Serum Lipid Profile in Early Rheumatoid Arthritis

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Abstract
Several investigators reported an excess of cardiovascular morbidity and mortality among rheumatoid arthritis (RA) patients. The majority of cardiovascular deaths result from accelerated atherosclerosis. Elevated plasma total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), decreased high-density lipoprotein cholesterol (HDL-C) are strong risk factors for atherosclerotic events. Twenty five patients with early rheumatoid arthritis (ERA) who met the American College of Rheumatology (ACR) 1987 criteria for Rheumatoid Arthritis (RA) had early disease with disease duration of less than one year without prior use of disease modifying antirheumatic drugs (DMARDs) and/or systemic steroids were examined for their lipid profile level and the relation of the atherogenic ratio to their disease were investigated during the period between March – December 2006 in the Department of Rheumatology at Al-Kadhimiya Teaching Hospital. Lipid profile (TC, LDL-C, HDL-C and TG), ESR and C-reactive protein were determined for both the patients and control groups. The results of the study revealed that ERA patients exhibited higher serum levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG), whereas their serum high-density lipoprotein cholesterol (HDL-C) levels were significantly lower compared to controls. As a consequence, the atherogenic ratio of TC/HDL-C as well as that of LDL-C/HDL-C was significantly higher in ERA patients compared to controls and these changes were correlated with laboratory changes, especially CRP and ESR. ERA patients are characterized by an atherogenic lipid profile in comparison with the healthy control subjects. Recognition and treatment of early rheumatoid arthritis and reduction of these and other cardiac risk factors has greater impact on the course of the disease.
Introduction

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disorder of unknown etiology that primarily involves joints. Extra-articular features of RA, including anemia, fatigue, subcutaneous ("rheumatoid") nodules, pleuropericarditis, neuropathy, scleritis, splenomegaly, Sjögren's syndrome, vasculitis, and renal disease may occur during the course of the disease (1). There is an increased risk of premature death due to coronary artery disease in patients with RA and there may be an increased risk of heart failure (2). The risk for decreased life expectancy and early cardiovascular mortality in particular, among people with rheumatoid arthritis is increasingly recognized. The increased risk of coronary heart disease may precede the onset and diagnosis of RA (3).

The risk in RA for cardiovascular death, thought to be increased more than twofold over the general population, appears to be independent of the known cardiac risk factors. Risk factors for atherosclerotic events and cardiovascular disease include male sex, increased age, elevated plasma total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), decreased high-density lipoprotein cholesterol (HDL-C), high blood pressure, smoking and diabetes mellitus (4).

The risk of sudden death and myocardial infarction appear to be increased in patients with RA. Atheromatous plaques in the carotid artery and greater intima-media thickness are two markers that suggest the presence of generalized atherosclerosis. By these measures, patients with RA have a greater burden of atherosclerotic disease than controls. The prevalence of carotid plaques as detected ultrasonographically in patients with RA is correlated with the duration of disease (5). In general, and with some variations between different studies, the lipid profile of patients with active or untreated RA is primarily characterized by a decrease in serum levels of HDL-C whereas contrasting results have been published on the serum levels of TC and LDL-C (5-10).

Importantly, the reduction in HDL-C has as a consequence the increase in the TC/HDL-C ratio. This ratio represents an atherogenic index, which is an important prognostic marker for cardiovascular disease (5).

Indeed, the risk of myocardial infarction increases considerably when this ratio is higher than five, and it should ideally be four or less (5, 6). The serum TC and HDL-C levels in RA are inversely correlated with disease activity (5), suggesting a potential role for inflammation in the atherogenic profile and the higher atherosclerotic risk observed in RA (7). Use of methotrexate and anti-tumor necrosis factor (anti-TNF) agents may have a beneficial effect upon cardiovascular morbidity and mortality. Because an increased prevalence of coronary atherosclerosis may contribute to the elevated mortality rates of patients with RA, the combination of lipid-lowering and anti-inflammatory would be a compelling rationale for the use of statins (8).

The aim of this study was to show the changes in lipid profile in those patients diagnosed to have early rheumatoid arthritis.

Patients and Methods

Patients

Inclusion Criteria: Twenty five patients with a mean age of 54.2 ± 9.6 years old and male to female ratio of 3/22, who met the American College of Rheumatology (ACR) 1987 criteria for Rheumatoid Arthritis (RA) had early disease with duration of less than one year without prior use of disease modifying antirheumatic drugs (DMARDs) and or systemic steroids, were investigated during the period between March – December 2006 in the Department of Rheumatology at Alkadhimiya Teaching Hospital.

Exclusion Criteria: Smokers or patients suffering from conditions that affect the
lipid profile, such as diabetes mellitus, hypothyroidism, liver or kidney disease, Cushing's syndrome, obesity (body mass index >30) and a history of familial dyslipidemia, were excluded. In addition, patients receiving medications affecting lipid metabolism, such as lipid-lowering drugs, beta-blockers, oral contraceptives, estrogen, progestin, thyroxin and vitamin E, were excluded from the study. Twenty five apparently healthy, non-smoking subjects with a mean age of 55.4±10.4 years old and male to female ratio of 5/20 also participated in the study and were considered as a control group. These subjects fulfilled the same exclusion criteria reported for the patient group. None of the subjects participating in the control group had a history of CAD. The control group was proportionally matched for age and sex to the patient group.

**Methods**

Overnight fasting blood samples were obtained from both ERA patients and the control groups. Serum lipids were determined within six hours of blood sampling. TC, triglycerides and HDL-C were determined with enzymatic colorimetric method using Shimadzu micro-flow meter CL-720. LDL-C was estimated using the Friedewald formula. Friedewald formula = Serum TC – [SerumHDL+Serum TG/5](9). IgM rheumatoid factor was measured by ELISA (Enzyme Linked Immuno Sorbent Assay) method (18). ESR was measured by the modified Westergren method. In addition, complete blood count with differential, as well as serum glucose, liver and kidney function tests, were performed for all patients.

**Statistical Analysis:**

All data were analyzed by excel programme using the independent t-test of unequal variances considering (p<0.05) as significant difference.

**Results**

During the selection period (March-December 2006), twenty-five patients were included in the study. There were 22 women and 3 men with a mean age of 54.2±9.6 years and mean disease duration of 0.5±0.3 years. The clinical characteristics and lipid profiles of patients and controls are described in Table 1.

The results of the patients had shown a high mean serum level of cholesterol in comparison to control group with a significant difference (p<0.05) as shown in table (2). The mean serum level of LDL-C in patients was higher than the mean serum level of LDL-C in control group. But a non-significant difference (p>0.05) as shown in table (3).

On the other hand the mean serum TG level in patients was higher than the mean serum TG level in control group. There was a non-significant difference (p>0.05) as shown in table (4).

The mean serum level of HDL-C in patients with ERA was lower than the mean serum level of control group. With a significant difference (p<0.05) as shown in table (5).

As a consequence of the above mentioned results regarding Total Cholesterol, LDL-C, HDL-C and TG the mean atherogenic ratio of TC/HDL-C was higher in patients with ERA than in control group with a significant difference (p<0.05), as shown in table (6). The LDL-C/HDL-C was also higher in patients with ERA than the control group with a significant difference (p<0.05) as shown in table (7).

There was a significant direct correlation between serum TC and CRP (C-reactive Protein) in patients with ERA (p<0.05), as shown in figure (1). Serum HDL-C had shown a significant correlation in relation to CRP in patients with ERA (p<0.05), with an inverse correlation as shown in figure (2). Serum TC had a significant correlation to ESR in patients with ERA (p<0.05), with a direct correlation as shown in figure (3). Serum HDL-C had a significant correlation with ESR in patients with ERA (p<0.05), with an inverse correlation as shown in figure (4).
Discussion
The objective of this study was to determine the lipid profile of ERA patients and to investigate whether this could be influenced by disease activity in the early stages of rheumatoid arthritis. According to the results, patients with ERA exhibited an atherogenic lipid profile characterized by a significantly reduced serum level of HDL-C and as a consequence an increase in the atherogenic ratio of TC/HDL-C or LDL-C/HDL-C was observed in ERA patients, suggesting that these patients are possibly exposed to a higher risk of atherosclerosis. The lipid profile of patients with ERA has been evaluated in several studies. Some of these studies have reported lower levels of HDL-C and TC, higher TC/HDL-C and LDL-C/HDL-C ratios in active and/or untreated disease than in general population (10,11). On the other hand other studies did not show significantly different lipid levels from those observed in the healthy population (12,13), while others referred to an overall reduction in all lipid subfractions in cases of active disease (11,14). These contrasting results may be attributed to the size of the samples, the type of the study (prospective or cross-sectional), and differences in the disease type (established or early) or to differences in disease activity. Patients in remission or with controlled disease show an increase in HDL-C levels and a reduction in the atherogenic index compared to patients with active disease (5). Systemic inflammation may also play a role in the development of atherosclerosis (12,15). In fact the increase in acute phase reactants in cardiovascular events has already been documented (14). It has even been suggested that RA and atherosclerosis may share a common predisposing factor (12,17,18). CRP is the common denominator for both diseases (19,20). CRP which increases in active disease, may contribute to atherosclerosis because it stimulates macrophages to produce tissue factor, a procoagulant that is found in atherosclerotic plaques. The presence of CRP in atheromatic lesions also suggests a (cause and effect) relationship between this acute phase reactant and coronary events (20,21). An important observation is that ERA patients exhibit low HDL serum levels. The decrement in HDL-C was inversely correlated with the increment of either CRP levels or ESR values. This suggests that inflammation is an important determinant for the reduced HDL-C levels observed in ERA patients. It is possible that RA patients may have some classic risk factors for atherosclerosis development. However, it is not correct to attribute the increased prevalence of atherosclerosis observed in RA patients to these factors. In our study, we tried to exclude patients with classic risk factors for atherosclerosis and we found that ERA patients with high disease activity showed an adverse lipid profile before the commencement of therapy.

References
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    immune system and inflammatory activity in relation to markers of atherothrombotic
Tables and Figures

**Table (1)** Comparison between mean values ± standard deviation of patients with ERA and control group.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Controls values±S.D.</th>
<th>ERA patients values±S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>5/20</td>
<td>3/22</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55.4±10.4</td>
<td>54.2±9.6</td>
</tr>
<tr>
<td>Body Mass Index (BMI) (kg/m²)</td>
<td>25.3±1.8</td>
<td>25.2±2.4</td>
</tr>
<tr>
<td>IgM Rheumatoid factor (+/-)</td>
<td>0/0</td>
<td>21/4</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>2.1±0.7</td>
<td>24.4±10.8</td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
<td>5.1±1.7</td>
<td>49.9±11.2</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>192.2±18.5</td>
<td>217.9±37.5</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>125.7±14.7</td>
<td>141.2±24.2</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>52.0±5.5</td>
<td>40.5±7.9</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>98.3±13.4</td>
<td>133.4±27.5</td>
</tr>
<tr>
<td>TC/HDL-C</td>
<td>3.74±0.7</td>
<td>5.69±1.37</td>
</tr>
<tr>
<td>LDL-C/HDL-C</td>
<td>2.5±0.57</td>
<td>4.04±0.9</td>
</tr>
</tbody>
</table>

**Table (2)** the relationship between Serum Total Cholesterol level in ERA patients and control group.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Serum level of Total Cholesterol (Mean±S.D) mg/dl</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ERA</td>
<td>217.9±37.5</td>
<td>0.004</td>
</tr>
<tr>
<td>Control group</td>
<td>192.2±18.5</td>
<td></td>
</tr>
</tbody>
</table>

**Table (3)** the relationship between Serum LDL level in ERA patients and control group.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Serum level of LDL-C (Mean±S.D) mg/dl</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ERA</td>
<td>141.2±24.2</td>
<td>0.07</td>
</tr>
<tr>
<td>Control group</td>
<td>125.7±14.7</td>
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</tbody>
</table>

**Table (4)** the relationship between Serum TG level in ERA patients and control group.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Serum level of TG (Mean±S.D) mg/dl</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ERA</td>
<td>133.4±27.5</td>
<td>1.72</td>
</tr>
<tr>
<td>Control group</td>
<td>98.3±13.4</td>
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**Table (5)** the relationship between Serum HDL-C level in ERA patients and control group.
Table (6) Atherogenic ratio in ERA patients and control Group.

<table>
<thead>
<tr>
<th>Groups</th>
<th>TG/HDL-C (Mean±S.D)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ERA</td>
<td>5.6±1.3</td>
<td>0.004</td>
</tr>
<tr>
<td>Control group</td>
<td>3.7±0.7</td>
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</tbody>
</table>

Table (7) LDL/HDL in ERA patients and control group.

<table>
<thead>
<tr>
<th>Groups</th>
<th>LDL-C/HDL-C (Mean±S.D)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ERA</td>
<td>4.04±0.9</td>
<td>0.004</td>
</tr>
<tr>
<td>Control group</td>
<td>2.5±0.5</td>
<td></td>
</tr>
</tbody>
</table>

Figure (1) The correlation between CRP and TC in ERA Patients

Figure (2) The correlation between CRP and HDL-C in ERA Patients
**Figure (2)** The correlation between CRP and HDL-C in ERA Patients

![ESR and TC](image1)

**Figure (3)** The correlation between ESR and TC in ERA patients.

![ESR and HDL-C](image2)

**Figure (4)** The correlation between HDL and ESR in ERA patients.