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# STUDY ON CAROTID INTIMAL THICKNESS IN RHEUMATOID ARTHRITIS PATIENTS AS MARKER OF ATHEROSCLEROSIS IN RURAL POPULATION OF KOLAR DISTRICT

**[1]Dr. Prabhakar K., [2*]Dr. Sridhar Sreenivasan G., [3]Dr. Reddy Prasad K., [4]Dr. Vidyasagar R. and [5]Dr. Prajeet R.**

[1]Professor, Department of General Medicine, Sri Devaraj Urs Medical College, Tamaka, Kolar, India.
[2*]Junior Resident, Department of General Medicine, Sri Devaraj Urs Medical College, Tamaka, Kolar, India.
[3]Assistant Professor, Department of General Medicine, Sri Devaraj Urs Medical College, Tamaka, Kolar, India.
[4]Professor, Department of General Medicine, Sri Devaraj Urs Medical College, Tamaka, Kolar, India.
[5]Undergraduate Student, Sri Devaraj Urs Medical College, Tamaka, Kolar, India.

***Author for Correspondence: Dr. Sridhar Sreenivasan G.**
Junior Resident, Department of General Medicine, Sri Devaraj Urs Medical College, Tamaka, Kolar, India.

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## ABSTRACT

**Objectives:** 1.) To find the association of carotid intimal thickness in rheumatoid arthritis patients. 2.) To study carotid intimal thickness in healthy controls. 3.) To compare the carotid intimal thickness in rheumatoid arthritis patients with age and sex matched healthy controls. **Materials and Methods:** A total of 138 people were selected for the study. Subjects for the study were selected from R. L. Jalappa Hospital and Sri Narasimharaja (SNR) Government Hospital, Kolar, who were diagnosed with rheumatoid arthritis according to the RA ACR/EULAR 2010 criteria. The control group consisted of healthy, non-diabetic, non-hypertensive and non-smoking subjects who were selected from the patient bystanders attending the hospital. Carotid intima-media thickness was measured in both sets of cases and was compared with age and sex matched controls. **Results:** A significant difference was found between cases and controls. Mean Right CIMT (mm) in cases was 0.58 ± 0.15 and in controls was 0.47 ± 0.04. Mean Left CIMT (mm) in cases was 0.60 ± 0.15 and in controls was 0.46 ± 0.04, which shows a positive correlation between rheumatoid arthritis and an increase in carotid intima-media thickness (CIMT). ESR, CRP and RA factor also showed a positive correlation with CIMT. **Conclusion:** The study established that subclinical atherosclerosis, identified through CIMT, is a surrogate marker in patients with rheumatoid arthritis. A positive correlation was also established between duration of disease, ESR, CRP, RA factor and increasing CIMT.

**KEYWORDS:** rheumatoid arthritis, atherosclerosis, carotid intima-media thickness.

## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of the joints with predominant symptoms of pain, swelling and stiffness.[1] The prevalence of rheumatoid arthritis around the world is between 0.7% to 1.5%.[2] Malaviya et al found the prevalence in Indian rural population to be 0.75%.[3] Rheumatoid arthritis (RA) is associated with an elevated risk of cardiovascular and cerebrovascular disease due to accelerated atherosclerosis, as RA disease-related inflammation is thought to affect the vasculature and contribute to endothelial dysfunction and atherosclerosis.[4]

People of Asian Indian ethnicity are generally predisposed to a higher risk of premature atherosclerosis, leading to coronary artery disease (CAD) and cerebrovascular disease (CVD).[5] Studies that have focused on an association between the two conditions have generated data that positively correlates RA with atherosclerosis.[6][7] Single photon emission computed tomography (SPECT) studies have also observed that abnormalities of myocardial perfusion occur earlier than normal in patients with RA.[8]

Atherosclerosis leading to premature cardiovascular disease and cerebrovascular disease has been recognized as a significant cause of morbidity and mortality in rheumatoid arthritis (RA).[9] The extent of systemic and articular inflammation determines the destructive course of the disease. In RA, the increased risk of cardiovascular mortality due to accelerated atherogenesis is thought to be directly linked to the level of inflammation.[10] This obviously potentiates the need to assess the cardiovascular and cerebrovascular risk status of RA patients.[11] Due to the high incidence of CAD/CVD events observed in patients with RA, an important step forward might be to identify high-risk individuals who could benefit from steps to delay disease progression.

Long-standing persistent immune inflammation is considered to be a novel risk factor for the identification of atherosclerosis.[12] In this regard, non-invasive imaging techniques offer clinicians an opportunity to study the relationship between the development of atherosclerosis and such surrogate markers.[13] Among them, ultrasound techniques measuring the intimal thickness are considered to be the most efficient way of measuring subclinical atherosclerosis.[14]

Carotid intima-media thickness (CIMT) is a simple, inexpensive, reliable and non-invasive marker that is increasingly being used to detect subclinical atherosclerosis, and is routinely recommended as a screening test for heart disease in apparently healthy individuals.[15] [16] Moreover, mortality due to coronary artery disease is 59 per cent higher in RA patients than in the general population.[17] Thus, the measurement of CIMT in RA patients as a marker for atherosclerosis can be used to determine those at risk of developing CAD, allowing for an early initiation of treatment and a subsequent reduction in mortality.[18] [19]

## MATERIALS AND METHODS

### Source of Data

A total of 138 people were selected for the study. Subjects for the study were selected from patients at the outpatient clinics as well as inpatients of R. L. Jalappa Hospital and Sri Narasimharaja (SNR) Government Hospital, Kolar. The first 69 subjects who were diagnosed as having rheumatoid arthritis according to the RA ACR/EULAR 2010 criteria were taken as cases. The control group of 69 subjects consisted of non-diabetic, non-hypertensive and non-smoking subjects who were selected from the patient bystanders attending the hospital.

### Study Procedure

The study was cleared by the Ethical Committee of the institute. A written, informed consent was also obtained from all participants. A thorough history was obtained and a detailed physical examination was carried out. In addition, the following laboratory investigations were carried out: complete haemogram, ESR, CRP, serum lipids, rheumatoid Factor, anti-CCP (in suspected cases), electrocardiogram and carotid intima-media thickness (CIMT).

### Exclusion Criteria

Patients with clinically proven history of any of the conditions mentioned below were excluded from the study – (i) SLE, systemic sclerosis and antiphospholipid syndrome (ii) giant cell arteritis and Sjorgen's syndrome (iii) Gout and syphilis (iv) chronic kidney disease (v) family history of IHD and stroke.

### Study Design

The study conducted was a cross-sectional study. All patients were evaluated with detailed history – age, sex, duration of RA, presence of morning stiffness, list of painful joints, presence of other systemic disease and history of extra-articular manifestations of RA were documented. Treatment history was also noted. A systemic examination of all joints was done for features of activity, tender joint count and swollen joint count estimate. A simplified 28 joint articular index as described by Fuch's et al was used to assess disease activity. The 28 joints included 10 proximal interphalangeal joints of the fingers, 10 metacarpophalangeal joints, and the wrist, elbow, shoulder and the knee joints bilaterally. Cardiovascular examination was done in detail. Abdominal, respiratory and neurological examination was also done. Extra articular manifestations were carefully looked for and documented.

### Special Investigations

*Erythrocyte sedimentation rate* - was obtained by Westergren method. Venous blood was anti-coagulated with trisodium citrate dihydrate in the ratio of 4:1 and thoroughly mixed by gentle, repeated inversion and used to fill a Westergren-Katz tube to the zero mark. The tube was then replaced in a vertical position in a rack, which was not exposed to direct sunlight, draught or vibration and incubated at room temperature for 60 minutes. After this time, the distance (in mm) from the bottom of the surface meniscus to the top of red cells sediment was read and reported as the ESR result. Tests were performed within 2 hours of taking the blood sample. *Rheumatoid factor (IgG)* – a quantitative assay was performed using a latex fixation lab kit. *C-reactive protein* – a quantitative assay was performed using a latex agglutination kit. *Anti-CCP assay*– was done using QUANTA Lite CCP IgG ELISA. *Electrocardiography* – A 12 lead electrocardiogram was performed on all subjects in the study.

### Measurement of CIMT

In both cases and controls, ultrasound examination of the carotids was performed using a GE LOGIQ S7 diagnostic ultrasound system (GE Healthcare, USA). Bilateral measurements were made at the carotid bulb, at the distal 1 cm of the common carotid artery, and at the initial section of the internal carotid artery, close to its origin. The CIMT was calculated from the mean of the six obtained measurements. Both right and left CIMT values were taken for the study. Plaque was taken to be any focal protrusion of greater than 50 per cent from the surrounding wall.

## RESULTS

The data from the 69 test subjects was analyzed using IBM SSPS Statistics v22.0 software. In the study in both groups there was no difference with respect to age group distribution. The mean age of participants was 44.70 ± 15.01 years. In both cases and controls, 17.4% were in the age group < 30 yrs, 29% were in the age group 31 - 40 yrs, 17.4% were in the age group 41 - 50 yrs and 36.2% were in the age group > 50 yrs. In the study, majority of the participants were females (71%) and 29%

were males in both cases and controls.

**Table 1: Complaints Comparison Between Cases and Controls.**

| | | Groups | | | | P value |
|---|---|---|---|---|---|---|
| | | Cases | | Controls | | |
| | | Count | % | Count | % | |
| Painful Joints | No | 0 | 0.0% | 69 | 100.0% | <0.001* |
| | Yes | 69 | 100.0% | 0 | 0.0% | |
| Back pain | No | 32 | 46.4% | 66 | 95.7% | <0.001* |
| | Yes | 37 | 53.6% | 3 | 4.3% | |
| Joint Swelling Of > 6 Months | No | 14 | 20.3% | 69 | 100.0% | <0.001* |

All the cases had painful joints, 53.6% had back pain and 79.7% had joint swelling for > 6 months. Only 4.3% of controls had back pain. There was no history of painful joints or joint swelling in controls. This observation was statistically significant. In cases, 10.1% had morning stiffness for < 60 mins, 63.8% had morning stiffness for > 60 mins and in 26.1%, no morning stiffness was noted.

**Table 2: Descriptive Statistics for RA Factor (IU) in Cases.**

| RA Factor in IU | | | | | | |
|---|---|---|---|---|---|---|
| N | Mean | SD | Minimum | Median | Maximum | Range |
| 69 | 220.93 | 301.490 | 10 | 160.00 | 1280 | 1270 |

**Table 3: Descriptive Statistics for ESR in Cases.**

| Groups | | ESR |
|---|---|---|
| Cases | N | 69 |
| | Mean | 41.48 |
| | Std. Deviation | 13.57 |
| | Minimum | 20 |
| | Median | 40.00 |
| | Maximum | 70 |
| | Range | 50 |

**Table 4: Descriptive Statistics for CRP in Cases.**

| Groups | | CRP |
|---|---|---|
| Cases | N | 69 |
| | Mean | 49.59 |
| | Std. Deviation | 32.680 |
| | Minimum | 12 |
| | Median | 48.00 |
| | Maximum | 192 |
| | Range | 180 |

Mean cholesterol was 159.59 ± 15.49 in cases and 156.54 ± 14.60 in controls. There was no significant difference between cases and controls. Mean triglycerides was 109.94 ± 21.64 in cases and 103.20 ± 17.04 in controls. Mean HDL levels were 46.45 ± 6.27 in cases and 48.87 ± 4.50 in controls. Mean LDL Cholesterol was 66.49 ± 12.16 in cases and 61.81 ± 12.64 in controls. For the last three measurements, there was a significant difference between cases and controls.

**Table 5: Lipid Profile Comparison Between Cases and Controls.**

| | Groups | | | | P value |
|---|---|---|---|---|---|
| | Cases | | Controls | | |
| | Mean | SD | Mean | SD | |
| Cholesterol | 159.59 | 15.49 | 156.54 | 14.60 | 0.235 |
| Triglycerides | 109.94 | 21.64 | 103.20 | 17.04 | 0.044* |
| HDL Cholesterol | 46.87 | 6.27 | 48.45 | 4.50 | 0.091* |
| LDL Cholesterol | 66.49 | 12.16 | 61.81 | 12.64 | 0.028* |

Mean Right CIMT was 0.58 ± 0.15 in cases and 0.47 ± 0.04 in controls. Mean Left CIMT was 0.60 ± 0.15 in cases and 0.46 ± 0.04 in controls. For the above two measurements, there was a significant difference between cases and controls.

**Table 6: Comparison of Right and Left CIMT with Cases and Controls.**

| | Groups | | | | P value |
|---|---|---|---|---|---|
| | Cases | | Controls | | |
| | Mean | SD | Mean | SD | |
| Right CIMT | 0.58 | 0.15 | 0.47 | 0.04 | <0.001* |
| Left CIMT | 0.60 | 0.15 | 0.46 | 0.04 | <0.001* |

The study found a significant positive correlation between CIMT on the right side with RA factor and CRP - i.e. with an increase in CIMT, there was an increase in RA factor and CRP in cases at a significant level. Similarly, there was a significant positive correlation between CIMT on the left side with RA factor, ESR and CRP - i.e. with an increase in CIMT, there was an increase in RA factor, ESR and CRP in cases at a significant level. The study also found significant positive correlation between CIMT on right and left sides with duration of complaints - i.e. with increase in duration of complaints, there was a significant increase in CIMT on right and left sides.

**Table 7: Correlation of Right and Left CIMT with RA Factor, ESR and CRP in cases.**

| | | RA Factor | ESR | CRP |
|---|---|---|---|---|
| Right CIMT | Pearson Correlation | 0.436** | 0.231 | 0.348** |
| | P value | <0.0001* | 0.056 | 0.003* |
| | N | 69 | 69 | 69 |
| Left CIMT | Pearson Correlation | 0.411** | 0.269* | 0.313** |
| | P value | <0.0001* | 0.025* | 0.009* |
| | N | 69 | 69 | 69 |
| **. Correlation is significant at the 0.01 level (2-tailed). | | | | |
| *. Correlation is significant at the 0.05 level (2-tailed). | | | | |

In Table 8, it is observed that at a CIMT of 0.570 on the right side, the highest sensitivity and specificity was noted. Hence, a cut-off of around 0.570 in rheumatoid arthritis can predict atherosclerosis. This observation was statistically significant.

**Table 8: Area Under Curve in Cases for CIMT on Right Side.**

| Area Under the Curve | | | | |
|---|---|---|---|---|
| Test Result Variable(s): Right CIMT | | | | |
| Area | SE | P value | Asymptotic 95% Confidence Interval | |
| | | | Lower Bound | Upper Bound |
| 0.755 | 0.045 | <0.0001* | 0.666 | 0.843 |

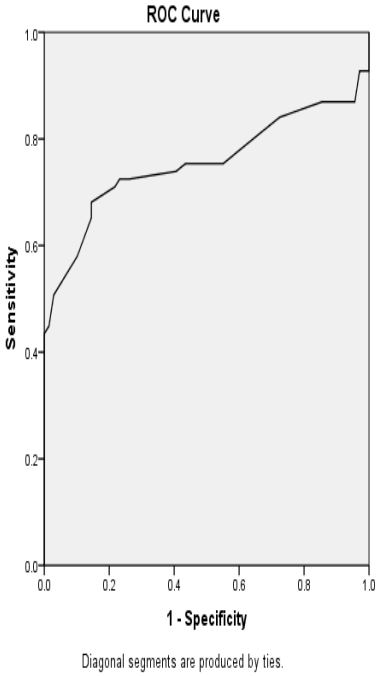


**Figure 1: ROC Curve Showing Area Under Curve for CIMT on Right Side in Cases.**

In Table 9, it is observed that at a CIMT of 0.565 on the left side, the highest sensitivity and specificity was noted. Hence, a cut-off of around 0.565 in rheumatoid arthritis can predict atherosclerosis. This observation was statistically significant.

**Table 9: Area Under Curve in Cases for CIMT on Left Side.**

| Area Under the Curve | | | | |
|---|---|---|---|---|
| Test Result Variable(s): Left CIMT | | | | |
| Area | SE | P value | Asymptotic 95% Confidence Interval | |
| | | | Lower Bound | Upper Bound |
| 0.794 | 0.044 | <0.0001* | 0.708 | 0.881 |

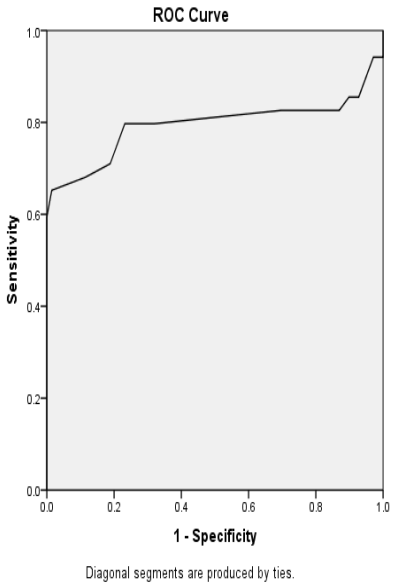


**Figure 2: ROC Curve Showing Area Under Curve for CIMT on Left Side in Cases.**

## DISCUSSION

Rheumatoid arthritis is a chronic systemic disease with a inflammatory background resulting in atherosclerosis.[20] Previous studies have shown the predominance of rheumatoid arthritis in patients in the 5th decade of their lives.[21] The measurement of carotid intima-media thickness as a surrogate marker is very much essential for the detection of subclinical atherosclerosis.[22] The majority of patients with RA in this study were females (n=49). As RA largely affects only women, and is an independent risk factor for subclinical atherosclerosis, a study conducted in women using CIMT is justified.

Recent studies in the general population of the US indicated that, among various markers of inflammation, the CRP level was a particularly powerful predictor of cardiovascular disease independently of serum lipid levels.[23] CRP is also hypothesized to be causally involved in the pathophysiology of atherosclerosis and its complications.[24] The chronic inflammatory response in RA patients has often bees associated with CIMT. In long-standing RA patients, where mean C-reactive protein (CRP) levels were greater than 15 mg/dl, the CIMT values were higher than in those with lower CRP levels.[25] In the present study, there was significant positive correlation between CIMT and CRP - i.e. with increase in CIMT, there was increase in CRP in cases at a significant level.

Elevated erythrocyte sedimentation rate (ESR) independently predicts radiographic progression of joint disease, increased disability, and poorer outcomes in RA.[26] ESR also increases linearly with increased carotid artery intimal-medial thickness in both patients with RA and healthy controls.[27] Patients with RA with elevated ESR have a higher rate of cardiovascular death than do those without elevated ESR.[28] Similarly, in the present

study, there was significant positive correlation between CIMT with RA factor and ESR - i.e. with increase in CIMT, there was increase in RA factor and ESR in cases at a significant level.

There are several possible explanations for the observed association between arterial wall thickness and RA. The first is a possible relationship between atherosclerosis and chronic inflammation due to RA. It has recently been hypothesized that inflammation plays a major role in the process of atherosclerosis.[29] Previous studies have demonstrated that atherosclerosis shares many similarities with other inflammatory diseases.[30] Although many other factors besides inflammation cause atherosclerosis, inflammation at the site of vascular injury probably mediates atherogenesis. It is therefore not surprising that the arterial wall was found to be thicker in patients with RA characterized by chronic inflammation. It has been suggested that vasculitis has a major effect on the increase in cardiovascular disease in RA patients[31], and that a low-grade inflammatory response might enhance the arterial wall changes in these patients. In the present study, there was significant positive correlation between CIMT and RA factor. The values of RA factor also had a positive correlation with the increased CIMT - i.e. with increase in CIMT, there was increase in RA factor in cases at a significant level.

Data on dyslipidemia in RA are conflicting, and in the more convincing findings, a decrease of high-density lipoprotein (HDL) cholesterol and an increase in low-density lipoprotein (LDL) levels, appear to be secondary to chronic inflammation rather than to primary metabolic alteration in RA.[32]

A question that needs to be answered is whether carotid ultrasonography should routinely be performed in all patients with RA to improve CV risk management. With respect to this question, carotid IMT was found to be an independent predictor of vascular events in high-risk individuals without RA in whom risk factors were managed clinically. Since the risk of CV disease is increased in patients with RA, carotid ultrasound might be a potential additional tool for stratifying CV risk in patients with RA.[33]

Multiple studies revealed a significant association between RA and the common carotid artery IMT.[34] Moreover, the common carotid artery IMT in RA patients was positively associated with disease duration. No significant association was found between corticosteroid treatment and common carotid artery IMT. In the present study, there was significant positive correlation between CIMT on right and left sides with duration of complaints - i.e. with increase in duration of complaints, there was significant increase in CIMT on right and left sides. Multiple studies have also showed that the presence of RA was an independent risk factor associated with arterial wall thickness.[35]

CIMT has been recommended as a screening tool for heart disease in apparently healthy individuals, and has been used in evaluating the progression of atherosclerotic coronary artery disease.[36] CIMT has the benefit of being low-cost and non-invasive, so it offers considerable convenience and convenience for the patient. The mean CIMT value among patients with RA was significantly higher than that observed among normal control subjects in the present study. Similar observations have been reported from other studies conducted in India[37] and in other parts of the world.[38]

The study shows a significant increase in CIMT in patients compared to healthy controls. CIMT is thus a surrogate marker of atherosclerosis in patients with RA, and screening of rheumatoid arthritis patients for atherosclerosis helps in predicting the risk of CAD. Our findings strongly suggest that RA itself is an independent risk factor for arterial wall thickening, and that the chronicity and severity of RA are associated with the arterial wall changes we identified. The measurement of CIMT was found to be a inexpensive, safe and a viable strategy for the detection of subclinical atherosclerosis.

## CONCLUSION

The current study established that subclinical atherosclerosis, detected by CIMT, is a reliable surrogate marker in patients with RA. A positive co-relation was also established between duration of disease, ESR, CRP, RA factor and increasing CIMT.

## REFERENCES

1. Sandoo A, Veldhuijzen van zanten JJ, Metsios GS, Carroll D, Kitas GD. Vascular function and morphology in rheumatoid arthritis: a systematic review. Rheumatology (Oxford)., 2011; 50(11): 2125-39.
2. Alamanos Y, Drosos AA. Epidemiology of adult rheumatoid arthritis. Autoimmun Rev., 2005; 4(3): 130-6.
3. Malaviya AN, Kapoor SK, Singh RR, Kumar A, Pande I. Prevalence of rheumatoid arthritis in the adult Indian population. Rheumatol Int., 1993; 13(4): 131-4.
4. Kaplan MJ. Cardiovascular complications of rheumatoid arthritis: assessment, prevention, and treatment. Rheum Dis Clin North Am., 2010; 36(2): 405-26.
5. Misra A, Khurana L. The metabolic syndrome in South Asians: epidemiology, determinants, and prevention. Metab Syndr Relat Disord., 2009; 7(6): 497-514.
6. Bartoloni E, Alunno A, Bistoni O, Gerli R. How early is the atherosclerotic risk in rheumatoid arthritis? Autoimmun Rev., 2010; 9(10): 701-7.
7. Ozbalkan Z, Efe C, Cesur M, et al. An update on the relationships between rheumatoid arthritis and atherosclerosis. Atherosclerosis., 2010; 212(2): 377-82.
8. Kitas GD, Erb N. Tackling ischaemic heart disease

in rheumatoid arthritis. Rheumatology (Oxford)., 2003; 42(5): 607-13.
9. Turesson C, Jacobsson LT, Matteson EL. Cardiovascular co-morbidity in rheumatic diseases. Vasc Health Risk Manag., 2008; 4(3): 605-14.
10. Gonzalez-gay MA, Gonzalez-juanatey C, Martin J. Rheumatoid arthritis: a disease associated with accelerated atherogenesis. Semin Arthritis Rheum., 2005; 35(1): 8-17.
11. Van den oever IA, Van sijl AM, Nurmohamed MT. Management of cardiovascular risk in patients with rheumatoid arthritis: evidence and expert opinion. Ther Adv Musculoskelet Dis., 2013; 5(4): 166-81.
12. Kriszbacher I, Koppán M, Bódis J. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med., 2005; 353(4): 429-30.
13. Feinstein SB, Voci P, Pizzuto F. Noninvasive surrogate markers of atherosclerosis. Am J Cardiol., 2002; 89(5A): 31C-43C.
14. Darabian S, Hormuz M, Latif MA, Pahlevan S, Budoff MJ. The role of carotid intimal thickness testing and risk prediction in the development of coronary atherosclerosis. Curr Atheroscler Rep., 2013; 15(3): 306.
15. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation., 2010; 122(25): e584-636.
16. Stein JH, Korcarz CE, Hurst RT, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. J Am Soc Echocardiogr., 2008; 21(2): 93-111.
17. Aviña-zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. Arthritis Rheum., 2008; 59(12): 1690-7.
18. Gonzalez-juanatey C, Llorca J, Martin J, Gonzalez-gay MA. Carotid intima-media thickness predicts the development of cardiovascular events in patients with rheumatoid arthritis. Semin Arthritis Rheum., 2009; 38(5): 366-71.
19. Evans MR, Escalante A, Battafarano DF, Freeman GL, O'leary DH, Del rincón I. Carotid atherosclerosis predicts incident acute coronary syndromes in rheumatoid arthritis. Arthritis Rheum., 2011; 63(5): 1211-20.
20. Mcinnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med., 2011; 365(23): 2205-19.
21. Grossman JM, Brahn E. Rheumatoid arthritis: current clinical and research directions. J Womens Health., 1997; 6(6): 627-38.
22. Appropriate use criteria for carotid intima media thickness testing. Atherosclerosis., 2011; 214(1): 43-6.
23. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med., 2000; 342(12): 836-43.
24. Osman R, L'allier PL, Elgharib N, Tardif JC. Critical appraisal of C-reactive protein throughout the spectrum of cardiovascular disease. Vasc Health Risk Manag., 2006; 2(3): 221-37.
25. Gonzalez-gay MA, Gonzalez-juanatey C, Piñeiro A, Garcia-porrua C, Testa A, Llorca J. High-grade C-reactive protein elevation correlates with accelerated atherogenesis in patients with rheumatoid arthritis. J Rheumatol., 2005; 32(7): 1219-23.
26. Heidari B. Rheumatoid Arthritis: Early diagnosis and treatment outcomes. Caspian J Intern Med., 2011; 2(1): 161-70.
27. Del rincón I, Williams K, Stern MP, Freeman GL, O'leary DH, Escalante A. Association between carotid atherosclerosis and markers of inflammation in rheumatoid arthritis patients and healthy subjects. Arthritis Rheum., 2003; 48(7): 1833-40.
28. Gabriel SE. Heart disease and rheumatoid arthritis: understanding the risks. Ann Rheum Dis., 2010; 69(Suppl 1): i61-64.
29. Galkina E, Ley K. Immune and inflammatory mechanisms of atherosclerosis (*). Annu Rev Immunol., 2009; 27: 165-97.
30. Pasceri V, Yeh ET. A tale of two diseases: atherosclerosis and rheumatoid arthritis. Circulation., 1999; 100(21): 2124-6.
31. Crowson CS, Liao KP, Davis JM, et al. Rheumatoid arthritis and cardiovascular disease. Am Heart J., 2013; 166(4): 622-628.e1.
32. García-gómez C, Bianchi M, De la fuente D, et al. Inflammation, lipid metabolism and cardiovascular risk in rheumatoid arthritis: A qualitative relationship?. World J Orthop., 2014; 5(3): 304-11.
33. Corrales A, González-juanatey C, Peiró ME, Blanco R, Llorca J, González-gay MA. Carotid ultrasound is useful for the cardiovascular risk stratification of patients with rheumatoid arthritis: results of a population-based study. Ann Rheum Dis., 2014; 73(4): 722-7.
34. Kumeda Y, Inaba M, Goto H, et al. Increased thickness of the arterial intima-media detected by ultrasonography in patients with rheumatoid arthritis. Arthritis Rheum., 2002; 46(6): 1489-97.
35. Ristić GG, Lepić T, Glisić B, et al. Rheumatoid arthritis is an independent risk factor for increased carotid intima-media thickness: impact of anti-inflammatory treatment. Rheumatology (Oxford)., 2010; 49(6): 1076-81.
36. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force

on Practice Guidelines. Circulation., 2010; 122(25): e584-636.
37. Chatterjee Adhikari M, Guin A, Chakraborty S, Sinhamahapatra P, Ghosh A. Subclinical atherosclerosis and endothelial dysfunction in patients with early rheumatoid arthritis as evidenced by measurement of carotid intima-media thickness and flow-mediated vasodilatation: an observational study. Semin Arthritis Rheum., 2012; 41(5): 669-75.
38. Daza L, Aguirre M, Jimenez M, Herrera R, Bollain JJ. Common carotid intima-media thickness and von Willebrand factor serum levels in rheumatoid arthritis female patients without cardiovascular risk factors. Clin Rheumatol., 2007; 26(4): 533-7.