Research Article

Asymptomatic Atherosclerosis in Egyptian Rheumatoid Arthritis Patients and Its Relation to Disease Activity

Rawhya R. Elshereef, Aymen Darwish, Amal Ali, Mohammed Abdel-kadar, and Lamiaa Hamdy

1Rheumatology and Rehabilitation Department, Minia University, P.O. Box 61519, Minia 61111, Egypt
2Cardiology Department, Minia University, P.O. Box 61519, Minia 61111, Egypt
3Clinical Pathology Department, Minia University, P.O. Box 61519, Minia 61111, Egypt

Correspondence should be addressed to Rawhya R. Elshereef; rawhyaelshereef@yahoo.com

Received 15 September 2014; Revised 6 January 2015; Accepted 11 January 2015

1. Introduction

Rheumatoid arthritis is a chronic inflammatory disease. Cardiovascular events are the most important cause of mortality and morbidity in patients with rheumatoid arthritis [1]. Patients with rheumatoid arthritis (RA) have a two to five times increased risk of developing premature cardiovascular disease that shortens life expectancy by 5–10 years. Thus, in patients with active rheumatoid arthritis, the majority of cardiovascular deaths result from accelerated atherosclerosis [2, 3]. The inflammatory events in RA patients play an important role in acceleration of atherosclerosis process. Many similarities have emerged between the paradigm of inflammation in the pathogenesis of atherosclerosis and the well-established mechanisms of inflammation in the pathogenesis of RA. Hence, the inflammation in RA is not confined to the joints but also present in the vessel wall [2]. Atherosclerosis, previously thought to be a passive disease of lipid accumulation, is now widely acknowledged as a dynamic inflammatory process beginning with endothelial activation, leukocyte recruitment, lipid oxidation, and culminating with plaque destabilization and thrombosis [4]. Subclinical atherosclerosis can be demonstrated by an increased main carotid artery intima media thickness (IMT), a good marker of generalized atherosclerosis. Measurement of carotid artery IMT is a noninvasive, sensitive, cost-effective method to determine subclinical atherosclerosis and to diagnose at-risk patient groups [5, 6].

2. Patients and Methods

2.1. Patients

2.1.1. Group [I]: Rheumatoid Arthritis Patients. One hundred and twelve patients with RA were included in the present study, 94 women and 18 men; their age ranged from 21 to 49 years and disease duration ranged from six months to fifteen years. Patients were diagnosed according to...
the American College of Rheumatology (ACR) 1987 revised
criteria for the classification of rheumatoid arthritis [7].
They were consecutively recruited from the outpatient clinic
of Rheumatology and Rehabilitation Department El-Minia
University Hospital. The RA patients were further subdivided
according to disease activity into group 1A (patients with
moderate and sever RA) and group 1B (mild RA and RA with
remission).

Exclusion Criteria. Control and RA patients with known
atherosclerotic complications such as stroke and MI; those
undergoing hemodialysis; patients with peripheral vascular
disease, malignancy, or infections; hypertensive and diabetic
patients; and smokers were excluded; patients complaining
of any cardiac symptoms or signs (chest pain, dyspnea,
palpitation, LL edema, etc.) were also excluded.

2.1.2. Group [II]: Control Persons. Forty age and sex matched
healthy subjects were recruited as controls for laboratory
investigations and duplex ultrasonographic evaluation.

2.2. Methods. All patients underwent a complete history
taking and clinical examination according to the standard
protocol. General and locomotor examinations were done for
all patients.

Assessment of disability by the Health Assessment Ques-
tionnaire (HAQ) disability index: The Arabic version of
disability index of the Stanford Health Assessment Question-
naire was used to assess disability [8] (assessment of pain by
visual analog scale: Ranged from no pain degree (0) to worst
pain degree (100%); assessment of disease activity by the 28
joint disease activity score (DAS28) [9]). DAS28 includes 10
PIPs, 10 MCPs, both wrists, both elbows, both shoulders, and
both knees. DAS28 (formula with four variants) is as follows:
DAS28 = 0.56(√(TEN28) + 0.28(√(SW28) + 0.70Ln(ESR) +
0.014(GH)), mild < 3.2, moderate = 3.2–5.1, and severe > 5.1.

2.2.1. Laboratory Investigations. The following was done for
each patient and controls: Complete blood count (RBCs,
WBCs, and platelets), using an automated cell counter,
Sysmex NE; erythrocyte sedimentation rate (ESR) (by West-
egren method); rheumatoid factor (RF); latex agglutination
slide test for the qualitative and semiquantitative determi-
nation of rheumatoid factor in nondiluted serum [10]; liver
functions tests, done on dimension ES chemical autoana-
lyzer: serum aspartate transaminase (AsT), serum alanine
transaminase (A1T); lipid profile: total cholesterol (normal
up to 130 mg/dL); triglycerides (normal range 50–150 mg/dL);
HDL, high density lipoprotein (normal range 0–80 mg/dL);
LDL, low density lipoprotein (normal range 80–130 mg/dL);
and highly sensitive C-reactive protein (ELIZA).

2.2.2. Imaging Evaluation. Anteroposterior radiographs of
both hands and feet were done. Simple Erosion Narrowing
Score (SENS) was used for X-ray scoring [11]. It is a simplified
method of scoring radiographs based on the Sharp/van der
Heijde score [12]. Radiographs were scored by a consultant
rheumatologist in random order. The latter was blinded to
patients’ personal and clinical data at the time of scoring.

2.2.3. Duplex Ultrasonographic Evaluation. Evaluation is
done as follows:

(1) Duplex ultrasonography of both carotids;
(2) ultrasonography to right brachial artery to detect
endothelial function.

(II) Endothelial Function. To assess endothelial function non-
invasively with B-mode ultrasound, conduit vessel endothe-
lium-dependent vasodilation was induced by reactive
hyperemia, while endothelium-independent vasodilation
was induced by administration of sublingual nitroglycerine
(glyceryl trinitrate; GTN) as described by Yim and his
colleagues [16]. Measurements were made of changes in the
diameter of the brachial artery using color duplex Doppler
ultrasound. The ultrasound examination was performed in
quiet room at temperature between 21°C and 32°C. Subjects
rested in a supine position for 15 minutes before examination.
AB-mode scan was obtained of the right brachial artery in
longitudinal section. A resting measurement was taken (pre-
FMD), and a pneumatic cuff was then inflated to a pressure pf
200 mm Hg for 5 minutes; then the diameter of the artery was
recorded again 45–60 seconds after deflation (post-FMD). A
period of 15 minutes was allowed for recovery before testing
for endothelium-independent relaxation. A repeat baseline
measurement of the diameter was before a 400 µg dose of
sublingual GTN spry was administrated (pre-GTN). The
brachial artery diameter was again measured 3–4 minutes
after the GTN was given (post-GTN). A single investigator
performed all imaging and analysis, blinded to the subject’s disease [17]. FMD, GTN, and dilatation were calculated as follows:

\[
\text{FMD} = \left( \frac{(\text{Post FMD} - \text{Pre FMD})}{\text{Pre FMD}} \right) \times 100,
\]

\[
\text{GTN} = \left( \frac{(\text{Post GTN} - \text{Pre GTN})}{\text{Pre GTN}} \right) \times 100,
\]

\[
\text{Dilatation ratio} = \frac{\text{FMD}}{\text{GTN}}.
\]

Data were coded, entered, and analyzed by the statistical package for the Social Sciences (SPSS for windows version 11.0) [18]. Two-tailed tests were used throughout and statistical significance was set at the conventional 0.05 level. The following statistics were carried out. Descriptive statistics: The range, means, and standard deviation were calculated for interval and ordinary variables and frequencies and percentages for categorical variables [19]. Group comparisons: Comparisons were done by two procedures. *Student’s t-test: The independent samples T test was used to compare the means of two groups of cases. *The chi-squared (\( \chi^2 \)) test: We used the \( \chi^2 \) test to test the significance of the differences between the two groups in categorical variables. Correlations: The bivariate correlations procedure computes Pearson’s correlation coefficient with its significance levels. Pearson’s correlation coefficient is a measure of linear association.

### 3. Results

This study was carried out on 112 RA patients (group 1) and 40 age and sex matched healthy controls (group II). Patients were classified by DAS28 scores into the following: patients in remission (defined as DAS28 score <2.4) was observed in six out of 112 (5.4%) cases; low disease activity (<3.2) was found in 14 (12.5%); moderate activity (3.2–5.1) in 28 (25%); and high disease activity (>5.1) in 64 (57.1%) RA patients.

#### 3.1. Descriptive Study. The demographic data of the RA patients and controls are shown in Table 1.

#### 3.2. Patient Characteristics

#### 3.2.1. General Clinical Features of RA Patients. The mean disease duration was 6.03 ± 3.9 years (ranging from 6 months to 15 years) and 19.64% of our patients were of recent onset (<2 years). The DAS28 ranged between 1.2 and 7.81 with a mean of 5.21 ± 1.68. The visual analog scale of pain ranged between 0 and 1.77 with a mean of 0.742 ± 0.501. The body mass index ranged between 17.7 and 42.25 with a mean of 26.02 ± 6.42; also the waist circumferences ranged between 61 and 120 cm with a mean of 90.86 ± 11.94. Regarding deformities, they were present in 68 (60.71%) patients while rheumatoid nodules were present also in 18 (16.07%) patients. At the time of the study, 10 (8.93%) patients only were not using NSAIDs. 58 patients (51.8%) were using steroids. Ninety patients (80.4%) were using antimalarial drugs, while 98 patients (87.5%) were using MTX. Twenty patients (17.9%) were using Sulphasalazine. 44 (39.3%) patients were using Leflunomide.

#### Table 1: Demographic data of patients and control group.

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
<th>Patients (N = 112)</th>
<th>Control (N = 40)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± St.D.</td>
<td>36.50 ± 7.22</td>
<td>34.6 ± 8.22</td>
<td>0.350</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18 (16.07%)</td>
<td>6 (15.8%)</td>
<td></td>
<td>0.977</td>
</tr>
<tr>
<td>Female</td>
<td>94 (83.92%)</td>
<td>32 (84.2%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Table 2: Laboratory features of RA patients and controls.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>RA patients</th>
<th>Controls (n = 40)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (gm%)</td>
<td>11.82 ± 2.04</td>
<td>12.82 ± 1.79</td>
<td>0.05</td>
</tr>
<tr>
<td>WBCs (/mm)</td>
<td>6.08 ± 2.28</td>
<td>7.46 ± 2.74</td>
<td>0.5</td>
</tr>
<tr>
<td>Platelets (/mm)</td>
<td>286.68 ± 88.33</td>
<td>269.79 ± 60.95</td>
<td>0.4</td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
<td>40.82 ± 42.27</td>
<td>7.74 ± 1.3</td>
<td>0.000***</td>
</tr>
<tr>
<td>FBS (mg%)</td>
<td>90.7 ± 17.43</td>
<td>88.42 ± 10.27</td>
<td>0.5</td>
</tr>
<tr>
<td>AIr</td>
<td>23.05 ± 11.61</td>
<td>21.37 ± 8.32</td>
<td>0.5</td>
</tr>
<tr>
<td>AsT</td>
<td>24.73 ± 21.14</td>
<td>24.37 ± 8.48</td>
<td>0.9</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>166.25 ± 30.76</td>
<td>170.42 ± 36.65</td>
<td>0.63</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>90.70 ± 30.72</td>
<td>81.42 ± 26.8</td>
<td>0.22</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>42.8 ± 3.4</td>
<td>42.37 ± 4.4</td>
<td>0.63</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>114.45 ± 33.48</td>
<td>122.26 ± 35.41</td>
<td>0.406</td>
</tr>
</tbody>
</table>

**Hb** = hemoglobin, **WBC** = white blood cells, **ESR** = erythrocyte sedimentation rate, **FBS** = fasting blood sugar, **AIr** = alanine transaminase, **AsT** = aspartate transaminase, and **RF** = rheumatoid factor.

***Highly significant.
our mind, we found the same number of our patient had atherosclerosis. But another author showed carotid artery IMT >0.90 mm was a marker of atherosclerosis; the number of our patients who had IMT >0.90 mm was only four (3.6%).

The mean and standard deviation of disease duration of all patients was 6.4 ± 3.9. The mean of disease duration in patients with and without atherosclerosis was 10.5 ± 3.1 and 4.7 ± 2.9, respectively. The mean of disease activity index in patients with and without atherosclerosis was 5.8 ± 1.5 and 2.8 ± 1.3, respectively (Figures 1 and 2). There is highly statistically significant relation between presence of atherosclerosis with disease duration and disease activity ($P < 0.0001^{**}$, $P < 0.002^{**}$, resp.).

**Intimal Medial Thickness.** Tables 4, 5, and 6 showed a comparison of ultrasonographic duplex findings in RA patients and its subgroups with controls. The comparison between group 1 and group II and comparison between group IA and group II with respect to ultrasonographic duplex findings of carotid arteries showed the mean maximum and left IMT were significantly higher in patients compared to the controls, while the comparison between group IB and group II reported no significant differences.

Table 7 summarized the comparison of ultrasonographic duplex findings of carotid arteries in RA patients; the mean, maximum, and left IMT were also significantly higher in group IA.

**Endothelial Function.** Tables 8, 9, and 10 showed a comparison of parameters which assess the endothelial function between all patients, patients subgroups with controls, and reported that post FMD ($P < 0.000^{**}$), FMD dilatation percent...
Table 6: Comparison of ultrasonographic duplex findings between group IB and controls.

<table>
<thead>
<tr>
<th></th>
<th>Group IB (n = 20)</th>
<th>Controls (n = 40)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean IMT</td>
<td>0.054 ± 0.017</td>
<td>0.050 ± 0.007</td>
<td>0.4</td>
</tr>
<tr>
<td>Left IMT</td>
<td>0.054 ± 0.017</td>
<td>0.049 ± 0.008</td>
<td>0.4</td>
</tr>
<tr>
<td>Right IMT</td>
<td>0.053 ± 0.017</td>
<td>0.0495 ± 0.0869</td>
<td>0.4</td>
</tr>
<tr>
<td>Maximum</td>
<td>0.056 ± 0.018</td>
<td>0.0526 ± 0.008</td>
<td>0.6</td>
</tr>
</tbody>
</table>

IMT = intima media thickness.

Table 7: Comparison of ultrasonographic duplex findings in RA patients.

<table>
<thead>
<tr>
<th></th>
<th>Group 1A (n = 92)</th>
<th>Group 1B (n = 20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean IMT</td>
<td>0.057 ± 0.011</td>
<td>0.053 ± 0.017</td>
<td>0.04*</td>
</tr>
<tr>
<td>Lt. IMT</td>
<td>0.058 ± 0.016</td>
<td>0.054 ± 0.017</td>
<td>0.01*</td>
</tr>
<tr>
<td>Rt. IMT</td>
<td>0.052 ± 0.016</td>
<td>0.053 ± 0.017</td>
<td>0.55</td>
</tr>
<tr>
<td>Maximum</td>
<td>0.059 ± 0.017</td>
<td>0.056 ± 0.018</td>
<td>0.04*</td>
</tr>
</tbody>
</table>

IMT = intima media thickness.

*Significant.

Table 8: Comparison of endothelial function in RA patients and controls.

<table>
<thead>
<tr>
<th></th>
<th>RA patients (n = 112)</th>
<th>Controls (n = 40)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| FMD = flow mediated dilatation, GTN = glyceryl trinitrate.

**Highly significant.

(P < 0.0000***), and dilatation ratio (P < 0.0000***)) were significantly lower in patient than controls, even in group IB.

Table 11 showed a comparison of parameters which asses the endothelial function in RA patients groups; post FMD (P < 0.04*), FMD dilatation percent (P < 0.03*), and dilatation ratio (P < 0.01*) were significantly lower in the first group than the second.

Atherosclerosis and Steroid Use. There are 58 patients (51.8%) of current steroid users and 54 patients (48.2%) are nonsteroid users in RA patients, nearly similar prevalence of cases with increased mean IMT in patient using glucocorticoids (18 cases; 51.4% of the thickened IMT) than nonusers (17 cases, 48.6% of the thickened IMT). No significant differences were found in comparison of parameters which asses the endothelial function in RA patients and ultrasonographic duplex of their carotid arteries in patients who used steroids with patients who do not use steroids (Tables 12, 13, and 14).
when complex intima media is $<$0.09 cm; therefore, IMT values $0.09$ cm were considered indicative of thickened intima.

Atherosclerosis and Disease Activity. There is association between DAS28 and IMT and presence of plaques with a significant negative correlation between DAS28 score and endothelial function parameters in RA patients, FMD dilatation percent and dilatation ratio ($P < 0.005^{**}$, $P < 0.007^{**}$, resp.), and also it has a significant correlation with ultrasonographic duplex findings of carotid arteries maximum, left IMT, and mean IMT ($P < 0.01^*$, $P < 0.001^{**}$, and $P < 0.0001^{***}$, resp.) (Tables 15 and 16).

**4. Discussion**

In the present study there is an overall higher prevalence of premature atherosclerosis in RA patients than controls; in addition, the mean IMT was significantly higher in RA patients than our healthy controls ($0.57 \pm 0.05$ versus $0.49 \pm 0.072$ mm, resp.) ($P = 0.01^*$). In addition to the two markers of subclinical atherosclerosis; the mean right and left IMT were higher in patients compared to the controls. Plaques were also more frequently observed in RA ($P = 0.02$). And by comparison of parameters which assess the endothelial function in RA patients and controls. Only FMD ($P = 0.043$) and dilatation ratio ($P = 0.001$) were significantly lower in patient than controls. These result in agreement of other studies [20–22].

In accordance with our result, a study by La Montagna and his colleague [21] confirmed that the prevalence of the atherosclerosis is higher in RA patients than in the general population.

Our finding indicated that accelerated atherosclerosis is a well-defined feature of RA which was in agreement with many other studies [23–25].

In our study, the cut-off point of intima media thickness is considered abnormal if $>0.072$ cm which is in agreement with other studies [21, 26, 27]. The cut-off point between normal and high IMT was different between studies. In Doria and his colleagues [13] study normal IMT was defined when complex intima media is $<0.09$ cm; therefore, IMT values $0.09$ cm were considered indicative of thickened intima.

**Table 12**: Percentages of steroid user to nonusers in RA patients and the relationship with thickened IMT.

<table>
<thead>
<tr>
<th>RA patients $N = 56$</th>
<th>IMT $\leq 0.72$ mm</th>
<th>IMT $&gt; 0.72$ mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids user $n = 58$ (51.7%)</td>
<td>40</td>
<td>18</td>
</tr>
<tr>
<td>Steroids nonuser $n = 54$ (48.2%)</td>
<td>37</td>
<td>17</td>
</tr>
</tbody>
</table>

IMT = intima media thickness.

**Table 13**: Comparison of parameters which assess the endothelial function in RA patients who use steroids and RA patients who do not use steroids.

<table>
<thead>
<tr>
<th>RA patients who use steroids ($n = 58$)</th>
<th>RA patients who do not use steroids ($n = 54$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>Pre-FMD (average)</td>
<td>3.67 ± 0.56</td>
<td>3.73 ± 0.45</td>
</tr>
<tr>
<td>Post-FMD (average)</td>
<td>4.33 ± 0.61</td>
<td>4.3 ± 0.6</td>
</tr>
<tr>
<td>FMD dilatation %</td>
<td>18.31 ± 7.78</td>
<td>15.86 ± 7.93</td>
</tr>
<tr>
<td>Pre-GTN (average)</td>
<td>3.7 ± 0.59</td>
<td>3.75 ± 0.47</td>
</tr>
<tr>
<td>Post-GTN (average)</td>
<td>4.63 ± 0.74</td>
<td>4.6 ± 0.7</td>
</tr>
<tr>
<td>GTN dilatation %</td>
<td>26.03 ± 8.01</td>
<td>23.19 ± 10.3</td>
</tr>
<tr>
<td>Dilatation ratio</td>
<td>0.7 ± 0.26</td>
<td>0.72 ± 0.26</td>
</tr>
</tbody>
</table>

FMD = flow mediated dilatation, GTN = glyceryl trinitrate.

**Table 14**: Comparison of ultrasonographic duplex findings in RA patients who use steroids and RA patients who do not use steroids.

<table>
<thead>
<tr>
<th>RA patients who use steroids ($n = 58$)</th>
<th>RA patients who do not use steroids ($n = 54$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>Mean IMT</td>
<td>0.058 ± 0.016</td>
<td>0.055 ± 0.016</td>
</tr>
<tr>
<td>Left IMT</td>
<td>0.059 ± 0.017</td>
<td>0.055 ± 0.015</td>
</tr>
<tr>
<td>Right IMT</td>
<td>0.078 ± 0.12</td>
<td>0.055 ± 0.017</td>
</tr>
<tr>
<td>Maximum</td>
<td>0.061 ± 0.018</td>
<td>0.058 ± 0.016</td>
</tr>
</tbody>
</table>

IMT = intima media thickness.

**Table 15**: Correlation between DAS28 and endothelial function in RA patients.

<table>
<thead>
<tr>
<th>Endothelial function</th>
<th>DAS28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-FMD (average)</td>
<td>0.064</td>
</tr>
<tr>
<td>Post-FMD (average)</td>
<td>0.048</td>
</tr>
<tr>
<td>FMD dilatation %</td>
<td>-0.249</td>
</tr>
<tr>
<td>Pre-GTN (average)</td>
<td>0.044</td>
</tr>
<tr>
<td>Post-GTN (average)</td>
<td>0.028</td>
</tr>
<tr>
<td>GTN dilatation %</td>
<td>0.002</td>
</tr>
<tr>
<td>Dilatation ratio</td>
<td>-0.355</td>
</tr>
</tbody>
</table>

$r = $ Correlation coefficient, FMD = flow mediated dilatation, and GTN = glyceryl trinitrate. *Moderate significant.

**Table 16**: Correlation between DAS28 and ultrasonographic duplex findings in RA patients.

<table>
<thead>
<tr>
<th>Duplex findings</th>
<th>DAS28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right IMT</td>
<td>0.110</td>
</tr>
<tr>
<td>Left IMT</td>
<td>0.339</td>
</tr>
<tr>
<td>Mean IMT</td>
<td>0.324</td>
</tr>
<tr>
<td>Maximum</td>
<td>0.321</td>
</tr>
</tbody>
</table>

IMT = intima media thickness, $r = $ correlation coefficient. *Significant, **moderate significant, and ***highly significant.
While in Marasini et al. [14] study, the subclinical atherosclerosis IMT cut-off value detected was >0.7 mm. Differences in the ultrasound equipment or even using the same equipment with different frequency or different resolution could result in such variability. Common carotid IMT using ultrasound with a high frequency may allow more accurate results than of limited resolution. Different scanning and reading protocols could also influence the results. Another factor reported that IMT in men is significantly thicker than that in women when estimated using 7-8 MHz frequency ultrasound [28], difference in the methodology for assessment of atherosclerosis may lead to different results.

Disease duration is the best predictor of plaque and atherosclerosis development. We did not find evidence of this in patients with short disease duration (the mean and standard deviation was 10.5 ± 3.1). This was in agreement with other authors [29] who showed no atherosclerosis in disease duration <7 years.

In our study, there was no significant difference found between the two groups.

As regards the prevalence of traditional cardiovascular risk factors. In our study, obesity, as defined by BMI >30.0, was reported in 40 (35.7%) of our RA patients versus 12 (30%) of our healthy controls with no significant statistical differences between both groups. Our results were similar to other study [21]. Most authors have pointed out low levels of HDL-cholesterol [30, 31]. However, we did not find this association in the present study, this agrees with results of other studies [21]. The discrepancy in results is likely to depend on differences among the cohorts of patients investigated, including differences in their nutritional habits. Nevertheless traditional risk factors clearly play a role in the pathogenesis of atherosclerosis in RA and must be investigated when evaluating the individual RA patient [32].

Inflammation is considered to be an important risk factor for premature atherosclerosis in RA. This was a very consistent finding in the present study as measured by acute phase reactants including high level erythrocyte sedimentation rate and CRP. As expected, higher levels of ESR (P < 0.001) were detected in RA compared to healthy controls; this is in agreement with the previous study [22]. These data definitely support systemic inflammation as a factor of importance for premature atherosclerosis in RA patients.

In this study, the relationship with DAS28, a composite disease activity index in RA, supports role for chronic inflammation in the development of atherosclerosis. The relationship between IMT, DAS28, and glucocorticoid cumulative doses confirmed that atherosclerosis in RA is associated with inflammation in agreement with La Montagna and his colleague [21].

In this study the percentages of steroid user are 51.8% and nonusers are 48.2% in RA patients. No significant differences were found between the two groups in ultrasonographic duplex of their carotid arteries; and no significant differences were found in the endothelial function; but there is a significant association between the cumulative doses of steroids and the thickened IMT (P < 0.05∗). Other authors saw that patients requiring GCs as part of their disease management are likely to have aggressive disease, which contributes to a reduction in mobility as a result of joint stiffness and damage. Therefore, GC use in this subset of patients may result in suppression of disease activity and allow patients to lead a more active lifestyle with a further beneficial effect on HDL levels as well as aggressive control of inflammatory disease activity with available means, including judicious usage of GCs [33]. Thus, accurate drug history and accurate dose determination was a problem, exclusively in illiterate patients and on those with long disease duration. In practice, therefore, judicious use of steroids to control inflammation is probably beneficial. Excessive dosing may exacerbate metabolic factors. Achieving the correct balance, therefore, remains a major clinical challenge.

5. Conclusion

Egyptian asymptomatic RA patients exhibited increased carotid IMT and impaired FMD with increasing the frequency of atherosclerosis compared with general population. Thus carotid ultrasonography and endothelial function by flow mediated vasodilatation must be done in all RA patients, which could be simple noninvasive method of identifying preclinical atherosclerosis, in addition to the need for control of rheumatoid disease activity and its inflammatory burden because uncontrolled chronic inflammation is probably the major factor for premature atherosclerosis.

Recommendation

Research focusing on sensitive predictors of premature atherosclerosis including biomarkers like adhesive molecule, proinflammatory cytokines, and chemokines should be addressed so that some intervention model could be prepared for the prevention of cardiovascular-disease-related morbidities and mortalities in the RA population.

Conflict of Interests

The authors declare no potential conflict of interests in this paper.

Acknowledgment

All thanks are due to all members of rheumatology and cardiology department for their cooperation.

References


