM, *et al*. Is the incidence of rheumatoid arthritis rising? Results from Olmsted County, Minnesota, 1955-2007. Arthritis Rheum 2010; 62: 1576-82. https://doi.org/10.1002/art.27425

[20] Pawlowska J, Solenska Z, Daca A, *et al*. Older age of rheumatoid arthritis onset is associated with higher activation

status of peripheral blood $CD4^+$ T cells and disease activity. Clin Exp Immunol 2011; 163(2): 157-184. https://doi.org/10.1111/j.1365-2249.2010.04294.x

[21] Jawaheer D, Olsen J, Lahiff M, *et al*. Gender, body mass index and rheumatoid arthritis disease activity: results from the QUEST-RA study. Clin Exp Rheumatol 2010; 28(4): 454-461.

[22] Extra-Articular-Manifestations-Of-Rheumatoid-Arthritis-Now.pdf [Internet]. [cited 2017 Oct 15]. Available from: http://emjreviews.com/wp-content/uploads/Extra-Articular-Manifestations-Of-Rheumatoid-Arthritis-Now.pdf.

[23] Syed KM, Pinals RS, *et al*. Leukocytosis in Rheumatoid Arthritis. J Clin Rheumat 1996; 2(4): 197-202. https://doi.org/10.1097/00124743-199608000-00007

[24] Silva I, Mateus M, Branco JC, *et al*. Assessment of ESR and CRP on RA activity prediction. Acta Rhematol Port 2010; 35(5): 456-62.

[25] Park Y-B, Ahn C-W, Choi HK. Atherosclerosis in rheumatoid arthritis: Morphologic evidence obtained by carotid ultrasound. Arthritis Rheum 2002; 46: 1714-19. https://doi.org/10.1002/art.10359

[26] Harrison's principles of Internal Medicine,19th Edition, chap 380: p. 2898.

[27] Del Val del Amo N, Ibanez Bosch R, Fito Manteca C. Anti-cyclic citrullinated peptide antibody in rheumatoid arthritis: relation with disease aggressiveness. Clin Exp Rheumatol 2006; 24(3): 281-6.

[28] Itcheson CT, Peebles C, Joslin F. Characteristics of anti neuclear antibodies in rheumatoid arthritis. Arthritis Rheum 1980; 23: 528-38. https://doi.org/10.1002/art.1780230503

[29] Cardiovascular involvement in Rheumatoid Arthritis. pdf [Internet]. [cited 2017 Nov 15]. Available from http://www.apiindia.org/pdf/ medicine_update_2011/48_cardiovascular_involvement_ in.pdf.

[30] Roman Matty J, Moeller E, Adrienne D, *et al*. Preclinical carotid atherosclerosis in patients with RA. Ann Intern Med 2006; 144: 249-56. https://doi.org/10.7326/0003-4819-144-4-200602210-00006

[31] Pope JE, Nevskaya T, Barra L, *et al*. Varotid Artery Atherosclerosis in patients with active Rheumatoid Arthitis. Open Rheumat J 2016: 10: 49-59. https://doi.org/10.2174/1874312901610010049

[32] Gonzalez JC, Llorca J, Terta A, *et al*. Increased prevalence of severe sub-clinical atherosclerosis findings in long-term treated RA patients without clinically evident atherosclerotic disease. Medicine (Baltimore) 2003; 82: 407-13. https://doi.org/10.1097/01.md.0000101572.76273.60

[33] DelRincon I, Freeman GL, Hass RW, *et al*. Relative contribution of cardiovascular risk factors and rheumatoid arthritis clinical manifestation to atherosclerosis. Arthritis Rheum 2005; 52: 3413-23. https://doi.org/10.1002/art.21397

[34] Mahajan V, Handa R, Kumar U, *et al*. Assessment of atherosclerosis by carotid intimomedial thickness in patients with rheumatoid arthritis. JAPI 2008; 56: 587-90.

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