Brachial artery flow-mediated dilation and carotid intima-media thickness for assessment of subclinical atherosclerosis in rheumatoid arthritis

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Objectives
The aim of this study was to assess subclinical atherosclerosis in rheumatoid arthritis (RA) patients using flow-mediated dilation (FMD) and carotid intima–media thickness (CIMT) and find their relation to disease activity.

Patients and methods
Totally, 30 RA patients without cardiac involvement and 10 controls were included in the study. Disease activity was evaluated using disease activity score 28 (DAS28) score. Low disease activity is defined by DAS28 of 3.2 or less, moderate disease activity as DAS28 3.3–5.3, and severe disease activity as DAS28 of 5.4 or more. Endothelial dysfunction is considered to be present when FMD on B-mode ultrasonography is below 4.5%. CIMT was calculated by measuring the greatest distance between lumen–intima and media–adventitia interface [mean value of two sides (right and left) was taken] using B-mode ultrasonography.

Results
The mean CIMT was significantly higher in the RA patients (1.8±0.2) than in healthy controls (1.5±0.1) (P=0.001). Taking the mean±SD of the control group (1.6 mm) as the upper limit of the normal CIMT, 22 (73.3%) RA patients and three (30%) controls had abnormal mean CIMT, which was statistically significant. Brachial FMD% in RA patients was significantly lower (22.9±11.0) as compared with controls (35.5±23.2) (P=0.027). A statistically significant positive correlation was observed between CIMT values of patients with age, C-reactive protein, and low-density lipoprotein. There was a significant negative correlation between CIMT and hemoglobin and brachial FMD. FMD% showed a statistically significant negative correlation with age, disease duration, low-density lipoprotein, Framingham cardiovascular risk score, and mean CIMT.

Conclusion
Carotid ultrasound and endothelial function assessment by means of FMD may be a useful tool to predict the increased risk for cardiovascular disease in patients with RA, which requires aggressive therapy.

Keywords:
carotid intima–media thickness, flow-mediated dilation, rheumatoid arthritis, subclinical atherosclerosis

Introduction
Rheumatoid arthritis (RA) is a chronic systemic inflammatory, autoimmune disease of unknown origin that affects 1–2% of adult populations with characteristic persistent symmetric polyarthritis (synovitis) and extra-articular involvement of the skin, heart, lungs, and eye [1]. The systemic and articular inflammatory load drives the destructive progression of the disease, and the extent of inflammation in RA has been linked to an increased risk for cardiovascular (CV) mortality resulting from accelerated atherogenesis [2]. RA is associated with an increased CV morbidity and mortality as compared with the general population, and the reported relative risk for cardiovascular disease (CVD) in RA patients ranges from 1.5 to 4.0 [3,4]. The exact mechanism of association between RA and CVD remains unclear. Available studies indicated that adjustment for conventional cardiovascular disease risk (CVR) factors does not account for the higher rates of CV events in RA populations, suggesting that, the process of inflammation, probably the driving force for premature atherosclerosis in RA because striking parallels can be drawn between the atherosclerotic plaque and synovitis in RA at the tissue level, is an independent risk factor for CVD [5]. Besides

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traditional CVR factors and chronic inflammation, recent studies have also highlighted the involvement of genetic factors and the influence of several gene polymorphisms in the risk for accelerated atherosclerosis of patients with RA [6].

Carotid B-mode ultrasound (US) is a convenient noninvasive method for detecting subclinical atherosclerosis [7]. Carotid intima–media thickness (CIMT) and the presence of plaque in the carotid arteries are strongly associated with CVR factors and generalized atherosclerosis [8,9], and are also a strong predictor of future CV events.

CIMT has been used in several clinical trials as a surrogate endpoint for evaluating the regression and/or progression of atherosclerotic CVD [10,11].

The importance of abnormally high CIMT and plaques as predictors of CV events in patients with RA has been emphasized [12,13].

The human vascular endothelium provides structural and functional roles within the body. A healthy endothelium allows for mechanical to chemical signal transduction to maintain homeostasis of the blood vessel [14]. Endothelial dysfunction is an imbalance of these mediators and the first step in vascular disease, present before histological evidence of atherosclerosis. A noninvasive, in-vivo method for quantifying the vasodilatory function of human artery exists. This method, endothelium-dependent, flow-mediated vasodilation (FMD), is widely used in clinical trials.

Importantly, endothelial dysfunction can be observed in individuals without diagnosed CVD and is predictive of future CV events [15,16,17]. Endothelial dysfunction determined by flow-mediated endothelium-dependent vasodilation (FMD) has been observed in both patients with recent onset and low disease activity as well as longstanding RA patients [18,19].

Several studies suggest that CIMT, structural measure of early atherosclerosis in RA patients and brachial artery FMD%, a physiologic measure of subclinical atherosclerosis are reliable methods to assess the subclinical atherosclerosis and may measure different stages of early atherogenesis in RA patients [20].

Aim
The aim of this study was to assess subclinical atherosclerosis in RA patients using FMD and CIMT and find their relation with disease activity.

Patients and methods

Patients
Our study was conducted in the Rheumatology Unit, Internal Medicine Department, Assiut University Hospitals, Egypt. It is a case–control study. Totally, 40 individuals were divided into two groups: the patient group and the control group. The patient group included 30 patients with RA without cardiac involvement; every patient fulfilled the 2010 ACR/EULAR Rheumatoid Arthritis Classification Criteria [21]. The control group consisted of 10 healthy individuals matched for age and sex.

Exclusion criteria
(1) Age more than 70 or less than 18 years at entry.
(2) Current pregnancy.
(3) Comorbid diseases/conditions: diabetes, obesity (BMI: \( \geq 30 \)), familial dyslipidemia, hypertension, coronary artery disease, cerebrovascular accident, peripheral vascular disease, hypothyroidism, renal disease (serum creatinine: \( \geq 3.0 \text{ mg/dl} \) or creatinine clearance: \( \leq 30 \text{ ml/min} \)), liver disease, and Cushing’s syndrome.
(4) Concurrent treatment with lipid-lowering drugs, \( \beta \)-blockers, oral contraceptives, estrogens, progestin, thyroxin, and steroids.
(5) Refusal to be enrolled in the study.

Ethical considerations
Written informed consent was taken from all study participants and the study protocol was approved by the Ethical Committee of the Faculty of Medicine.

Methods
(1) Full history taking, including age, sex, duration of the disease, and type of treatment.
(2) Complete clinical examination, BMI, and joint examination, which included tender joint count (TJC), swollen joint count (SJC), and deformity. A composite disease activity score 28 (DAS28) was calculated using three variables: SJC (28), TJC (28), and Westergren’s erythrocyte sedimentation rate (ESR). The low disease activity is defined by DAS28 of 3.2 or less, moderate disease activity as DAS28 3.3–5.3, and severe disease activity as DAS28 of 5.4 or more [22]. Framingham CVR score was calculated depending mainly on blood pressure (BP) and lipid profile for evaluation of risk for heart disease in 10 years [23].
(3) Laboratory investigations:
   (a) Complete blood count was performed using automated cell counter.
   (b) ESR was measured using the modified Westergren’s method.
   (c) C-reactive protein (CRP) and rheumatoid factor (RF) were measured using the latex agglutination method.
   (d) Serum levels of cholesterol, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) were determined using a semi auto analyzer.
   (e) Blood urea and serum creatinine, fasting blood glucose, and serum uric acid were measured using the spectrophotometric method using stat fax.
   (f) Complete urine analysis was performed by means of microscopic examination.
   (g) Radiography of the hands and feet was performed to assess radiological bone and cartilage changes using van der Heijde modification of Sharp score of joint involvement by RA on plain radiographs [24].

(4) Ultrasonographic scanning of the carotid artery was performed using an echographic system to detect CIMT. CIMT was increased if it was more than 0.7 mm.

(5) Flow-mediated vasodilatation of brachial artery. The procedure was performed by a single radiologist. The participants were asked to abstain from alcohol, caffeine, and smoking at least 8 h before the procedure. The participant was made to lie in a supine position for 10 min. The right brachial artery was scanned in longitudinal section 2–15 cm above the antecubital fossa with B-mode ultrasonography images using 7–12-MHz broadband linear array transducer. The center of the artery was identified where the clearest picture of the anterior and posterior intimal layers was available. In this suitable transducer position, which was kept constant throughout the procedure, a resting scan was obtained. The luminal diameter of the brachial artery was measured using pulsed Doppler (D1). A sphygmomanometer cuff placed around forearm distal to the scanned region was inflated to 200 mmHg for 4.5 min and then released, which induced increased flow. A second scan was taken at this stage and again luminal diameter of the artery was measured 60 s after cuff deflation (D2). Endothelial dysfunction is considered to be present when FMD is below 4.5% [25,26]. The endothelium-dependent function is defined by the following formula:

\[
\frac{(D2D1)}{D1} \times 100
\]

The higher the numeric value of the study, the better is the endothelial function (Figs 1 and 2).

Statistical analysis
Statistical analysis was performed using statistical package for the social sciences, version 16.0, for Window software (SPSS Inc., Chicago, Illinois, USA). Mean and SDs were used to express quantitative data. For continuous variables, testing between two groups was performed using the Mann–Whitney U-test. Categorical variables were compared using Pearson’s \( \chi^2 \)-test when very small proportions were analyzed. A correlation between variables was examined using the Pearson’s correlation coefficient. Multiple linear regression analysis was used to explore a predictive relationship between FMD and CIMT with major variables. \( P \) values of less than 0.05 were considered statistically significant. \( P \) values of more than 0.05 were considered statistically nonsignificant.

Results
This study included 30 patients (27 women and three men) with an average age of 47.4±11.9 years and average disease duration of 9.0±5.5 years. As regards controls, there were 10 healthy controls (five women and five men) with an average age of 38.0±12.2. Twenty-five (83.3%) patients were RF positive (RF titer 121.7±127.8 IU/ml). Three (10%) patients had low DAS 28 score (2.0–3.1), 14 (46.6%) patients had moderate DAS 28 score (3.5–5.3), and 13 (43.3%) patients had high DAS28 score (Tables 1 and 2).

There were no significant differences between patients and controls in most clinical variables such as BP and BMI. Age and sex were significantly higher in RA patients as compared with controls (Table 1).

Figure 1
Comparison between mean carotid intima–media thickness (CIMT) of both patients and controls. As shown in this figure, the mean CIMT was significantly higher in the rheumatoid arthritis patients (1.8±0.2) than in the healthy controls (1.5±0.1; \( P=0.001 \)). Taking the mean±SD of the control group (1.6 mm) as the upper limit of the normal CIMT, 22 (73.3%) rheumatoid arthritis patients and three (30%) controls had abnormal mean CIMT, which was statistically significant.
On comparing laboratory and radiological findings between RA patients and controls, ESR, LDL, mean CIMT, and brachial FMD were significantly higher in RA patients as compared with the control group (Table 2 and Figs 3 and 4).

We looked for any correlation of high CIMT and low FMD% values of patients with factors such as disease duration, ESR, CRP, RF titer, Framingham CVR, and DAS28 to assess how these factors contributed to atherosclerosis in RA. A statistically significant positive correlation was observed between CIMT values of patients with age, CRP, and LDL. However, there was no significant correlation between CIMT and the other variables except hemoglobin and brachial FMD with which there was a negative correlation (Table 3).

Among the above contributing factors, FMD% showed a negative correlation with most variables as expected but the correlation was statistically significant with age, disease duration, LDL, Framingham CVR score, and mean CIMT, as shown in Table 3. Bold values are statistically significant.

Multiple regression analysis involving most clinical and laboratory features with FMD revealed disease duration, hemoglobin level, serum creatinine level, and Framingham CVR score to be significant determinants for FMD when adjusted for other independent variables. This analysis also revealed no significant factors for CIMT (Table 4).

### Discussion

RA is associated with increased CV mortality as a result of accelerated atherosclerosis [2].

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### Table 1 Clinical data of the rheumatoid arthritis patients and healthy controls

| Variables                  | RA patients (n=30) | Healthy controls (n=10) | P value |
|----------------------------|--------------------|-------------------------|---------|
| Age (years)                | 47.4±11.9          | 38.0±12.2               | 0.037   |
| Sex (female/male)          | 27/3               | 5/5                     | 0.005   |
| Disease duration (years)   | 9.0±5.5            | ––                      |         |
| Morning stiffness (h)      | 0.79±0.87          | ––                      |         |
| RAI                        | 14.6±9.2           | ––                      |         |
| TJJC                       | 11.3±5.8           | ––                      |         |
| SJJC                       | 1.8±2.3            | ––                      |         |
| Deformity (present/ not)   | 11/19              | ––                      |         |
| BMI (kg/m²)                | 25.8±4.4           | 24.2±4.4                | 0.308   |
| Systolic BP (mmHg)         | 127±15.7           | 126±10.7                | 0.854   |
| Diastolic BP (mmHg)        | 81±11.5            | 80±9.4                  | 0.806   |

Data are expressed as mean±SD. Bold values are statistically significant. BP, blood pressure; RA, rheumatoid arthritis; RAI, Ritchie articular index; SJJC, swollen joint count; TJJC, tender joint count.

### Table 2 Laboratory and radiological data of the rheumatoid arthritis patients and controls

| Variables                  | RA patients (n=30) | Healthy controls (n=10) | P value |
|----------------------------|--------------------|-------------------------|---------|
| Hemoglobin (g/dl)          | 11.1±1.9           | 12.2±0.8                | 0.093   |
| ESR (mm/first hour)        | 48.8±31.4          | 7.7±4.4                 | 0.000   |
| CRP (mg/l)                 | 62.9±127           | 1.2±0.8                 | 0.136   |
| RF titer (IU/ml)           | 121.7±127.8        | ––                      |         |
| Blood urea (mmol/l)        | 5.3±5.5            | 4.9±1.2                 | 0.727   |
| Serum creatinine (μmol/l)  | 68.1±35.7          | 68.3±9.1                | 0.986   |
| Uric acid (mg/dl)          | 4.5±2.6            | 4.6±1.3                 | 0.923   |
| Cholesterol (mg/dl)        | 178.1±47.1         | 185.0±37.3              | 0.678   |
| Triglycerides (mg/dl)      | 111±53.9           | 85.1±15.9               | 0.145   |
| HDL (mg/dl)                | 49.8±16.4          | 60.3±12.4               | 0.076   |
| LDL (mg/dl)                | 107.3±41.3         | 75.6±14.4               | 0.024   |
| Framingham CVR score       | 6.9±6.8            | 3.2±3.6                 | 0.112   |
| DAS28                      | 5.0±1.2            | ––                      |         |
| Mean CIMT (mm)             | 1.8±0.2            | 1.5±0.1                 | 0.001   |
| Brachial FMD%              | 22.9±23.2          | 35.5±23.2               | 0.027   |

CIMT, carotid intima–media thickness; CRP, C-reactive protein; CVR, cardiovascular risk; DAS28, disease activity score 28; ESR, erythrocyte sedimentation rate; FBG, fasting blood glucose; FMD, flow-mediated vasodilatation; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RA, rheumatoid arthritis; RF, rheumatoid factor. Bold value mean the significant one.
Two important noninvasive techniques were useful in the assessment of subclinical atherosclerosis, the evaluation of endothelial function by FMD%, and the measurement of CIMT using high-resolution B-mode ultrasonography [28].

Therefore, in our study, we selected patients with RA without clinically evident CVDs. There were no significant differences between patients and controls in most clinical variables such as systolic BP, diastolic BP, and BMI. However, other clinical variables such as disease duration, morning stiffness, Ritchie articular index, TJC, SJC, and RA deformities are not correlated with the controls.

Our results show that the CIMT has a high predictive value for the development of CVD. The results implicate that the mean CIMT of the common carotid artery was significantly higher in RA patients than in healthy individuals.

Our results were the same as Gonzalez and colleagues [12,20,29,30,31,32,33], in which the presence of subclinical atherosclerosis, manifested by increased value of CIMT is consistent with the high rate of silent ischemic heart diseases and sudden cardiac death observed in RA patients and had high predictive power for the development of CVD events over a 5-year follow-up period.

Endothelial dysfunction plays a key role in early atherosclerosis and contributes to the development of clinical features in the later stages of CVD [34]. Because endothelial function in brachial circulation is correlated with endothelial function observed in coronary circulation, vascular US examination is now considered a safe noninvasive technique for examining FMD.

The results of our study show that FMD of brachial artery has a significant endothelial dysfunction in RA patients than in healthy controls. Similar to the present study, other studies such as that by Amin et al. [20] have found a significant endothelial dysfunction in patients with autoimmune disease such as RA by means of FMD. The presence of systemic inflammation predisposes to atherosclerosis, affecting the endothelial function and decreasing the production of nitric oxide by the endothelium; this decrease in the nitric oxide production leads to a smaller arterial dilatation upon induced ischemia [20].

Our study showed a significant correlation of CIMT and FMD in RA patients with several clinical
variables such as age of the patient. There was a significant positive correlation with CIMT and a significant negative correlation with FMD. Disease duration has a significant negative correlation with FMD.

Our results are similar to other studies worldwide, which reported that, on multivariate analysis, only age and disease duration were found to have a significant correlation with CIMT [35,36]. Moreover, Fan et al. [29] confirmed our results and stated that, on the univariate analysis, a significantly positive correlation was observed between CIMT and age of the patients, disease duration, DAS, CRP, and systolic BP and a statistically inverse correlation was observed between CIMT and HDL cholesterol [29]. Adhikari et al. [31] supported our results and stated that age, systolic BP, TJC, and SJC had significant correlations with patient’s CIMT.

Our study does not coincide with that of Schroeder et al. [37], in which the age of the patient does not affect the endothelial function evaluation with FMD.

Our results showed significantly higher differences between RA patients and controls in ESR level but CRP level showed no significance. CRP showed a significant positive correlation with CIMT only. Castro et al. [38] demonstrates that patients with RA present endothelial dysfunction, and FMD does not correlate with CRP, patient’s age, and disease duration.

No significant correlation of CIMT and ESR or DAS28 was found in our study. It might be due to the fact that DAS28 and ESR levels often fluctuate in chronic inflammatory diseases, and their measurement at a single point only can show the inflammatory burden at that point of time and fails to reveal the inflammatory burden of the entire disease duration.
The same finding was also observed in previous studies [39,40,41].

In our study, Framingham CVR score showed a significant negative correlation with FMD. However, there was no significant difference between RA patients and controls.

In our study, the mean CIMT had a significant negative correlation with brachial FMD. This may be attributed to the techniques used in making the measurements of FMD% and CIMT. However, both CIMT and endothelial function measurements were performed by the same experienced radiologist and following common standardized protocols, which suggest that our techniques of measurements are accurate. Therefore, we believe that our findings support the other possibility that, in RA patients with relatively few risk factors, CIMT and brachial artery FMD% provide independent information about the atherosclerotic process. Furthermore, previous studies in patients with CVD indicate an inverse correlation between CIMT and brachial FMD [20]. These findings are also in agreement with Fan et al. [29], who stated that there is no correlation between measurements of CIMT and brachial artery FMD% in RA patient cohort without CVD and with relatively few risk factors. Moreover, they reported that atherosclerosis is a complex disease and may have complex pathways. Thus, both endothelial dysfunction and intima-media thickness may be stages in the pathogenesis of atherosclerosis but they are in different pathways, all of which lead to clinical CVD [29].

Lipid levels appear to be altered as a result of RA disease activity. In our study, LDL only had higher significance in RA patients than in healthy controls, whereas other parameters including total cholesterol, triglycerides, and HDL are not significant. Moreover, LDL only showed a significant positive correlation with CIMT and a negative correlation with FMD.

In previous studies, data on total cholesterol and LDL cholesterol levels in patients with RA are conflicting; some studies demonstrate similar [42] or lower [43] levels of total cholesterol, whereas others demonstrate increased levels of total cholesterol and LDL cholesterol in patients with early inactive RA [44].

Although reports on lipid profiles in RA patients vary, growing evidence suggests that patients with untreated RA have reduced total cholesterol, LDL cholesterol, and HDL cholesterol levels [45]. Regardless of the total cholesterol changes in RA patients, several studies support the notion that RA leads to a more atherogenic lipid profile (ratio of total cholesterol to HDL cholesterol), which is correlated with disease activity and improves after treatment with antirheumatic medications [46].

In our study, multiple regression analysis involving most clinical and laboratory features with FMD revealed that disease duration, hemoglobin level, serum creatinine level, and Framingham CVR score were significant determinants for FMD when adjusted for other independent variables. This analysis also revealed no significant factors for CIMT.

Quyyumi [47] affirms that systemic inflammation markers such as FMD and CIMT arise as a method for evaluating the atherosclerosis risk. He recommends the inclusion of these methods in randomized study for screening and diagnosis of CVR. Considering that a high level of systemic inflammation affects the endothelial function, inflammation markers such as FMD may provide a better evaluation for the CVR in patients with RA [47].

Therefore, in our study we demonstrate that the FMD and CIMT are promising methods for the evaluation of RA and are very helpful for the prevention of vascular risk.

Conclusion
The results from the present study support the use of carotid US and endothelial function assessment by means of FMD as a useful tool to predict the increased risk for CVD in patients with RA. We suggest that the carotid artery US should be performed for all patients with RA to establish the risk for CV complication, which requires more aggressive therapy.

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Nil.

Conflicts of interest
There are no conflicts of interest.

References
1 Kobayashi H, Giles JT, Polak JF, Blumenthal RS, Leffell MS, Szklø M, et al. Increased prevalence of carotid artery atherosclerosis in rheumatoid arthritis is artery-specific. J Rheumatol 2010; 37:730–739.
2 Gonzalez-Gay MA, Gonzalez-Juanatey C, Martin J. Rheumatoid arthritis: a disease associated with accelerated atherogenesis. Semin Arthritis Rheum 2005; 35:8–17.
Van Doornum S, McColl G, Wicks IP. Accelerated atherosclerosis: an extraarticular feature of rheumatoid arthritis? Arthritis Rheum 2002; 46:862–873.

Avina-Zubieta JA, Choi HK, Sadatsafavi M, Elmimouni M, Esdaile JM, Lacroix D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analytical overview of observational studies. Arthritis Rheum 2008; 59: 1690–1697.

Szekanecz Z, Kerekes G, Der H, Sandor Z, Szabo Z, Vegvari A, et al. Accelerated atherosclerosis in rheumatoid arthritis. Ann N Y Acad Sci 2007; 1108:349–358.

Rodriguez-Rodriguez L, Lopez-Mejias R, Garcia-Bermudez M, Gonzalez-Juanatey C, Gonzalez-Gay MA, Martin J. Genetic markers of cardiovascular disease in rheumatoid disease. Mediat Inflamm 2012; 2012:574817.

Farzaneh-Far A, Roman MJ. Accelerated atherosclerosis in rheumatoid arthritis and systemic lupus erythematosus. Int J Clin Pract 2005; 59:823–824.

Kawamori R, Yamasaki Y, Matsushita H, Nishizawa H, Nao K, Hougaku H, et al. Prevalence of carotid atherosclerosis in diabetic patients. Ultrasound high-resolution B-mode imaging on carotid arteries. Diabetes Care 1992; 15: 1290–1294.

Lorenz MW, von Kegler S, Steinmetz H, Markus HS, Sitzer M. Carotid intima-media thickness indicates a higher vascular risk across a wide age range: prospective data from the Carotid Atherosclerosis Progression Study (CAPS). Stroke 2006; 37:87–92.

Greenland P, Alger JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, et al. ACC/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:e584–e636.

Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, et al. American Society of Echocardiography Carotid Intima-Media Thickness Task Force. 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 Cardiovascular Angiography and Interventions. J Am Soc Echocardiogr 2008; 21:93–111.

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; 38:366–371.

Evans MR, Escalante A, Battafarano DF, Freeman GL, O’Leary DH, Del Rincon I. Carotid atherosclerosis predicts incident acute coronary syndromes in rheumatoid arthritis. Arthritis Rheum 2011; 63:1211–1220.

Gerlach E, Nees S, Becker BF. The vascular endothelium: a survey of some newly evolving biochemical and physiological features. Basic Res Cardiol 1985; 80:459–474.

Suwaidi JA, Rabinovich D, Katzenmeyer K, Gruenewald T, Heri BM, Llorca J. Endothelial dysfunction, carotid intima-media thickness, and accelerated atherosclerosis in rheumatoid arthritis. Semin Arthritis Rheum 2008; 38:67–70.

Rojas-Villarraga A, Ortega-Hernandez OD, Gomez LF, Parido AL, Lopez-Guzman S, Arango-Ferreira C. Risk factors associated with different stages of atherosclerosis in Colombian patients with rheumatoid arthritis. Semin Arthritis Rheum 2008; 38:71–82.

Fan CY, Zhang ZY, Mei YF, Wu CJ, Shun BZ. Impaired brachial artery flow-mediated dilation and increased carotid intima-media thickness in rheumatoid arthritis patients. Chin Med J (Engl) 2012; 125:832–837.

Noha MAM, Hytham HE. Endothelial dysfunction and subclinical atherosclerosis as evidenced by the measurement of flow mediated dilatation of brachial artery and carotid intima media thickness in patients with rheumatoid arthritis. Egypt J Radiol Nucl Med 2013;44:237–243.

Adhikari MC, Chakraborty AG, Ghosh PS. 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; 41:669–675.

Wang P, Guan S-Y, Xu S-Z, Li H-M, Leng R-X, Li X-P, Fan H-F. Increased carotid intima-media thickness in rheumatoid arthritis: an update meta analysis. Clin Rheumatol 2016; 35:315–323.

Saigal R, Mathur V, Goyal L. Carotid intima media thickness as a marker of subclinical atherosclerosis in rheumatoid arthritis: a case control study. Int J Adv Med 2016; 3:942–946.

Vita JA, Keaney JF Jr. Endothelial function: a barometer for cardiovascular risk? Circulation 2002; 106:640–642.

Majahan V, Handa R, Kumar U, Sharma S, Gulati G, Pandey RM, et al. Assessment of atherosclerosis by carotid intimalmedial thickness in patients with rheumatoid arthritis. J Assoc Physicians India 2008; 56:587–590.

Grover S, Sinha RP, Singh U, Teварi S, Aggarwal A, Misra R. Subclinical atherosclerosis in rheumatoid arthritis in India. J Rheumatol 2006; 33:244–247.

Schroeder S, Endler MD, Baumbach A, Ossen R, Herdeg C, Kuettner A, Karch KR. Influence of vessel size, age and body mass index on the flow mediated dilation (FMD%) of the brachial artery. Int J Cardiol 2000; 76:219–225.

Castro PT, Montenegro CA, Carvalho ACP, Filho JF, Bianchi W, Bianchi DV, Leite SP. Brachial artery flow-mediated dilation in women with rheumatoid arthritis. Radiol Bras 2007; 40:247–250.

Tyrell PN, Beyeu J, Feldman BM, McCrindle BW, Silverman ED, Bradley TJ. Rheumatic disease and carotid intima-media thickness: a systematic review and metaanalysis. Arterioscler Thromb Vasc Biol 2010; 30: 1014–1026.

Khodivounkit W, Kim MS, Memon RA. Effects of infection and inflammation on lipid and lipoprotein metabolism: mechanisms and consequences to the host. J Lipid Res 2004; 45:1169–1196.

Romain MJ, Moelter E, Davis A, Paget SA, Crow MK, Lockshin MD. Preclinical carotid atherosclerosis in patients with rheumatoid arthritis. Ann Intern Med 2006; 144:249–256.

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: 1701–1704.

Boers M, Nurmohamed MT, Doelman CJ, Lard LR, Verhoeven AC, Voskuyl AE, et al. Influence of guanoctoic acid and disease activity on total and high density lipoprotein cholesterol in patients with rheumatoid arthritis. Ann Rheum Dis 2003; 62:842–845.
44 Shah SAR, Baba MS, Khaliq A, Jeelani I, Shah SJ, Nadeem S. Lipid profile in rheumatoid arthritis and its relation with inflammatory markers. Insights Biomed 2017; 2:1.

45 Myasoedova E, Crowson CS, Kremers HM, Roger VL, Fitz-Gibbon PD, Themeau TM, Gabriel SE. Lipid paradox in rheumatoid arthritis: the impact of serum lipid measures and systemic inflammation on the risk of cardiovascular disease. Ann Rheum Dis 2011; 70:482–487.

46 van Halm VP, Nielen MMJ, Nurmohamed MT, van Schaardenburg D, Reesink HW, Voskuyl AE, et al. Lipids and inflammation: serial measurements of the lipid profile of blood donors who later developed rheumatoid arthritis. Ann Rheum Dis 2007; 66: 184–188.

47 Quyyumi AA. Inflamed joints and stiff arteries: is rheumatoid arthritis a cardiovascular risk factor? Circulation 2006; 114:1137–1139.