ORIGINAL ARTICLE

Brachial artery flow mediated dilatation and carotid intima media thickness measured by high resolution B-mode ultrasound in patients with rheumatoid arthritis

Mohamed A. Amin a, Alsiagy A. Salama a,*, Ashraf M. Elaggan a, Salwa E. Elsayed b

a Radiodiagnosis & Imaging Department, Faculty of Medicine, Tanta University, Tanta, Egypt
b Physical Medicine, Rheumatology and Rehabilitation Department, Faculty of Medicine, Tanta University, Tanta, Egypt

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KEYWORDS
Carotid intima media thickness; Brachial artery flow mediated dilatation; Rheumatoid arthritis

Abstract Objectives: Firstly to assess the prevalence of subclinical atherosclerosis and endothelial dysfunction by high resolution ultrasound measurements of carotid intima media thickness (CIMT) and brachial artery flow mediated dilatation percentage (FMD%) in patients with rheumatoid arthritis (RA), secondly to analyze the correlation of CIMT and FMD% with different clinical and laboratory parameters, third aim was to analyze the relationship between CIMT and FMD%.

Patients and methods: The prospective case-control study included 50 patients with RA and 50 healthy age and sex matched controls. All participants were subjected to carotid and brachial arteries ultrasound for measuring CIMT and FMD%, in addition to detailed history and physical examination.

Abbreviations: RA, rheumatoid arthritis; CIMT, carotid intima media thickness; FMD%, flow mediated dilatation percentage; DM, diabetes mellitus; HAQ, Health Assessment Questionnaire; DAS, Disease Activity Score; CRP, C-reactive protein; HDL-c, high density lipoprotein-cholesterol; LDL-c, low density lipoprotein-cholesterol; CVD, cardiovascular disease; ACR, American college of Rheumatology; BMI, body mass index; PVD, peripheral vascular disease; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor

* Corresponding author at: Radiodiagnosis & Imaging Department, Tanta Faculty of Medicine, Tanta, Gharbiya, Egypt. Mobile: +20 111355893; fax: +20 40 3407734.
E-mail address: siagyali33@yahoo.com (A.A. Salama).

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Results: Patients with RA had significantly higher CIMT and significantly lower FMD% than the controls ($P < 0.001$). In RA patients a significant correlation was found between CIMT and the patient’s age, disease duration, systolic blood pressure, HAQ, DAS, CRP and HDL-c, however no detectable correlation between the brachial artery FMD% and the clinical and laboratory parameters in RA patients. There was no significant correlation between CIMT and FMD%.

Conclusion: FMD% and CIMT are important non-invasive independent imaging methods for early prediction of subclinical atherosclerosis in RA patients.

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1. Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune inflammatory disease that affects synovial joints and lead to chronic pain, bone erosions and progressive disability. Approximately 1% of the adult population in the United States has RA, and the overall world prevalence range from 0.5% to 1%, qualifying it as the most common chronic inflammatory condition (1).

Cardiovascular (CV) disease is the most common cause of mortality in patients with rheumatoid arthritis (RA) with a relative risk of about 2 compared with age matched controls (2). The presence of chronic immuno-inflammatory process is responsible for the development of subclinical atherosclerosis and increased incidence of CV events in these patients (3,4).

Endothelial dysfunction mediated by inflammation is thought to be an important event in early atherogenesis and also contributes to the development of clinical features in the later stages of vascular disease including progression of atherosclerotic plaque (5).

A noninvasive physiologic technique to test endothelial function is to assess the post occlusion flow-mediated vasodilation (FMD) of brachial artery using high sensitivity ultrasonography (6). In this method, FMD is the response of endothelium to shear stress induced by reactive hyperaemia. So FMD is considered endothelium dependent vasodilation and any impairment of brachial artery FMD is considered a marker of endothelial dysfunction (7).

Another clinical useful tool indicating subclinical atherosclerosis (without clinically evident atherosclerosis e.g. CVDs, PVD, etc. or its complications) is to measure carotid artery intima-media thickness (CIMT) with high resolution B-mode ultrasonography, providing noninvasive anatomic structural measure of subclinical atherosclerosis (8). It constitutes an excellent surrogate marker of macrovascular atherosclerotic disease. This is the most popular technique used to study the early structural changes in the arterial wall. A number of studies have proved that carotid intima-media thickness is significantly higher in RA patients than in age, sex and cardiovascular risk factors matched controls (9).

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 (10), so the aim of this study was to assess the prevalence of subclinical atherosclerosis and endothelial dysfunction by high resolution ultrasound measurement of carotid intima media thickness (CIMT) and brachial artery flow mediated dilatation percentage (FMD%) in RA patients, secondly to analyze the correlation of the CIMT and FMD% with different clinical & laboratory parameters as well as the relation between the CIMT and FMD%.

2. Patients and methods

2.1. Study participants

This prospective case-control study was performed between January 2013 and January 2014 on fifty patients (44 females, 6 males) with RA (diagnosed according to the revised American college of Rheumatology –ACR – criteria) (11) who were referred to the ultrasound unit of the Tanta diagnostic and medical imaging department from the outpatient clinic of the rheumatology and Rehabilitation department of the Tanta university hospitals, their age ranged between 28 and 65 years with a mean of 42 ± 6.2 years, and the duration of the disease ranged between 5 and 27 years, another 50 age and sex matched healthy controls were also included in this study.

Exclusion criteria for both RA patient and control subjects included hypertension (blood pressure > 140/90 mmHg), current or history of smoking, diabetes mellitus, hyperlipidaemia, history of oral contraceptive pills intake, obesity (body mass index -BMI- ñ 30 kg/m²), chronic medical diseases such as liver and renal diseases, patients not fulfilling the revised ACR criteria for the diagnosis of RA and clinically manifest atherosclerosis by the way of CAD, peripheral vascular disease (PVD), cerebrovascular disease etc.

The institutional ethics committee approved the study protocol and written consents were taken from all patients and control groups.

Clinical assessment of both RA patients and control groups included: BMI, blood pressure, disease activity score (DAS), disease duration, Health Assessment Questionnaire (HAQ) score, laboratory investigations included, ESR, RF, CRP, lipid profile including total cholesterol, high density lipoprotein-cholesterol (HDL-c), low density lipoprotein-cholesterol (LDL-c) and triglycerides.

2.2. High resolution B-mode ultrasound assessments

2.2.1. Carotid intima wall thickness

Carotid intima media thickness (CIMT) was measured using a high resolution B-mode ultrasound machine (Biomedical P-K, Denmark) equipped with an 11-MHz frequency linear probe, the procedure was done by the same radiologist on the same ultrasound machine. All subjects (patients and control) were examined in supine position, neck extended and chin facing
the contralateral side, both common carotid arteries were examined in both longitudinal and transverse scans, three consecutive measurements of intima media thickness were taken from the far wall of both common carotid arteries, 1–2 cm proximal to the carotid bulb over the common carotid artery and in the proximal most portion of the internal carotid artery near its origin and the average of these 6 measurements from both sides was taken for final statistical analysis. All measurements were made manually.

2.2.2. Measurement of brachial artery flow mediated dilatation
Brachial artery ultrasound study was performed in a quiet, dark, temperature-controlled room, all the participants were in supine position, resting for 10 min, and the measurements of brachial artery were taken in longitudinal scan in the arm 5–10 cm above the antecubital fossa without permanent vascular access. The luminal diameter of the artery was measured between the proximal and distal intima. After recording the baseline diameter of the brachial artery (D0), transient ischemia was induced by cuff which was placed around the forearm and inflated to 200 mmHg (or 50 mmHg more than the systolic blood pressure) for 5 min and the cuff was deflated and a second scan for arterial diameter measurements was taken about 40–60 s after deflation (D1), flow mediated dilatation (FMD) was expressed as a percentage change in the brachial artery diameter from the baseline to ischemia (FMD%) and calculated by the following formula (D1 − D0/D0 × 100), and the higher the percentage value the better the endothelial function.

2.3. Statistical analysis
Analysis was done using SPSS for Windows version 10.0 (SPSS Inc., USA). Data are expressed as mean ± standard deviation, the differences between patients and controls were assessed by the X²-test for the comparison of non-numerical data and by student’s t-test for the comparison of normally distributed variables. Univariate regression analysis was used to examine the relationship between the CIMT and FMD% and several study variables. Regression analysis was used to study the relationship between the CIMT and FMD% in the RA patients group with CIMT used as a dependent variable. Values of P < 0.05 were considered significant and those with P-value > 0.05 were insignificant.

3. Results
This prospective case-control study was performed on fifty patients (44 females, 6 males) with RA, with a mean age of 42 years and a mean duration of the disease of 12.4 years, another 50 age and sex matched healthy controls were also included in this study.

The clinical and laboratory characteristics of both RA patients and healthy controls are shown in Table 1. Females constituted 88% of the 50 patients and 50 controls studied. Out of the 88 female patients, 52 (59%) were pre-menopausal and 36 (41%) were post-menopausal. There was no statistically significant difference in the mean of age, BMI, systolic blood pressure, diastolic blood pressure, and lipid profile of the patient and control groups. Patients with RA had a significantly higher mean values than the controls of both ESR ((27.4 ± 13.1) vs. (9.8 ± 5.3)) and CRP ((16.2 ± 4.6) vs. (3.7 ± 0.6)) respectively; P < 0.001. Rheumatoid factor was positive in 42 patients (84%) (Table 1).

Patients with RA had a significantly higher CIMT (0.91 ± 0.19 mm) than the controls (0.58 ± 0.04 mm) (P < 0.001), however brachial artery FMD% was significantly lower in patients with RA than the control group (5.2 ± 3.11 vs. 10.1 ± 2.6% respectively; P < 0.001) (Table 2, Figs. 1 and 2).

By using the univariate analysis, in RA patients a significant positive correlation was found between CIMT and the patient’s age, disease duration, systolic blood pressure, HAQ, DAS and CRP and a statistically inverse correlation was observed between the CIMT and the HDL-c, however no detectable correlation was found between the brachial FMD% and the clinical and laboratory parameters in RA patients (Table 3).

In the RA patients, there was no detectable correlation between the CIMT (as a dependent variable) (β coefficient = 0.2341, P > 0.05) and the FMD% (as a continuous variable). No significant correlation was found using regression analysis including age, sex, disease duration, systolic blood pressure, CRP, DAS and HDL-c (Table 4).

4. Discussion
Rheumatoid arthritis (RA) causes significant morbidity as a result of synovial inflammation, joint destruction, and associated disability in addition to these articular manifestations of RA, there is a growing recognition of an excess mortality and the most common cause of mortality in RA is cardiovascular disease (12,13).

At present, several noninvasive imaging techniques offer a unique opportunity to study the relation of surrogate markers for the development of atherosclerosis. The use of these techniques may help identify high-risk individuals who may benefit from active therapy to prevent clinical disease (14).

Two important non-invasive techniques were useful in the assessment of subclinical atherosclerosis, the evaluation of endothelial function by flow mediated (endothelium dependent) vasodilatation (FMD%) and the measurement of carotid intima-media thickness (CIMT) by high-resolution B-mode ultrasonography (15) (Fig. 3).

So in this study we planned to evaluate the extent of the subclinical atherosclerosis in rheumatoid arthritis patients by the measurement of the carotid intima media thickness (CIMT) and brachial artery flow mediated dilatation percentage (FMD%) & analyzing the correlation of the CIMT and FMD% with different clinical & laboratory parameters as well as the relation between the CIMT and FMD% (Figs. 4–6).

The measurement of CIMT by B-mode high resolution ultrasonography is a valid noninvasive anatomic structural method for assessing subclinical asymptomatic atherosclerosis in the general population (16). CIMT is defined as the width of the vessel intima and media, which consists of endothelium, connective tissue and smooth muscle. This is also the site of lipid deposition and plaque formation (17).

In the present study, we demonstrate that compared with the healthy control subjects, RA patients had subclinical atherosclerosis in terms of impaired FMD% and increased CIMT. The clinical factors associated with CIMT were not all related to FMD%. There is also no relationship between brachial FMD, a physiologic measure of subclinical
Atherosclerosis and CIMT, a structural measure of early atherosclerosis in RA patients without risk factors for atherosclerosis or clinical evidence of cardiovascular disease. So FMD% and CIMT may measure a different stage of subclinical atherosclerosis in RA patients.

In the current study, RA patients had a significantly higher CIMT (0.91 ± 0.19) than the controls (0.58 ± 0.04) \((P < 0.001)\), so our patients, who did not show any evidence of known atherosclerotic disease, may have subclinical atherosclerosis with subsequent higher risk for development of cardiovascular events. These findings are consistent with the results of previous studies \((10,18,19)\).

### Table 1 Clinical and laboratory characteristics in both rheumatoid arthritis patients and healthy controls.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Patients ((n = 50))</th>
<th>Control ((n = 50))</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>42.3 ± 6.2</td>
<td>40.1 ± 5.6</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (female/male)</td>
<td>44/6</td>
<td>44/6</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>22.3 ± 2.1</td>
<td>20.5 ± 3.26</td>
<td>NS</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>12.4 ± 4.6</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>116 ± 9.3</td>
<td>112 ± 10.2</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>71.34 ± 7.2</td>
<td>70.58 ± 8.4</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>211.21 ± 23.42</td>
<td>215 ± 22.3</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-c (mg/dl)</td>
<td>43.31 ± 5.2</td>
<td>48.7 ± 3.7</td>
<td>NS</td>
</tr>
<tr>
<td>LDL-c (mg/dl)</td>
<td>129.2 ± 17.3</td>
<td>128.4 ± 19.6</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>116.61 ± 38.2</td>
<td>119.37 ± 35.2</td>
<td>NS</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>27.4 ± 13.1</td>
<td>9.8 ± 5.3</td>
<td>&lt;0.001 (HS)</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>16.2 ± 4.6</td>
<td>3.7 ± 0.6</td>
<td>&lt;0.001 (HS)</td>
</tr>
<tr>
<td>RF positivity (n (%))</td>
<td>42 (84%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>DAS</td>
<td>3.49 ± 92</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>HAQ</td>
<td>1.23 ± 0.62</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Values are expressed in mean ± SD, NS = not statistically significant, HS = highly significant.

### Table 2 B-mode ultrasound measurements of the carotid intima media thickness and brachial flow mediated dilatation percentage in both rheumatoid arthritis patients and healthy controls.

<table>
<thead>
<tr>
<th>Ultrasound parameters</th>
<th>RA patients ((n = 50))</th>
<th>Controls ((n = 50))</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIMT (mm)</td>
<td>0.91 ± 0.19</td>
<td>0.58 ± 0.04</td>
<td>&lt;0.001 (HS)</td>
</tr>
<tr>
<td>FMD%</td>
<td>5.2 ± 3.11</td>
<td>10.1 ± 2.6</td>
<td>&lt;0.001 (HS)</td>
</tr>
</tbody>
</table>

Values are expressed in mean ± SD, HS = highly significant, CIMT = carotid intima media thickness, FMD% = flow mediated dilatation percentage.

![Boxplot of CIMT in RA vs. Control](image1)

![Boxplot of FMD% in RA vs. Control](image2)

Fig. 1 Boxplot revealed correlation between mean carotid intima-media thickness (IMT) of both RA patients & controls (value are expressed as mean ± SD).

Fig. 2 Boxplot revealed correlation between mean percentages of brachial artery flow mediated vasodilatation (FMD%) of both patients & controls (value are expressed as mean ± SD).

In our study, there were significant positive correlations between the CIMT and patient’s age, disease duration, systolic blood pressure, HAQ Score, DAS and CRP but negative correlation was found between the CIMT and HDL-c. Our results are similar to other studies worldwide which reported that on multivariate analysis, only age and disease duration were found to have significant correlation with CIMT \((20,21)\).
Also Fan et al. (10) confirmed our results and stated that at the univariate analysis, a significantly positive correlation was observed between CIMT and age of the patients, disease duration, DAS, CRP and systolic blood pressure and a statistically inverse correlation was observed between CIMT and HDL-cholesterol. Adhikari et al. (19) supported our results.

**Table 3** Correlation between CIMT and FMD% measurements in RA patients and clinical and laboratory parameters.

<table>
<thead>
<tr>
<th>Variables</th>
<th>CIMT</th>
<th>FMD%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Correlation coefficient</td>
<td>P-value</td>
</tr>
<tr>
<td>Age</td>
<td>+0.153</td>
<td>&lt; 0.05 (S)</td>
</tr>
<tr>
<td>Disease duration</td>
<td>+0.196</td>
<td>&lt; 0.05 (S)</td>
</tr>
<tr>
<td>BMI</td>
<td>+0.39</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>+0.258</td>
<td>&lt; 0.05 (S)</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>+0.104</td>
<td>NS</td>
</tr>
<tr>
<td>HAQ</td>
<td>+0.81</td>
<td>&lt; 0.05 (S)</td>
</tr>
<tr>
<td>DAS</td>
<td>+0.241</td>
<td>&lt; 0.05 (S)</td>
</tr>
<tr>
<td>CRP</td>
<td>+0.209</td>
<td>&lt; 0.05 (S)</td>
</tr>
<tr>
<td>ESR</td>
<td>0.073</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>+0.181</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-c</td>
<td>−0.489</td>
<td>&lt; 0.05 (S)</td>
</tr>
<tr>
<td>LDL-c</td>
<td>+0.179</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>+0.118</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = not statistically significant, S = statistically significant.

**Table 4** Relationship between CIMT (dependent variable) and brachial artery FMD% (continuous variable) in RA patients.

<table>
<thead>
<tr>
<th>Model</th>
<th>β coefficient</th>
<th>Standard error</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1 (unadjusted)</td>
<td>0.2341</td>
<td>0.1459</td>
<td>0.268 (&gt;0.05)</td>
</tr>
<tr>
<td>Model 2 (adjusted for age and sex)</td>
<td>0.2132</td>
<td>0.1479</td>
<td>0.216 (&gt;0.05)</td>
</tr>
<tr>
<td>Model 3 (full mode)</td>
<td>0.2054</td>
<td>0.1846</td>
<td>0.387 (&gt;0.05)</td>
</tr>
</tbody>
</table>

Full model adjusted for age, sex, duration of the disease, systolic blood pressure, CRP, DAS and HDL-c.

**Fig. 3** Normal control female aged 40 years with normal FMD = 10.86% (a, b) & normal CIMT = 0.4 mm (c) D0 (Baseline diameter of the brachial artery) and D1 (post-occlusion diameter of the brachial A).
Fig. 4  Rheumatoid arthritis female patient aged 42 years with low FMD = 6.38% (a, b) & high CIMT = 1.3 mm (c).

Fig. 5  Rheumatoid arthritis female patient aged 47 years with low FMD = 3.22% (a, b) & high CIMT = 1.0 mm (c).
and stated that age, systolic blood pressure, tender joint count, and swollen joint count had significant correlations with patient’s CIMT.

Also the results reported by Targońska-Stepniak (22) are consistent with us who stated that in RA patients, CIMT correlated positively with a number of immunological and inflammatory parameters and also with amino-terminal pro-brain natriuretic peptide (NT-proBNP), age, and metabolic variables (serum cholesterol, creatinine, cystatin C). In multiple linear regression analysis, significant association was found between CIMT and NT-proBNP and age. Patients without atherosclerosis (CIMT < 0.6 mm) were younger and had significantly lower concentrations of NT-proBNP and total cholesterol, as well as higher estimated glomerular filtration rate. The course of RA in patients without atherosclerosis was characterized by shorter disease duration, lower tender joint count, and C-reactive protein.

In our study we found that FMD% was significantly lower in rheumatoid arthritis patients compared to those of the healthy controls. These findings are similar to those reported in other studies (10,19). Low FMD% in our RA patients confirms results from previous studies who assessed the endothelial function in similar patients, which also showed that FMD% was associated with classical risk factors, such as hyperlipidaemia and systolic blood pressure (9,18), however, in our study, we found that FMD% had no association with any of these risk factors but this finding needs confirmation in a larger sample size as the atherosclerosis is a complex process and at different stages there may be different factors correlating with FMD%.

AbdelMaboud and Elsaid (18) demonstrated that FMD and CIMT are promising methods for the evaluation of RA and are very helpful for the prevention of vascular risk, however this study did not investigate a correlation between measurements of CIMT and brachial artery FMD% in RA patients.

In the current study, we did not find correlation between measurements of CIMT and brachial artery FMD% in RA patients. This may be owed 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.

These findings are in agreement with Fan et al. (10) who stated that there is no correlation between measurements of CIMT and brachial artery FMD% in cohort RA patients without CVD and with relatively few risk factors. Also 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 cardiovascular disease.

The limitations of our study were the lack of follow up of patients over a period of time to look for clinical events like myocardial infarction etc. and inability to comment on the influence of drugs.
5. Conclusion

FMD% and CIMT measured by high resolution B-mode ultrasound are important non invasive independent imaging methods for early prediction of the subclinical atherosclerosis in rheumatoid arthritis patients with subsequent early treatment and control of the disease vascular complications.

Conflict of interest

We have no conflict of interest to declare.

References