Risk Factors for Ischemic Heart Disease in Rheumatoid Arthritis
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Abstract

Objective: The study aims to evaluate some cardiovascular risk factors in patients with rheumatoid arthritis (RA) and their relationship to ischemic heart disease (IHD) and atherosclerosis.

Patients and Methods: The study included fifty patients with RA and twenty-five healthy controls. All patients and controls were subjected to full history taking, clinical examination and the following investigations: ECG, echocardiography, carotid Doppler ultrasonography, complete blood count, rheumatoid factor (RF), C-reactive protein (CRP), serum homocysteine, serum prolactin, serum uric acid, and lipid profile (total cholesterol, triglycerides (TG), HDL-C, LDL-C).

Results: The group of RA patients had significant higher number of patients with positive CRP, with high serum uric acid, higher mean serum homocysteine, higher mean serum prolactin, higher mean total cholesterol, higher mean TG, higher mean LDL-C and lower mean HDL-C levels than the control group. Also, the group of RA patients had significant higher number of patients with ischemic changes in both ECG and echocardiography, with carotid atheromatous plaques, and significant higher mean right and left carotid intima-media thickness (IMT) than the control group. In RA patients, there were significant positive correlations between the ischemic changes in both ECG and echocardiography, carotid IMT and carotid atheromatous plaques and all the following risk factors; serum CRP, serum uric acid, serum homocysteine, serum prolactin, serum total cholesterol, serum TG, serum LDL-C levels and prolonged disease duration.

Conclusion: IHD and atherosclerosis are common in RA patients. The risk factors for IHD are hyperlipidemia, hyperhomocysteinemia, hyperprolactinemia, hyperuricemia, elevated inflammatory markers such as CRP, and prolonged disease duration. Targeting these risk factors in RA patients could help in lowering incidence of IHD and its sequelae. We recommend ECG, echocardiography and carotid Doppler ultrasonography as non-invasive screening tests for early detection of IHD and atherosclerosis in RA patients.

Key Words: Rheumatoid arthritis – Heart disease – Ischemic.

Introduction

RHEUMATOID arthritis (RA) is one of the most common autoimmune diseases which cause chronic inflammation of the joints, the tissues around the joints, as well as other organs in the body. The cardiovascular disease (CVD) is the main cause of mortality in RA patients, accounting for as much as 50% of all reported deaths [1]. The risk for CVD in RA is significantly increased versus the general population and often in undertreated patients, leading to a decrease in life expectancy [2]. Traditional risk factors for CVD, such as smoking, hypertension, diabetes and hyperlipidemia, do not fully account for the increased risk of CVD in patients with RA [3]. In patients with RA, traditional and non-traditional risk factors play a role in the development and exacerbation of CVD [4]. Non-traditional risk factors, such as serum prolactin, C-reactive protein, serum homocysteine and serum uric acid have been implicated as factors that cause endothelial dysfunction and exacerbation of CVD [5].

Prolactin has a role in immunomodulation and it has been proposed that prolactin is a risk factor for development of autoimmunity. There is increased risk of developing RA postpartum and this further increases five-fold in breastfeeding and also, disease activity in RA improves with dopamine agonist. This suggests that prolactin may have role in the pathogenesis, or at least modulation of disease activity in RA [6]. Homocysteine as well as mediators of inflammation are considered to play role in increased cardiovascular morbidity and mortality [7]. Higher serum homocysteine concentrations are found in patients with RA than in normal controls [8]. Some studies have shown that methotrexate therapy in RA could raise serum homocysteine levels [9]. C-reactive protein (CRP) is an acute phase reactant produced by hepatocytes. In RA, although CRP has been shown to be a poor predictor of RA incidence, it is central in the evaluation of disease progression and response to therapeutic intervention, and increasingly suspected as a pro-atherogenic agent in affected patients [10]. Uric acid is a waste product normally presents in
the blood as a result of breakdown of purines. Raised serum uric acid concentration is a powerful predictor of cardiovascular risk and poor outcome. Studies have demonstrated mechanisms by which uric acid could be directly injurious to the endothelium and to cardiovascular function, paradoxically, uric acid elevation could be expected to confer protective antioxidant effect in cardiovascular system, but these potential benefits may be obscured by detrimental effects elsewhere [11]. Dyslipidemia observed in RA appears to be dependent on disease activity i.e. a higher disease activity is associated with lower total cholesterol levels and even more depressed high density lipoprotein levels, leading to a higher atherogenic index [12].

Atherosclerosis is the most common pathologic process leading to CVD including myocardial infarction and stroke. RA by itself, represents a significant risk factor for early atherosclerosis and the development of CVD [13]. Many methods are used now for detection of subclinical atherosclerosis in RA patients. Carotid Doppler ultrasonography has been found to be a reliable non-invasive method of detecting atherosclerosis which correlates strongly with the presence of coronary artery disease [14].

**Aim of work:**

This study aims to evaluate some cardiovascular risk factors and their relationship to ischemic heart disease (IHD) and carotid atherosclerosis in patients with RA.

**Patients and Methods**

Fifty patients (aged 20-60 years, 8 males and 42 females) with a diagnosis of RA, attending outpatient clinic of Rheumatology Unit of the Internal Medicine Department at Assiut University Hospitals during the year 2012, were recruited into a study investigating the risk factors for IHD and carotid atherosclerosis. All patients fulfilled the 2010 American College of Rheumatology criteria for RA and had a disease duration ranging from 3 months to 25 years. Twenty-five healthy controls (aged 21-58 years, 8 males and 17 females) were assembled, they were randomly selected from the populations register the same region. RA patients known to have IHD, diabetes, hypertension, smokers, pregnant and lactating females were excluded from the study. RA patients were then divided into active and remission groups according to disease activity score-28 (DAS-28); 32 patients were in activity (DAS-28 >2.6) and 18 patients were in remission (DAS-28 <2.6). Also, RA patients were classified into early and late groups according to disease duration; 20 patients had disease duration less than one year (early group) and 30 patients had disease duration more than one year (late group). All individuals were subjected to full history taking such as age, sex, and disease duration. All individuals were subjected to full clinical examination, including joints examination. The number of swollen and tender joints (28 joints count) and patients’ global assessment were registered and a disease activity score (DAS-28) including ESR calculated:

\[0.56^* (\text{tender joints}) + 0.28^* (\text{swollen joints}) + 0.70^* (\text{ESR}) + 0.014^* \text{visual analog score}\]

All individuals were subjected to the following investigations:

1. Twelve-lead ECG recordings and echocardiography were done to detect the ischemic changes which include; ST segment depression and T-wave changes (inversion or flat) in ECG and diastolic dysfunction and/or segmental or global hypokinesia in echocardiography.

2. Carotid Doppler ultrasonography: Carotid artery studies were performed with the individual in supine position with the neck extended and the chin turned away from the side being examined. Bilateral common carotid arteries, carotid bulbs and extracranial parts of internal carotid arteries were imaged in multiple longitudinal planes for the best resolution of the intima-media thickness (IMT), atheromatous plaques, hemodynamic changes, partially stenotic or occluded segments.

3. Laboratory investigations including:
   - Complete blood count (CBC).
   - Erythrocyte sedimentation rate (ESR).
   - Rheumatoid factor (RF).
   - C-reactive protein (CRP).
   - Serum homocysteine level: Performed by Glory Science Co, ltd kit and using Enzyme Linked Immunosorbent Assay technique.
   - Serum prolactin level: Preformed by biocheck inc and using Enzyme Linked Immunosorbent Assay technique.
   - Serum uric acid.
   - Lipid profile (total cholesterol, TG, HDL-C, LDL-C).
   - Kidney function tests.
   - Liver function tests.
   - Fasting and two-hour postprandial blood glucose.

Each of lipogram, serum uric acid, kidney and liver function tests and blood glucose were performed on Modular.
Statistical analysis:
The collected data were analysed by using the statistical package for Social Sciences (SPSS/PC/ version 17). Discrete variables were presented as numbers and percentages and continuous variables were presented as mean±standard deviation (SD). Student t-test was used to compare the mean difference between the groups, Chi-square test was used to compare the difference in proportions and Spearman’s rank correlation coefficient was used to detect the association between the risk factors of IHD and ECG, echocardiography and carotid Doppler findings. Significant test results were considered when p-value <0.05.

Results
This study was conducted on 50 patients with RA fulfilled the 2010 American College of Rheumatology criteria for RA, and 25 clinically normal subjects were chosen as control group. The mean age of RA patients was 43.7±11.7 years (ranging from 20 to 60 years) and this group included 8 males (16%) and 42 females (84%). The mean age of control group was 42.1±8.9 years (ranging from 21 to 58 years) and this group included 8 males (32%) and 17 females (68%). The study found that RA patients group had significant lower mean haemoglobin levels (10.7±3.4g/dl) than the control group (13.3±2.3g/dl) (p-value<0.001), and also the patients group had significant higher number of anaemic patients (n=39) than the control group (n=0) (p-value<0.001). Also, the study found that the group of cases had significant higher number of individuals with positive RF (n=38) than the control group (n=0) (p-value<0.001) (Table 1).

Table (1): Comparative analysis of the studied groups (cases vs. controls) regarding the demographic data and some routine laboratory investigations.

<table>
<thead>
<tr>
<th></th>
<th>Total (n=75)</th>
<th>Cases (n=50)</th>
<th>Controls (n=25)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>43.7±11.7</td>
<td>42.1±8.9</td>
<td>43.7±11.7</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (n=16)</td>
<td>8 (50%)</td>
<td>8 (50%)</td>
<td>8 (50%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Female (n=59)</td>
<td>42 (71.2%)</td>
<td>17 (28.8%)</td>
<td>25 (50%)</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>10.7±2.3</td>
<td>13.3±0.9</td>
<td>10.7±2.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anaemia:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n=36)</td>
<td>11 (30.6%)</td>
<td>25 (69.4%)</td>
<td>11 (30.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Yes (n=39)</td>
<td>59 (100%)</td>
<td>0 (0%)</td>
<td>59 (100%)</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid factor:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative (n=57)</td>
<td>12 (32.4%)</td>
<td>25 (67.6%)</td>
<td>12 (32.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Positive (n=38)</td>
<td>38 (100%)</td>
<td>0 (0%)</td>
<td>38 (100%)</td>
<td></td>
</tr>
</tbody>
</table>

The study revealed that the group of RA patients had significant higher number of patients with positive CRP (n=38) and with high serum uric acid (n=10) than the control group (n=0) (p-value <0.001, p-value<0.01 respectively). Also the study found that the patients group had significant higher mean serum homocysteine and mean serum pro-lactin levels than the control group (p<0.05 for each). As regard the lipogram, the group of RA patients had significantly higher mean total cholesterol, mean TG and mean LDL-C levels than the control group (p<0.01, p<0.05 and p<0.001 respectively), but the patients group had significant lower mean HDL-C level compared to the control group (p<0.05) (Table 2).

Table (2): Comparative analysis of the studied groups regarding risk factors of ischemic heart disease.

<table>
<thead>
<tr>
<th></th>
<th>Total (n=75)</th>
<th>Cases (n=50)</th>
<th>Controls (n=25)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative (n=37)</td>
<td>12 (32.4%)</td>
<td>25 (67.6%)</td>
<td>12 (32.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Positive (n=38)</td>
<td>38 (100%)</td>
<td>0 (0%)</td>
<td>38 (100%)</td>
<td></td>
</tr>
<tr>
<td>Uric Acid:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (n=65)</td>
<td>40 (61.5%)</td>
<td>25 (38.5%)</td>
<td>40 (61.5%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hyperuricemic (n=10)</td>
<td>10 (100%)</td>
<td>0 (0%)</td>
<td>10 (100%)</td>
<td></td>
</tr>
<tr>
<td>Lipogram (Mean±SD):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol (mg/dl)</td>
<td>165.5±36.4</td>
<td>139.3±25.3</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>129.8±38.3</td>
<td>87.7±21.8</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>42.1±19.2</td>
<td>50.6±5.1</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>98±30.2</td>
<td>71.1±26.4</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Homocysteine (μmol/L) (Mean±SD)</td>
<td>6.1±1.6</td>
<td>2.9±1.7</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Prolactin (ng/ml) (Mean±SD)</td>
<td>24.7±5.4</td>
<td>11.2±3.7</td>
<td>&lt;0.05</td>
<td></td>
</tr>
</tbody>
</table>

The study showed that the RA patients group had significant higher number of individuals with ischemic changes in both ECG (n=8) and echocardiography (n=14) than the control group (n=0) (p<0.05 and p<0.01 respectively). As regard the carotid Doppler findings, the patients group had significant higher mean right and left carotid IMT than the control group (p<0.001) and the patients group had significant higher number of individuals with carotid atheromatous plaques (n=10) than the control group (n=0) (p<0.05) (Table 3).

Table (3): ECG, Echo and carotid doppler findings in cases and controls.

<table>
<thead>
<tr>
<th></th>
<th>Total (n=75)</th>
<th>Cases (n=50)</th>
<th>Controls (n=25)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (n=67)</td>
<td>42 (62.7%)</td>
<td>25 (37.3%)</td>
<td>42 (62.7%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Ischemic Changes (n=8)</td>
<td>8 (100%)</td>
<td>0 (0%)</td>
<td>8 (100%)</td>
<td></td>
</tr>
<tr>
<td>Echo:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (n=61)</td>
<td>36 (59.0%)</td>
<td>25 (41.0%)</td>
<td>36 (59.0%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ischemic Changes (n=14)</td>
<td>14 (100%)</td>
<td>0 (0%)</td>
<td>14 (100%)</td>
<td></td>
</tr>
<tr>
<td>Intima-media thickness (IMT):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (n=41)</td>
<td>16 (39.0%)</td>
<td>25 (61.0%)</td>
<td>16 (39.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thick (n=34)</td>
<td>34 (100%)</td>
<td>0 (0%)</td>
<td>34 (100%)</td>
<td></td>
</tr>
<tr>
<td>IMT (mm) (Lt.) (Mean±SD)</td>
<td>11.5±3.6</td>
<td>7.1±1.3</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>IMT (mm) (Rt.) (Mean±SD)</td>
<td>11.4±3.4</td>
<td>7.1±1.3</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Atheromatous Plaques:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n=65)</td>
<td>40 (61.5%)</td>
<td>25 (38.5%)</td>
<td>40 (61.5%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Yes (n=10)</td>
<td>10 (100%)</td>
<td>0 (0%)</td>
<td>10 (100%)</td>
<td></td>
</tr>
</tbody>
</table>
In RA patients, the study showed that there were significant positive correlations between the ischemic changes in both ECG and echocardiography, carotid IMT and carotid atheromatous plaques and all the following risk factors; the age of RA patients, the occurrence of anaemia, positivity of RF, serum CRP, serum uric acid, serum homocysteine, serum prolactin, serum total cholesterol, serum triglyceride (TG), and serum LDL-C levels. There was significant negative correlation between the serum HDL-C in RA patients and carotid IMT (p<0.01), but there were no correlations between the serum HDL-C and ischemic changes in ECG, ischemic changes in echocardiography and carotid atheromatous plaques (Table 4).

The study showed that there were no correlations between the ischemic changes in ECG and echocardiography and both the RA disease duration and activity. As regard the carotid Doppler findings, there were significant positive correlations between the carotid IMT, carotid atheromatous plaques and RA disease duration (p<0.05). Although there was significant positive correlations between RA disease activity and the carotid IMT (p<0.05), there was no correlation with carotid atheromatous plaques (Table 4).

Table (4): Correlation between ECG, Echo, carotid doppler findings and and risk factors of IHD in RA patients.

<table>
<thead>
<tr>
<th></th>
<th>ECG</th>
<th></th>
<th>Echo</th>
<th></th>
<th>IMT</th>
<th></th>
<th>Plaque</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p value</td>
<td>r</td>
<td>p value</td>
<td>r</td>
<td>p value</td>
<td>r</td>
<td>p value</td>
</tr>
<tr>
<td>Age</td>
<td>0.20</td>
<td>&lt;0.05</td>
<td>0.21</td>
<td>&lt;0.05</td>
<td>0.71</td>
<td>&lt;0.001</td>
<td>0.43</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Disease Duration</td>
<td>0.13</td>
<td>&gt;0.05</td>
<td>−.04</td>
<td>&gt;0.05</td>
<td>0.22</td>
<td>&lt;0.05</td>
<td>0.21</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Disease Activity</td>
<td>−.01</td>
<td>&gt;0.05</td>
<td>0.19</td>
<td>&gt;0.05</td>
<td>0.20</td>
<td>&lt;0.05</td>
<td>0.17</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Anaemia</td>
<td>0.23</td>
<td>&lt;0.05</td>
<td>0.33</td>
<td>&lt;0.01</td>
<td>0.67</td>
<td>&lt;0.001</td>
<td>0.27</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>RF</td>
<td>0.25</td>
<td>&lt;0.05</td>
<td>0.35</td>
<td>&lt;0.01</td>
<td>0.52</td>
<td>&lt;0.001</td>
<td>0.28</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CRP</td>
<td>0.25</td>
<td>&lt;0.05</td>
<td>0.35</td>
<td>&lt;0.01</td>
<td>0.72</td>
<td>&lt;0.001</td>
<td>0.28</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Uric Acid</td>
<td>0.46</td>
<td>&lt;0.001</td>
<td>0.58</td>
<td>&lt;0.001</td>
<td>0.34</td>
<td>&lt;0.01</td>
<td>0.38</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>0.51</td>
<td>&lt;0.001</td>
<td>0.52</td>
<td>&lt;0.001</td>
<td>0.32</td>
<td>&lt;0.05</td>
<td>0.53</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TG</td>
<td>0.27</td>
<td>&lt;0.05</td>
<td>0.31</td>
<td>&lt;0.05</td>
<td>0.43</td>
<td>&lt;0.01</td>
<td>0.36</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HDL-C</td>
<td>−.18</td>
<td>&gt;0.05</td>
<td>−.13</td>
<td>&gt;0.05</td>
<td>−.36</td>
<td>&lt;0.01</td>
<td>−.02</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.55</td>
<td>&lt;0.001</td>
<td>0.46</td>
<td>&lt;0.001</td>
<td>0.38</td>
<td>&lt;0.01</td>
<td>0.48</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>0.36</td>
<td>&lt;0.01</td>
<td>0.75</td>
<td>&lt;0.001</td>
<td>0.32</td>
<td>&lt;0.05</td>
<td>0.26</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Prolactin</td>
<td>0.61</td>
<td>&lt;0.001</td>
<td>0.59</td>
<td>&lt;0.001</td>
<td>0.31</td>
<td>&lt;0.05</td>
<td>0.35</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

**Discussion**

Cardiovascular disease is being recognized as the major cause of excess mortality in rheumatoid arthritis [15], also cardiovascular morbidity is enhanced and there is an increased prevalence at all stages of atherogenesis from endothelial dysfunction to fatal and non-fatal myocardial infarction and stroke [16], moreover, the excess cardiovascular burden persists after adjustment for traditional cardiovascular risk factors [17]. Non-traditional risk factors, such as serum prolactin, C-reactive protein, serum homocysteine and serum uric acid have been implicated as factors that cause endothelial dysfunction and exacerbation of CVD [5].

The study aimed to evaluate some cardiovascular risk factors and their relationship to ischemic heart disease (IHD) and carotid atherosclerosis in patients with RA. This study showed that the RA patients group had significant higher positive CRP than the control group, this result was in concordance with the results of Molenaar et al., [18] who reported that CRP has a great value as an inflammatory marker in RA and has been suggested to mediate part of the complement activation in RA. CRP has been clearly shown to predict further cardiovascular risk [19]. Direct pathogenic role of CRP has been suggested and many studies have shown that CRP may facilitate an increase in cellular adhesion to the endothelium, encourage macrophage and uptake of LDL-C [20]. Also, serum uric acid was found significantly higher in RA patients group compared to the control group, this result was consistent with the results of Agudelo et al., [21] who studied hyperuricemia in rheumatoid arthritis. Raised serum uric acid concentration is a powerful predictor of cardiovascular risk and poor outcome. Studies have demonstrated mechanisms by which uric acid could be directly injurious to the endothelium and to cardiovascular function, paradoxically, uric acid elevation could be expected to confer protective antioxidant effect in cardiovascular system, but these potential benefits may be obscured by detrimental effects elsewhere [22].
In this study, we found that the patients group had significantly higher homocysteine levels compared to the control group, this result was in concordance with the results of Hernanz et al., [22] who reported that increased plasma levels of homocysteine and other thiol components in RA women. It is well known that vitamin deficiency can be derived from cell proliferation. Since inflammation promotes cell proliferation at the expense of excess vitamins leading to hyperhomocysteinemia, therefore, homocysteine can be used as a marker of inflammation [23]. The study showed that the mean prolactin level was significantly higher in RA patients group compared to the control group, this result was consistent with results of Mateol et al., [24] and Liederman et al., [6]. T-lymphocytes infiltrating the synovium produce prolactin and have been shown to induce excessive synovial cell function in RA patients; bromocriptine treatment in vitro suppressed lymphocyte prolactin as well as IL-6 and lymphocyte proliferation [25]. In the present study, we found that the RA patients group had significantly higher mean total cholesterol, TG and LDL-C levels and significantly lower HDL-C than the control group, these results were in concordance with the results of Lakatos et al., [26] and Nurmo-hamed [12] who studied the atherogenic lipid profiles and its management in patients with RA.

This study revealed that there was significantly higher number of individuals with ischemic changes in both ECG and echocardiography among RA patients compared to the control group, this agreed with Del Rincon et al., [27] who reported that high incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors, and also with Gerli et al., [28] who showed that T-lymphocytes contribute to early atherosclerotic damage in rheumatoid arthritis patients. Also, the study showed that the RA patients group had significant higher mean carotid IMT and higher carotid atheromatous plaques compared to the control group, and this agreed with Roman et al., [29] who reported that the prevalence of carotid atherosclerosis in RA is at least as high as in diabetes mellitus, and also, agreed with the studies of Ebrahim et al., [30] and Mannami et al., [31] who found that the intima-media thickness of extracranial carotid arteries provides an index of atherosclerosis in other vascular regions and has been shown to be associated with most risk factors for atherosclerosis.

In this study, we found significant positive correlation between the age of RA patients and the ischemic changes in both ECG and echocardiography, carotid IMT and carotid atheromatous plaques. These results were in consistent with results of Cecilia et al., [32]. As regard the disease duration, the study showed significant positive correlation between carotid IMT, carotid atheromatous plaques and RA disease duration and these results agreed with results of González-Juanatey et al., [33]. The present study showed no correlation between RA disease duration and ischemic changes in both ECG and echocardiography, and this goes hand to hand with the study of Galutina and Bychak [34]. On the contrary, Fielta and Delsante [35] reported that atherosclerosis is an early and common finding in RA patients, positively correlating to the disease duration and severity.

We also found that there was significant positive correlation between the ischemic changes in both ECG and echocardiography, increased IMT, carotid atheromatous plaques and elevated markers of inflammation, such as increased CRP, positive RF and this agreed with other studies as that of Chung et al., [36] who reported that the prevalence and severity of coronary calcification is increased in established RA and is related in part to elevated inflammatory markers. Maradit-Kremers et al., [37] confirmed that markers of systemic inflammation confer a statistically significant additional risk for cardiovascular death among patients with RA. Galutina and Bychak [34] also found that myocardial ischaemia in patients with RA was associated with high activity of inflammatory process. The present study showed that there was a significant positive correlation between the occurrence of anaemia in RA patients and ischemic changes in both ECG and echocardiography, carotid IMT and carotid atheromatous plaques, these results agreed with the studies of Varat et al., [38] and Kiechl et al., [39].

It was noticed that there was significant positive correlation between homocysteine levels and ischemic changes in ECG, ischemic changes in echocardiography and carotid IMT, and this agreed with the study of Boushey et al., [40]. The study also showed significant correlation between homocysteine levels and carotid atheromatous plaques and this agreed with the results of Spence et al., [41]. Several mechanisms for homocysteine-induced atherosclerosis have been proposed. These include endothelial dysfunction, enhancement of oxidative stress, reduction in nitric oxide bioavailability, and augmentation of thrombus formation. Folic acid supplementation down-regulates these inflammatory response [42]. As regard the uric acid in RA patients, the study showed significant positive correlation between the serum uric acid and myocardial ischemia, carotid IMT and carotid
atheromatous plaques, and this agreed with Panoulus et al., [43]. The present study showed that there was significant positive correlation between serum prolactin levels in RA patients and myocardial ischemia, carotid IMT and carotid atheromatous plaques, and this agreed with Martinez et al., [44] who reported that prolactin inhibits activation of endothelial nitric oxide synthesis, intracellular calcium mobilization, and endothelial dependent vasorelaxation. As regard the lipogram, this study revealed that there was significant positive correlation between myocardial ischemia, carotid IMT, carotid atheromatous plaques and the levels of total cholesterol, LDL-C and triglycerides, and this agreed with Georadias et al., [45] who reported that atherogenic lipid profile is a feature characteristic of patients with RA. Although the present study showed that there was significantly negative correlation between the serum HDL-C in RA patients and carotid IMT, this correlation was not present with carotid atheromatous plaques. Mathiesen et al., [46] found that low levels of high-density lipoprotein cholesterol are associated with echoluent carotid artery plaques, and also Amareno et al., [47] found that high-density lipoprotein-cholesterol are associated with the risk of stroke and carotid atherosclerosis.

Traditional cardiovascular risk factors can not fully account for atherosclerosis in patients with RA, therefore, inflammation itself may play a part in the progression of atherosclerosis. Atherosclerosis shares many similarities with inflammatory and autoimmune diseases such as RA [48]. Immunohistochemical studies suggest significant similarities between the mechanisms responsible for chronic synovitis and damage in the rheumatoid joint and the generation and rupture of atherosclerotic plaques. These include cellular infiltrates, adhesion molecule expression, the cytokine milieu and free radicals and degenerative enzymes release [49]. Chronic inflammation and immune dysregulation characterizing RA have a key role in accelerating atherosclerosis. Persistent endothelial dysfunction predisposes to organic damage of the vascular wall, that, in a preclinical stage can be detectable by ultrasound measurement of carotid IMT, carotid atheromatous plaques and hemodynamic changes [50].

In conclusion; IHD and atherosclerosis are common in RA patients. The risk factors for IHD are hyperlipidemia, hyperhomocysteinaemia, hyperprolactinemia, hyperuricemia, elevated inflammatory markers such as CRP, and prolonged disease duration. Targeting these risk factors in RA patients could help in lowering incidence of IHD and its sequelae. We recommend ECG, echocardiography and carotid Doppler ultrasonography as non-invasive screening tests for early detection of IHD and atherosclerosis in RA patients.

References


