



# **Carotid Intima Media Thickness and Endothelial Function: Useful Surrogate Markers for Cardiovascular Risk in Rheumatoid Arthritis Patients**

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## **Authors' contributions**

*This work was carried out in collaboration among all authors. Author RAES had significant contributions to the conception and design of the work, analysis and interpretation of data and drafted the manuscript. Authors AAS, RGE and MFS had substantial contributions to the conception of the work, interpretation and analysis of data and revision of the final manuscript. All authors read and approved the final manuscript.*

## **Article Information**

DOI: 10.9734/JAMMR/2021/v33i1330953

*Editor(s):*

(1) Dr. Sevgul Donmez, Mugla Sitki Kocman University, Turkey.

*Reviewers:*

(1) Ghazi Chabchoub, Tunisia.

(2) N. C. R. J. Anne Dushanthi Dargini, Sri Lanka.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/68784>

**Original Research Article**

**Received 22 March 2021**

**Accepted 02 June 2021**

**Published 07 June 2021**

## **ABSTRACT**

**Introduction:** Cardiovascular diseases (CVDs) are the main cause of morbidity and mortality in RA disease. In active RA patients, the majority of cardiovascular deaths result from accelerated atherosclerosis.

**Aim of the Work:** The aim of this work is to assess carotid intima media thickness (C-IMT) and endothelial function by brachial artery flow mediated dilatation (FMD) in Rheumatoid arthritis patients and relation to the disease activity.

**Subjects and Methods:** Our study included 50 RA patients, from Tanta University Hospital. 47 women and 3 men and their age ranged from 30-62 years. They were divided into group 1: 25 active RA patients, group 2: 25 inactive RA patients who were diagnosed by American College of

Rheumatology (ACR) revised criteria for diagnosis of RA 1987 and disease activity was evaluated using disease activity score 28(DAS28). Group 3: 25 normal subjects as a control group. We measured C-IMT and FMD in all groups.

**Results:** By comparing the groups, we found that active RA patients had increased C-IMT compared to inactive rheumatoid arthritis patients and controls which is indicator of atherosclerosis. FMD of the brachial artery impaired in RA patients compared to controls which is indicator of endothelial dysfunction. There was highly statistically significant relation between duration, activity of RA disease and atherosclerosis in RA patients.

**Conclusion:** With increasing the frequency of atherosclerosis in asymptomatic RA patients, carotid IMT increased and FMD impaired when compared with general population. Active RA patients have increased carotid IMT and impaired FMD compared with inactive RA patients.

**Keywords:** Carotid intima media thickness; endothelial function; cardiovascular risk; rheumatoid arthritis.

## ABBREVIATIONS

ACR	: American college of rheumatology
Anti CCP	: Antibodies to cyclic citrullinated peptide
CBC	: Complete blood count
C-IMT	: Carotid intima media thickness
CRP	: C-reactive protein
CVD	: Cardiovascular disease
DAS28	: Disease activity score28
ET-1	: Endotheline 1
ESR	: Erythrocyte sedimentation rate
FMD	: Flow mediated dilatation
LDL	: Low-density lipoprotein
NO	: Nitric oxide
RA	: Rheumatoid arthritis
RBCs	: Red blood cells
RF	: Rheumatoid factor
WBCs	: White blood cells

## 1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease, affecting multiple systemic due to multiple factors and autoimmune disorder of unknown etiology that affects mainly joints [1]. It is affecting many organs as joints, skin, eyes, lung and blood vessels [2]. Cardiovascular diseases are the main cause of mortality and morbidity in RA patients [3]. In active RA patients, the majority of cardiovascular deaths result from accelerates atherosclerosis [4,5]. In the past atherosclerosis, thought to be a passive disease due to accumulation of lipid, but now widely acknowledged as a dynamic inflammatory process starting with endothelial activation, leukocyte recruitment, lipid oxidation, and culminating with plaque destabilization and thrombosis [6].

Subclinical atherosclerosis can be detected by an increased main carotid artery intima media

thickness (IMT), which is a good marker of generalized atherosclerosis. Carotid artery IMT measuring is a noninvasive, sensitive, cost-effective method to demonstrate subclinical atherosclerosis and to diagnose at-risk patient groups [7,8]. The important sign of early atherosclerosis is endothelial dysfunction, it can be assess by simple non-invasive markers (FMD) of peripheral arteries [9].

## 2. MATERIALS AND METHODS

This study was carried on patients at Rheumatology outpatient clinic and wards of Internal Medicine department of Tanta University Hospital (Rheumatology unit) after obtaining their informed consent and within the approved ethical protocol of Tanta faculty of Medicine ethical committee (CAAE:30792/2/16). A total of 50 rheumatoid arthritis patients were included in our study.

Subjects in the study were divided into three groups: Group 1: 25 active rheumatoid arthritis patients. Their age ranged from 30-62 years. Twenty three patients were females and two patients were males. The duration of disease was varied from 4-15years. Group 2: 25 inactive rheumatoid arthritis patients. Their age ranged from 30-60 years. Twenty four patients were females and one patient was male. The duration of disease was varied from 1-7 years. Group 3: 25 healthy volunteers as a control group. Their age ranged from 30-59 years. Twenty three volunteers were females and two volunteers were males.

Rheumatoid arthritis patients were diagnosed according to the American College of Rheumatology (ACR) 1987 [10] revised criteria.

We excluded from the study patients who are suffering from atherosclerotic complications

such as stroke and MI, peripheral vascular disease, malignancy, infections, hypertensive, diabetes mellitus and on hemodialysis. All the previous studied groups were subjected to full medical history taking and complete physical examination. Laboratory investigations were done including complete blood count (RBCs, HB, WBCs, and platelets), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), Anti CCP, liver functions tests, total lipid profile (total cholesterol (TC), triglyceride, high-density lipoprotein (HDL), low-density lipoprotein (LDL), C-reactive protein (CRP).

Assessment of disease activity using DAS28. Evaluation of RA activity using disease activity score (DAS28) score by counting number of swollen, tender joints, ESR and the affected person makes a subjective assessment (SA) of disease activity during the preceding 7 days on a scale between 0 and 100, where 0 is "no activity" and 100 is "highest activity possible". Then the result are put into mathematical formula to give score as fellow, DAS28 less than 2.6 means remission, between 2.6 - 3.2 means low disease activity, between 3.2–5.1 means moderate activity and > 5.1 means highly active disease [11].

$$\text{DAS28} = 0.56 \times \sqrt{\text{TJC28}} + 0.28 \times \sqrt{\text{SJC28}} + 0.70 \times \text{Ln}(\text{ESR}) + 0.014 \times \text{GH}$$

Anteroposterior radiographs of both hands and feet.

Assessment of carotid intima media wall thickness using GE Vivid 7 Dimension echo machine with 7.5–10 MHz linear phased array transducer. This measurement was performed on the left and right sides of the patient. Individuals in the study population were investigated in the supine position, arms along the body and head in moderate extension. The head turned away slightly from the sonographer. Common carotid arteries were examined using posterior approach by both transverse and longitudinal scans. Measurement of the intima media thickness (IMT) was taken at three points on each side: common carotid artery (10 mm before the bulb), bulb (5–10 mm cranially to the start of the bulb), and internal carotid artery (10 mm after the flow divider). The average of the 6 measurements was used for the analysis. All measurements were performed by investigators without knowledge of the clinical data. The mean IMT (the mean of both right and left sides) was assessed. IMT is considered abnormal if >0.7 mm [12].

Brachial artery flow mediated dilatation (FMD) was assessed to detect endothelial function.

FMD was assessed with the same echocardiographic machine used for the assessment of carotid IMT. The procedure was performed by a single cardiologist. The participants were asked to abstain from alcohol, caffeine, and smoking at least 8 h before the procedure. The ultrasound examination was performed in quiet room at temperature between 21°C and 32°C. The participant was made to lie in a supine position for 15 min. The right brachial artery was scanned longitudinally 7 cm above the antecubital crease using 10 MHz probe. The diameter of the brachial artery was measured on the interface between the media and adventitia of the anterior and posterior wall (pre-FMD). Hyperemia was induced by inflation of a pneumatic cuff at 230–250 mmHg for 4 min on the most proximal portion of the upper arm. The arterial diameter measurement was repeated 45–60 s after sudden deflation of the cuff (post-FMD). The endothelium-dependent function is defined by the following formula: [12].

$$\text{FMD} = \{(\text{Post FMD} - \text{Pre FMD}) / \text{Pre FMD}\} \times 100$$

### 3. RESULTS AND DISCUSSION

#### 3.1 Results

The current study was done on 50 RA patients 47 women (94%) and 3 men (6%) with mean age 45.22±9.67 and 25 age and sex matched healthy controls, 23 women (92%) and 2 men (8%) with mean age 45.24±9.13. There was no significant difference of age and sex between RA patients and controls. The disease duration ranged from 6 months to 15 years, the mean and standard deviation of disease duration in patients with atherosclerosis was 7.32 ± 2.97 and patients without atherosclerosis was 4.56 ± 1.92. The mean of disease activity index in patients with atherosclerosis was 4.79±0.68 and patients without atherosclerosis was 2.31 ± 0.15. There is highly significant relation between presence of atherosclerosis with disease duration (p < 0.001) and disease activity DAS28 (p < 0.001). Also there is significant relation between presence of atherosclerosis with CRP (p < 0.001) and RF (P <0.001) as shown in Table 1.

The mean value of carotid intima media thickness in RA patients was significantly higher as compared to control group (0.73 ±0.15 vs.

0.61±0.04) (p value <0.001) which is indicator of atherosclerosis (Table 2).

CIMT in patients with active rheumatoid arthritis (group 1) was significantly higher as compared to inactive rheumatoid arthritis patients (group 2)(0.83 ± 0.10 vs. 0.61 ± 0.05) (p value <0.001) Table 3 (Fig. 1).

Comparison of parameters which assess the endothelial function between all patients, and controls, reported that pre FMD (p < 0.001), post FMD (p < 0.001) and FMD dilatation percent (p < 0.001), were significantly lower in patient than controls (Table 4). FMD dilatation percent (p < 0.003\*) was significantly lower in the (group1) than (group2) Table 5.

Fig. 1 show: Transverse LT carotid duplex scanning of active RA case. Where IMT=0.8 mm which is indicator of atherosclerosis.

The RT brachial artery in active RA patient: Pre FMD was 4.3mm and Post FMD was 4.7mm. So there was endothelial dysfunction in the brachial artery (FMD%=9.3%) (Figs. 2, 3).

There was no correlation between DAS28 score of RA patients versus endothelial dependent flow mediated dilatation (FMD) of the brachial artery. As showing in (Fig. 4). There was a significant correlation of DAS28 of RA patients versus intima media thickness (IMT) of the carotid artery (Fig. 5).

### 3.2 Discussion

CV morbidity and mortality increased in RA patients as compared with the general population [13]. CVD in RA patients especially Coronary artery disease is an atherosclerosis-based disease [14].

The important sign of early atherosclerosis is endothelial dysfunction, it can be assessed by simple non-invasive markers (FMD) of peripheral arteries [9] and C-IMT which are a widely accepted surrogate markers of atherosclerosis [15].

The present study showed a highly significant association between subclinical atherosclerosis and the duration of the RA disease (P < 0.001) with mean 7.32 ± 2.97. These results corroborate those of Tiwari et al. [15] and Arts et al. [16], that possibly explanation as long-term progression of RA depend on chronic inflammation and that lead to the development of subclinical atherosclerosis [17]. In contrast Mulumba et al. [18], Jonsson et al. [19] and Alkaabi et al. [20]

didn't report association between disease duration and subclinical atherosclerosis.

In the present study as regards laboratory parameters RA patients showed significantly higher ESR and CRP than healthy controls (P < 0.001). This is in agreement with Yazici et al. [21] that included 97 RA patients and 33 ages and sex matched control subjects, they found that ESR and CRP were significantly higher in RA patients than healthy controls.

Inflammation plays an important role in premature atherosclerosis in RA. ESR and CRP are markers of inflammation in RA patients and associated with intimal media thickness which detect as a surrogate for atherosclerotic disease [22].

In our study, There was high significant association between presence of atherosclerosis and RF with mean (226.28±42.58), (p < 0.001) in contradictory with Elshereef et al. [23] who didn't report association between RF and subclinical atherosclerosis (P<0.5) as compare between 77 RA patient with atherosclerosis and 35 RA patients without atherosclerosis.

The pathogenesis of RA disease depend on B cells which produce RF and that have been also found in atherosclerotic plaque in RA patients, so RF can be considered to have role of atherogenesis in RA disease [24]. However, some more recent studies have not found an association between RF positivity and CVD risk [25].

In our study, the mean IMT in RA patients were significantly higher (0.73 ±0.15) than healthy controls (0.61±0.04 mm,) (P=0.001), and the mean IMT in active RA patients were significantly higher (0.83 ± 0.10) than inactive RA patients (0.61 ± 0.05). These result in agreement of Jayakumar et al. [26] that included 40 RA patients and were compared with 20 age and sex matched control subjects, they found that common carotid artery IMT in RA patients was significantly higher (0.65±0.06) when compared to healthy controls (0.57±0.049). Abd El-Monem et al. [27], Saigal et al. [28], Wang et al. [29] and Amin et al. [30] were also in agreement with our study.

Changes in C-IMT is result from a decrease in nitric oxide (NO) production and increase the level of ET-1, which lead to increase production of free radicals inflammatory cytokines, adhesion molecules and thrombotic factors leading to proliferation of the smooth muscle [31].

**Table 1. Comparison of patients features between RA patients with and without atherosclerosis**

	<b>Patients with atherosclerosis (N=16) Mean ± S.D</b>	<b>Patients without atherosclerosis (N=34) Mean ± S.D</b>	<b>P</b>
Age	46.36 ± 9.91	44.08 ± 9.48	0.410
Disease duration	7.32 ± 2.97	4.56 ± 1.92	0.001*
DAS 28	4.79±0.68	2.31 ± 0.15	0.001*
CRP	106.08±32.87	24.76±26.16	0.001*
RF	226.28±42.58	83.60±13.82	0.001*
Total cholesterol (mg/dl)	174.36 ± 27.44	166.12 ± 19.64	0.228
Triglycerides (mg/dl)	92.09 ± 22.26	87.72 ± 21.68	0.490
HDL(mg/dl)	41.44 ± 2.53	41.68 ± 3.01	0.762
LDL(mg/dl)	121.52 ± 25.28	115.84 ± 21.62	0.398

*DAS 28 = disease activity score, CRP = C - reactive protein, HDL = high density lipoprotein, LDL = low density lipoprotein*

**Table 2. Comparison of ultrasonographic duplex findings between RA patients and controls**

	<b>RA patients (N=50) Mean ± S.D</b>	<b>Controls (N=25) Mean ± S.D</b>	<b>P</b>
Mean IMT	0.73 ±0.15	0.61±0.04	0.001*
Left IMT	0.69 ± 0.14	0.60 ±0.03	0.001*
Right IMT	0.74 ± 0.15	0.62 ±0.02	0.001*

*IMT = intima media thickness*

**Table 3. Comparison of ultrasonographic duplex findings between active RA patients (group1) and inactive RA patients (group2)**

	<b>Active RA patients (N=25) Mean ± S.D</b>	<b>Inactive RA patients (N=25) Mean ± S.D</b>	<b>P</b>
Mean IMT	0.83 ±0.10	0.61±0.05	0.001*
Left IMT	0.76 ± 0.16	0.62 ±0.05	0.001*
Right IMT	0.86 ± 0.10	0.60 ±0.02	0.001*

*IMT = intima media thickness*

**Table 4. Comparison of endothelial function between RA patients and controls**

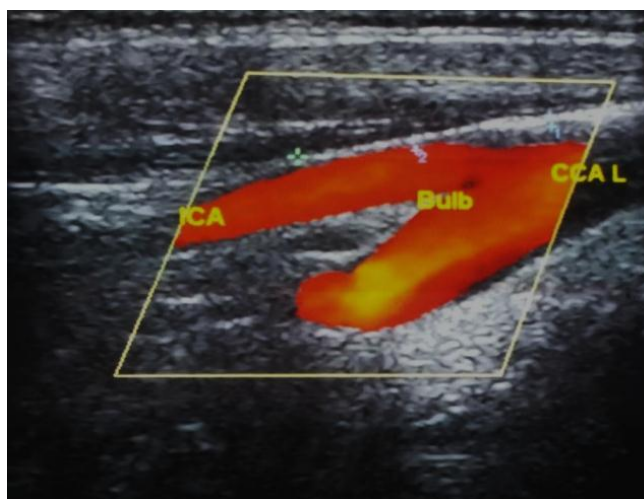
	<b>RA patients (N=50) Mean ± S.D</b>	<b>Controls (N=25) Mean ± S.D</b>	<b>P</b>
Pre FMD	34.34 ± 4.01	38.00± 3.04	0.001*
Post FMD	40.20 ±4.63	46.00 ±3.15	0.001*
FMD %	17.11± 4.55	21.81±2.48	0.001*

*FMD = flow mediated dilatation*

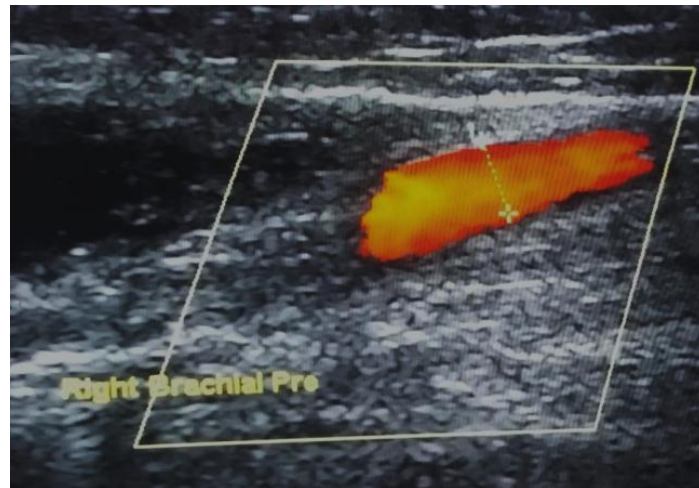
**Table 5. Comparison of endothelial function between active RA patients (group1) and inactive RA patients (group2)**

	Active RA patients (N=25) Mean ± S.D	Inactive RA patients (N=25) Mean ± S.D	P
Pre FMD	34.04 ± 4.99	34.64± 2.80	0.602
Post FMD	39.12 ±4.63	41.28 ±4.09	0.099
FMD %	15.23± 5.17	18.99±2.84	0.003*

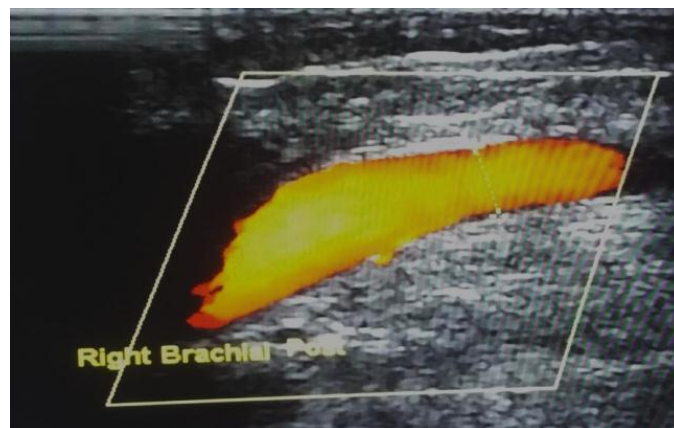
FMD= flow mediated dilatation



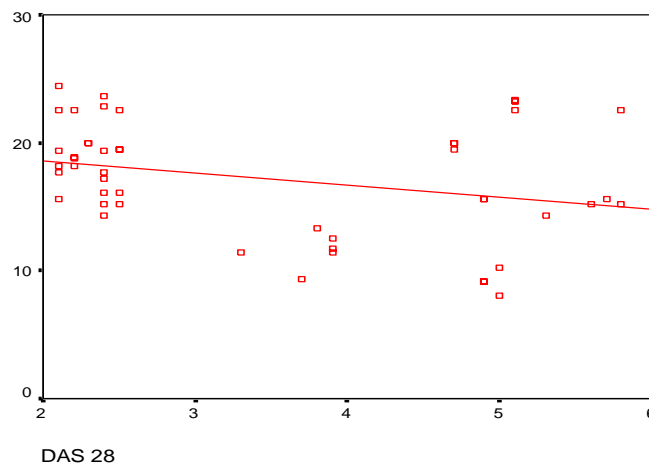
**Fig. 1. Transverse LT carotid duplex scanning of active RA case; Showing IMT=0.8 mm; ICA= internal carotid artery, CCA= common carotid artery, L= left, IMT = intima media thickness**



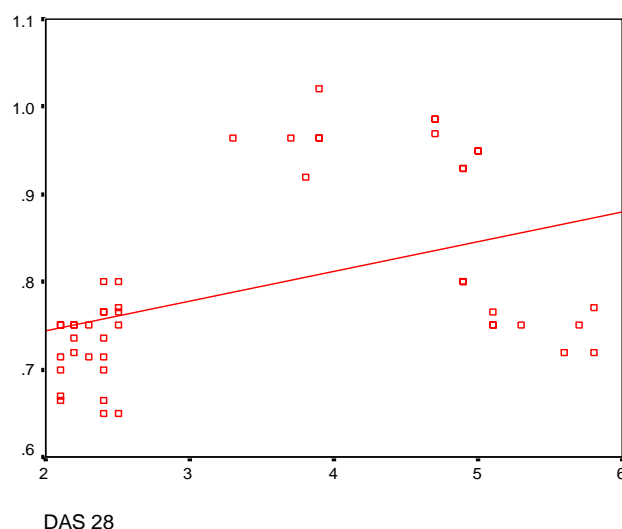
**Fig. 2. Ultrasound image of the RT brachial artery of active RA; Pre FMD was 4.3 mm; FMD= flow mediated dilatation**



**Fig. 3. Ultrasound image of the RT brachial artery of active RA patient; Post FMD was 4.7 mm; FMD= flow mediated dilatation**



**Fig. 4. Correlation between DAS28 and endothelial function in RA patients; FMD= flow mediated dilatation, disease activity score (DAS28)**



**Fig. 5. Correlation between DAS28 and mean IMT in RA patients; IMT = intima media thickness, disease activity score (DAS28)**

In the present study, FMD% were significantly lower in RA patients ( $17.11 \pm 4.55$ ), ( $P = 0.001$ ) than controls ( $21.81 \pm 2.48$ ). These result in agreement of El Zohri et al. [32] their study included 30 RA patients without cardiac diseases and 10 controls. They found brachial FMD% in RA patients was significantly lower ( $22.9 \pm 11.0$ ) than controls ( $35.5 \pm 23.2$ ) ( $P = 0.027$ ). Other studies such as Amin et al. [30] who included 50 RA patients and 50 controls, they found brachial FMD% was significantly lower in RA patients group than the control group ( $5.2 \pm 3.11\%$ ) ( $10.1 \pm 2.6\%$ ) respectively;  $P < 0.001$ ).

The normal healthy endothelium produces numerous dilator and constrictor substances which regulates vascular tone. Nitric oxide (NO) is the major vasodilator substance which leads to endothelial dysfunction when its production is reduced [33].

Our study showed a high significant association between subclinical atherosclerosis and DAS28 ( $P = 0.001$ ) with mean ( $4.79 \pm 0.68$ ). There was a significant positive correlation of DAS28 of RA patients versus intima media thickness (IMT) of the carotid artery where mean IMT  $r = 0.429$  and  $P < 0.002$ . Similar results were found by Abd El-Monem et al. [27]. This study included 30 RA patients and 30 healthy volunteers have the same age and sex as control groups, it found that there were significant positive correlations of average CIMT with DAS28 ( $r = 0.468$ ,  $P = 0.01$ ). Elshereef et al. [23], Gauri et al. [34] and Montagna et al. [35] also showed significant

positive correlation of DAS28 of RA patients versus intima media thickness (IMT) of the carotid artery. On the contrary, Saigal et al. [28] study on 40 cases of RA and 26 matched individuals were recruited found no significant correlations of CIMT with DAS28 ( $r = 0.033$ ,  $P = 0.05$ ). The same finding was also observed in El Zohri et al. [32], Tyrrell et al. [36] and Roman et al. 2006 [37].

In this study there was no correlation between DAS28 score of RA patients versus endothelial dependent flow mediated dilatation (FMD) % of the brachial artery, ( $r = -0.282$ ,  $P = 0.047$ ). Similar results were found by Elshereef et al. [23] where FMD dilatation percent and dilatation ratio were ( $P = 0.005$ ,  $P = 0.007$ , resp.) in RA patients.

#### 4. CONCLUSION

The results from our study support the use of Carotid ultrasonography and endothelial function assessment by flow mediated vasodilatation for all RA patients, which could be simple noninvasive method of identifying preclinical atherosclerosis, control of rheumatoid disease activity and its inflammatory burden which is the major factor for premature atherosclerosis.

#### 5. RECOMMENDATIONS

All patients with RA should be screened for early detection and management of subclinical cardiovascular affection that will prevent and manage early endothelial dysfunction and



accelerated atherosclerosis related to RA so that will improve CVD in RA patients.

Additional studies with large numbers of RA patients and more long-term follow up are recommended to suggest the better therapeutic strategies to prevent the occurrence of CVD in RA patients.

## CONSENT

All authors declare that 'written informed consent was obtained from the patient for publication of this case report and accompanying images'.

## ETHICAL APPROVAL

This study was carried on patients at Rheumatology unit of Internal Medicine department of Tanta University Hospital after obtaining their informed consent and within the approved ethical protocol of Tanta faculty of Medicine ethical committee (CAAE: 30792/2/16).

## ACKNOWLEDGEMENTS

The authors would like to appreciate all participants who took part in the study.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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