Dyslipoproteinemia in Patients with Active Rheumatoid Arthritis: Effects of Disease Activity, Sex, and Menopausal Status on Lipid Profiles

WAN-HEE YOO

ABSTRACT. Objective. To investigate the lipid profiles in patients with active rheumatoid arthritis (RA) and to assess the relationship of inflammatory disease activity markers, sex, and menopausal status with lipid profiles.

Methods. Three groups of patients with active RA (n = 184) were studied: men (n = 61, mean age 50.8 ± 4.81 yrs), premenopausal women (n = 58, mean age 39.2 ± 2.44 yrs), and postmenopausal women (n = 65, mean age 60.4 ± 2.14 yrs), and healthy controls (n = 161): men (n = 65, mean age 50.9 ± 3.42 yrs), premenopausal women (n = 47, mean age 40.3 ± 1.66 yrs), and postmenopausal women (n = 49, mean age 61.3 ± 3.16 yrs). We measured fasting plasma levels of total cholesterol (TC), triglyceride (TG), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), lipoprotein (a) [LP(a)], apolipoprotein A1 (apo A1), apolipoprotein B (apo B), and erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

Results. Male RA patients had significantly higher apo B/apo A1 and LP(a) and lower HDL-C than male controls. Female RA patients had significantly higher TC, LDL-C, and LP(a) than female controls. Premenopausal RA patients had significantly higher LDL-C, TC/HDL-C, LDL-C/HDL-C, and apo B/apo A1 and lower TG and HDL-C than premenopausal controls. Postmenopausal RA women had significantly higher TG and LP(a) and lower TC than postmenopausal controls. Female RA patients had higher HDL-C, apo A1, and TC/HDL-C and lower apo B/apo A1 than male RA patients. Postmenopausal RA patients had significantly higher TC, TG, TC/HDL-C, apo B, LP(a), and LDL-C/HDL-C than premenopausal RA patients. CRP correlated positively with TC/HDL-C, LDL-C/HDL-C, and apo B/apo A1 and negatively with HDL-C in male RA patients. In female RA patients CRP had positive correlation with TC/HDL-C and LDL-C/HDL-C and negative correlation with HDL-C.

Conclusion. These findings suggest that patients with active RA have altered lipid profiles and that disease activity, sex, and menopausal status affect lipid profiles, and these would be expected to change the pattern of atherosclerotic events in RA. (J Rheumatol 2004;31:1746–53)

Key Indexing Terms:
RHEUMATOID ARTHRITIS         ATHEROSCLEROSIS          LIPOPROTEINS

Rheumatoid arthritis (RA) is a chronic multisystem disease of unknown etiology predominantly involving multiple joints. Epidemiologic studies have shown an increased premature mortality in patients with RA compared with the general population. Several investigators reported an excess cardiovascular morbidity and morbidity in active RA and the majority of cardiovascular deaths in RA result from accelerated atherosclerosis. Recently, ultrasonic examination of carotid artery in patients with RA showed early atherosclerotic markers consistent with increased risk for atherosclerosis.

Risk factors for cardiovascular disease and atherosclerotic events include male sex, increased age, elevated plasma LDL-cholesterol (LDL-C), decreased HDL-C, high blood pressure, smoking, and diabetes mellitus. The inflammation of RA can cause systemic and metabolic alterations, and RA patients have been found to have hypercholesterolemia, decreased concentration of serum triglycerides (TG), and changes in concentrations of some apolipoproteins. Also, lipoprotein (a) [LP(a)] has characteristics of acute phase reactants and is known to be a risk factor for atherosclerosis. Although there were variable results, these reports suggest that altered lipoprotein pattern in patients with RA could be part of the cause of the increased risk of cardiovascular disease (CVD) in RA.

Some of the differences in CVD risk related to sex, age, and menopausal status may relate to differences in lipoprotein...
tein subspecies. Sex differences in plasma lipid concentrations have been reported and age and menopausal differences in lipid profiles have been documented. It has been suggested that these differences may at least in part explain the higher risk of CVD in men than women, and in postmenopausal women than in premenopausal women. Although few studies are available regarding lipid profiles in patients with RA, there had been no reports about the effects of sex and menopausal status on lipid profiles in RA.

The purpose of this study was to assess the pattern of lipid profiles and the relationship of the inflammatory activity of RA with lipid profiles, and to determine the effects of sex and menstrual status on plasma lipid profiles in patients with active RA.

MATERIALS AND METHODS

Patients. We studied 184 Korean patients who met the 1987 revised criteria for RA of the American College of Rheumatology, who were initially treated with steroid and disease modifying antirheumatic drugs (DMARD) at Chonbuk National University Hospital. Active RA was defined as ≥ 6 swollen or tender joint counts, morning stiffness > 1 h, and erythrocyte sedimentation rate (ESR) > 20 mm/h. Lipids and lipoproteins were measured, before the prescription of any drugs for RA, in 3 groups of patients with active RA: men (n = 65, mean age 50.8 ± 4.81 yrs), premenopausal women (n = 58, mean age 39.2 ± 2.44 yrs), defined as having had menses in the past year, and postmenopausal women (n = 47, mean age 40.3 ± 1.66 yrs), defined as having no menses in the past year (Table 1). No information about phase of menstrual cycle was obtained.

Women who had undergone a hysterectomy with or without an oophorectomy were excluded from the analysis. All subjects were living independently and were taking no medications known to affect lipoprotein metabolism (such as lipid-lowering agents, ß-blocker, oral contraceptive, estrogen, progestin, and thyroxine). Patients with signs of liver or kidney dysfunction, nephritic syndrome, alcoholism, and thyroid abnormalities were excluded. No patient was selected who had diabetes mellitus, syphilis, acute infection, malignant neoplasm, or sign of ischemic heart disease, iatrogenic Cushing's disease, or obesity. Pregnancy women were excluded, as were any patients with a history of blood transfusion. No patient was overweight, and none was on a vegetarian diet.

Controls. The control group consisted of 161 non-obese, age and sex matched healthy volunteers who took part in a screening program of lipid profiles among the working population of our hospital. They had similar age, weight, height, and body mass index distribution. Controls were defined into 3 groups as in RA patients: men (n = 65, mean age 50.9 ± 3.42 yrs), premenopausal women (n = 47, mean age 40.3 ± 1.66 yrs), and postmenopausal women (n = 49, mean age 61.3 ± 3.16 yrs) (Table 1). This study was conducted with approval of the Human Experimentation Committee of our institute and with the informed consent of the patients.

Lipid measurement. Blood samples were collected in the early morning for measurement of fasting lipid profiles. Plasma lipids were determined after 12 h overnight fast. Blood was allowed to clot 45 min at room temperature and serum was obtained immediately by centrifugation at 35,000 rpm for 10 min and stored at –70°C until analysis. Total cholesterol (TC), TG, and HDL-C were measured using the Boehringer diagnostic kits by an enzymatic colorimetric method. LDL-C was estimated by calculation, using the Friedewald formula. Apolipoprotein A1 (Apo A1), apo B, and LP(a) were determined by nephelometry.

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ESR (modified Westergren method) and C-reactive protein (CRP) were measured by routine methods. Clinical disease activity of patients with RA was measured by duration of morning stiffness, number of tender joints, number of swollen joints, number of deformed joints, modified Health Assessment Questionnaire (MHAQ), visual analog scale for pain (VAS), physician's global assessment, and functional status.

Statistical analysis. All data were analyzed with the SPSS 9.0 program. Comparison of lipoprotein and apolipoprotein concentrations between each group of patients with RA and controls was by unpaired Student t test. Correlations between variables were analyzed by Pearson's correlation test. A level of p < 0.05 was considered statistically significant.

RESULTS

Lipid profiles in controls. Levels of TC, HDL-C, and apo A1 were significantly higher in female than male controls. Although mean levels of apo A1 and the ratios of TC/HDL-C and LDL-C/HDL-C in female controls were higher than those of male controls, this was without statistical significa...
Lipid profiles in patients with RA. Levels of HDL-C and apo A1 were significantly higher in female than male patients with RA. Although mean levels of TC and LDL-C and the ratio of LDL-C/HDL-C in female RA patients were higher than in male RA patients, these findings were without statistical significance. The ratio of apo B/apo A1 was significantly lower in female than male controls. The levels of TG and apo B and the ratio of TC/HDL-C in female RA patients were lower than those of male patients (nonsignificant). Levels of TC, TG, apo B, and LP(a) and the ratios of LDL-C/HDL-C and TC/HDL-C in postmenopausal RA patients were significantly higher than those of premenopausal RA patients. Postmenopausal RA patients had higher levels of LDL-C and apo A1 and ratio of apo B/apo A1 compared with premenopausal RA patients (nonsignificant). Compared with premenopausal women, postmenopausal women had lower level of HDL-C (nonsignificant; Table 2).

Lipid profiles in controls and patients with RA. Compared with male controls, male RA patients had significantly higher levels of LP(a) and apo B/apo A1 ratio. Levels of TG, LDL-C, and apo B and the ratio of LDL-C/HDL-C in male RA patients were higher than male controls (nonsignificant). Male RA patients had significantly lower levels of HDL-C than male controls and lower levels of TC and apo A1 and TC/HDL-C ratio than male controls (nonsignificant; Figure 1A).

Female RA patients had significantly higher levels of LDL-C and LP(a) and lower level of TC than female controls. They also had higher levels of TG and apo B, and higher ratios of TC/HDL-C, LDL-C/HDL-C, and apo B/apo A1 than female controls (nonsignificant). Female RA patients had lower levels of HDL-C and apo A1 than female controls (nonsignificant; Figure 1B).

In premenopausal women, the level of LDL-C and ratios of TC/HDL-C, LDL-C/HDL-C, and apo B/apo A1 in premenopausal RA patients were significantly higher than in premenopausal controls. Premenopausal RA patients had higher levels of apo B compared with premenopausal controls (nonsignificant). Compared with premenopausal controls, premenopausal RA patients had significantly lower levels of TG and HDL-C. The levels of TC and apo A1 were lower in premenopausal RA patients than premenopausal control women, but with no statistical significance.

Levels of TG and LP(a) in postmenopausal RA patients were significantly higher than those of postmenopausal control women. Postmenopausal RA patients had higher ratios of LDL-C/HDL-C and apo B/apo A1 compared with postmenopausal control women (nonsignificant). Compared with postmenopausal controls, postmenopausal RA patients had significantly lower levels of TC. Levels of LDL-C, HDL-C, apo A1, and apo B and TC/HDL-C ratio were lower in postmenopausal RA patients than postmenopausal controls (significant; Table 2).

Lipid profiles and clinical activity indices and inflammation

Table 2. Comparison of lipid profiles in 3 groups of patients with RA and controls. Data are presented as mean ± SE.

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Male</th>
<th>Male</th>
<th>Female</th>
<th>Female</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>65</td>
<td>47</td>
<td>49</td>
<td>96</td>
<td>61</td>
<td>58</td>
<td>65</td>
</tr>
<tr>
<td>TC, mg/dl</td>
<td>173.8 ± 12.8</td>
<td>174.5 ± 8.77</td>
<td>196.0 ± 12.1</td>
<td>184.9 ± 14.2</td>
<td>169.8 ± 11.1</td>
<td>170.3 ± 10.0</td>
<td>182.4 ± 10.3</td>
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<tr>
<td>Triglyceride, mg/dl</td>
<td>132.9 ± 3.4</td>
<td>114.9 ± 18.4</td>
<td>126.1 ± 17.8</td>
<td>120.4 ± 18.2</td>
<td>134.2 ± 20.6</td>
<td>101.4 ± 15.5</td>
<td>2.34 ± 0.33</td>
</tr>
<tr>
<td>LDL-C, mg/dl</td>
<td>103.9 ± 10.9</td>
<td>93.2 ± 9.18</td>
<td>108.5 ± 17.8</td>
<td>100.1 ± 12.3</td>
<td>105.6 ± 10.1</td>
<td>103.2 ± 9.43</td>
<td>107.6 ± 9.41</td>
</tr>
<tr>
<td>HDL-C, mg/dl</td>
<td>47.5 ± 4.08</td>
<td>56.6 ± 3.20</td>
<td>48.4 ± 7.22</td>
<td>52.8 ± 5.44</td>
<td>43.7 ± 3.74</td>
<td>49.6 ± 4.24</td>
<td>47.3 ± 4.40</td>
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<tr>
<td>TC/HDL-C</td>
<td>3.28 ± 0.33</td>
<td>3.09 ± 0.37</td>
<td>4.05 ± 0.33</td>
<td>3.59 ± 0.35</td>
<td>3.92 ± 0.30</td>
<td>3.51 ± 0.35</td>
<td>4.03 ± 0.36</td>
</tr>
<tr>
<td>LDL-C/HDL-C</td>
<td>2.13 ± 0.47</td>
<td>1.69 ± 0.31</td>
<td>2.23 ± 0.38</td>
<td>1.91 ± 0.38</td>
<td>2.31 ± 0.38</td>
<td>2.06 ± 0.31</td>
<td>2.34 ± 0.33</td>
</tr>
<tr>
<td>Apo A1, g/l</td>
<td>1.35 ± 0.12</td>
<td>1.41 ± 0.09</td>
<td>1.39 ± 0.07</td>
<td>1.40 ± 0.08</td>
<td>1.25 ± 0.08</td>
<td>1.36 ± 0.06</td>
<td>1.37 ± 0.09</td>
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<tr>
<td>Apo B, g/l</td>
<td>0.93 ± 0.10</td>
<td>0.86 ± 0.09</td>
<td>0.94 ± 0.10</td>
<td>0.89 ± 0.10</td>
<td>0.95 ± 0.10</td>
<td>0.90 ± 0.11</td>
<td>0.93 ± 0.08</td>
</tr>
<tr>
<td>Apo B/apo A1</td>
<td>0.68 ± 0.11</td>
<td>0.61 ± 0.09</td>
<td>0.68 ± 0.08</td>
<td>0.65 ± 0.10</td>
<td>0.78 ± 0.10</td>
<td>0.68 ± 0.07</td>
<td>0.69 ± 0.08</td>
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<tr>
<td>LP(a), mg/dl</td>
<td>21.2 ± 6.87</td>
<td>22.4 ± 5.69</td>
<td>24.1 ± 5.76</td>
<td>23.1 ± 7.93</td>
<td>30.2 ± 7.27</td>
<td>23.6 ± 7.91</td>
<td>35.9 ± 11.7</td>
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</tbody>
</table>

TC: total cholesterol, LDL-C: LDL-cholesterol, HDL-C: HDL-cholesterol, Apo A1: apolipoprotein A1, Apo A: apolipoprotein B, LP(a): lipoprotein (a). In control groups: † p < 0.05 compared with male control, †† p < 0.05, † † p < 0.01 compared with premenopausal control. In RA groups: † p < 0.05, † † p < 0.01 compared with male RA patients. * p < 0.05, * † p < 0.01 compared with premenopausal RA patients. In control and RA groups: † p < 0.05 compared with male control, †† p < 0.05, † † p < 0.01 compared with premenopausal control. * p < 0.05, * † p < 0.01 compared with postmenopausal control. * p < 0.05 compared with female control.
There were no statistically significant correlations between lipid profiles and the clinical activity indices, including MHAQ, duration of morning stiffness, number of tender joints, number of swollen joints, VAS for pain, functional class, and physician's global assessment, in each group of patients with RA.

However, CRP correlated positively with TC/HDL-C ($r = 0.57, p < 0.01$), LDL-C/HDL-C ($r = 0.52, p < 0.01$), and apo B/apo A1 ($r = 0.41, p < 0.05$), and negatively with HDL-C ($r = -0.47, p < 0.01$) in male RA patients. A significant negative correlation was found between ESR and HDL-C ($r = -0.39, p < 0.05$) in male RA patients (Figure 2). In female RA patients, there were positive correlations between CRP and TC/HDL-C ($r = 0.24, p < 0.05$) and CRP and LDL-C/HDL-C ($r = 0.30, p < 0.05$), and negative correlations between CRP and HDL-C ($r = -0.28, p < 0.01$), ESR had positive correlation with TC/HDL-C ($r = 0.31, p < 0.05$) and negative correlation with HDL-C ($r = -0.37, p < 0.01$) in female RA patients (Figure 3). CRP had negative correlations with HDL-C ($r = -0.31, p < 0.05$) and ESR had negative correlations with the level of HDL-C ($r = -0.43, p < 0.01$) in premenopausal female RA patients (Figure 4). In postmenopausal female RA patients, positive correlation was found between CRP and TC/HDL-C ($r = 0.54, p < 0.01$), LDL-C/HDL-C ($r = 0.45, p < 0.05$), apo B/apo A1 ($r = 0.41, p < 0.05$), and ESR and apo B ($r = 0.38, p < 0.01$), and negative correlation between CRP and HDL-C ($r = -0.45, p < 0.05$) and ESR and HDL-C ($r = -0.43, p < 0.01$) (Figure 5).

Rheumatoid factor titers and lipid profiles. There were no differences in lipid profiles between RF positive and RF negative patients. There were also no correlations between RF titers and lipid profiles in RF positive patients in all groups of patients with RA.

**DISCUSSION**

The objective of this study was to determine whether there are altered lipid profiles in patients with active RA compared with healthy controls, and to assess the relationship of the inflammatory activity of RA with lipid profiles. The results revealed altered lipid profiles in patients with active RA compared with healthy controls: male RA patients showed significantly higher ratio of apo B/apo A1 and lower HDL-C than male controls, and female RA patients had significantly higher TC, LDL-C, and LP(a) than female controls. These results suggest that patients with active RA have altered lipid profiles compared to healthy controls, which may possibly expose them to higher risk of atherosclerosis.

Inflammation may be involved in the development of atherosclerosis, and there is a relationship between a marker of inflammation, CRP, and serum lipid levels in patients with RA. Data from this study showed that CRP correlated positively with the ratios of TC/HDL-C and LDL-C/HDL-C in male and female patients with RA. CRP also correlated positively with TC/HDL-C, LDL-C/HDL-C, and apo B/apo A1 in postmenopausal female RA patients. CRP was negatively correlated with HDL-C in all groups of RA patients. ESR had a positive correlation with TC/HDL-C in female RA patients and with apo B in postmenopausal female RA patients. There was a negative correlation of ESR with HDL-C in male and pre- and postmenopausal female RA patients.

Although there are different patterns of correlation depending on the sex and menopause status, inflammatory activity is associated with abnormal lipid profiles in RA. It is not known why there is a relationship between the degree of inflammation and lipid profile, or whether inflammation per se is directly associated with abnormal lipid metabolism in patients with active RA. Recently, the relation of acute phase response with insulin resistance and aberrant lipid metabolism was described as potential cardiovascular risk factors in RA. These data provide evidence that inflammation adversely affects the lipid profiles in active RA, and
also suggest that active RA may be a risk factor for atherosclerosis, at least partly due to the abnormal change of lipid metabolism. However, there were no relationships between lipid profiles and the clinical activity indices. Although reduced physical activity may affect the lipid profiles, no relation between clinical activity indices and lipid profiles makes this explanation for the lipid findings less likely.

Risk factors for CVD and atherosclerotic events include male sex, increased age, elevated plasma LDL-C, high blood pressure, smoking, and diabetes mellitus. Age, sex, and menopausal differences in lipid profiles have also been reported. However, the effects of sex and menopausal status on these measures have not been reported in RA. To define the effects of sex and menopausal status on lipid profile in RA patients, those parameters were compared. Female RA patients had higher levels of HDL-C and apo A1 and TC/HDL-C ratio, and lower values of apo B/apo A1 ratio than the male RA group. Postmenopausal female RA patients had higher levels of TC, TG, TC/HDL-C, LDL-C/HDL-C, apo B, and LP(a) than those of premenopausal RA patients. These results revealed the possibility that the lipid profiles of patients with active RA may differ according to the sex and menopause status, and these variably expose them to high risk of cardiovascular disease.

The reasons for the different effects of sex and menopausal status on lipid profiles in controls and RA patients remain unknown. Sex hormone imbalances have been detected in body fluids such as blood and synovial...
fluid of both male and female patients with RA and are considered a reason for the differences in lipoprotein related to sex and menopause status in patients with RA. Other unknown factors are thought to be responsible for the abnormalities of lipoprotein with the effects of sex and menopause status, and further studies are needed to define the exact role and mechanisms of the effects of sex and menopausal status on lipid profiles in RA.

LP(a) is a known risk factor for atherosclerosis, and increased serum level of LP(a) is associated with higher incidence of ischemic heart disease and stroke. Also, it has recently been reported to be associated with acute phase reactants. Our results showed that levels of LP(a) were significantly elevated in all groups of RA patients compared to controls, as in other reports, regardless of the sex and menopause status.

The major limitation of this study is that there was no consideration and analysis of the effects of patients’ average daily physical activity and therapeutic agents that may have been used before their recruitment to this study. However, the study was designed to measure lipoprotein and apolipoprotein levels when subjects initially visited our hospital, before prescription of any drugs that would modify these parameters. Studies on the effects of DMARD and steroid on these parameters according to sex and menopause status are under way. Although the small number of RA patients and controls may be a drawback, age and sex matched controls were included, and RA patients with any
Figure 4. Correlations of the inflammatory markers CRP and ESR and lipid profiles in premenopausal women with RA.

Figure 5. Correlations of the inflammatory markers CRP and ESR and lipid profiles in postmenopausal women with RA.
factors that affect lipid profiles were excluded. However, a large number of exclusion criteria in patients with RA might limit description of real lipid profiles in the general RA population.

In conclusion, patients with active RA have altered lipid profiles, and these abnormal patterns, associated with sex and menopausal status, would be expected to change the pattern of atherosclerotic events in RA. Further large-scale studies are warranted to define the effects of sex and menopausal status on lipoprotein and apolipoprotein activity in RA. It is also necessary to consider the effects of sex and menopausal status in studies of lipid profiles in the rheumatic diseases.

REFERENCES