Role of Insulin Resistance in Increased Frequency of Atherosclerosis Detected by Carotid Ultrasonography in Rheumatoid Arthritis

ÖMER NURI PAMUK, ERCÜMENT ÜNLÜ, and NECATI ÇAKIR

ABSTRACT. ***Objective.*** We evaluated the presence of subclinical atherosclerosis and factors influencing atherosclerosis, including insulin resistance (IR), in patients with rheumatoid arthritis (RA).

Methods. Sixty-three patients with RA and 34 controls were studied. Patients' cardiovascular risk factors were recorded; biochemical variables were determined. Intima-media thickness (IMT) of carotid arteries was determined by B-mode ultrasonography, and presence of atheromatous plaques was determined. IR was calculated according to the HOMA-IR homeostasis model.

Results. There were no differences in atherosclerotic risk factors between patients with RA and controls. In the RA group, the median carotid IMT was 0.61 mm (range 0.56–0.74), greater than the 0.54 mm (range 0.50–0.64) in controls ($p = 0.01$). There was a tendency to a higher frequency of carotid plaques in the RA group compared to controls [12 RA patients (19%) vs 2 controls (5.9%); $p = 0.10$]. Multivariate regression analysis revealed the factors that had an independent effect on increased carotid IMT: age ($p < 0.001$), male sex ($p = 0.01$), and total cholesterol level ($p = 0.02$). In RA patients with plaques, age (64.5 vs 48 yrs; $p = 0.005$), carotid IMT (0.75 vs 0.60 mm; $p = 0.001$), frequency of hypertension (58.3% vs 23.5%; $p = 0.03$), and IR (83.3% vs 29.4%; $p = 0.001$) were higher. Multivariate logistic regression analysis showed that factors independently associated with the presence of plaques were IR (OR 15.85, 95% CI 2.23–112.89, $p = 0.006$) and age (OR 1.11, 95% CI 1.02–1.21, $p = 0.02$). In RA patients, HOMA-IR correlated with age ($r = 0.26$, $p = 0.04$), Health Assessment Questionnaire score ($r = 0.28$, $p = 0.04$), and concentrations of triglyceride ($r = 0.39$, $p = 0.003$) and cholesterol ($r = 0.33$, $p = 0.02$).

Conclusion. IR in the setting of active rheumatoid disease may contribute to mechanisms of accelerated atherogenesis observed in patients with RA. (J Rheumatol 2006;33:2447–52)

Key Indexing Terms:
RHEUMATOID ARTHRITIS ATHEROSCLEROSIS INSULIN RESISTANCE
CAROTID INTIMA-MEDIA THICKNESS CAROTID PLAQUE

Recent data have shown that the frequency of coronary heart disease and cardiovascular mortality were increased in patients with rheumatoid arthritis (RA)[1,2]. Epidemiologic studies suggest that in addition to classical atherosclerosis risk factors, other mechanisms may play roles in the increased cardiovascular complications of RA[3]. Subclinical atherosclerosis can be demonstrated by an increased main carotid artery intima-media thickness (IMT), a good marker of generalized atherosclerosis[4,5]. Measurement of carotid artery IMT is a noninvasive, sensitive, cost-effective method to determine subclinical atherosclerosis and to diagnose at-risk patient groups[4,5]. It was reported that there was a significant relationship between carotid IMT and the future development of myocardial infarction (MI) and stroke. Many studies report increased carotid IMT and plaques in patients with RA[6-10].

Insulin resistance (IR) plays an important role in the development and progression of atherosclerotic cardiovascular disease[11]. IR is the key defect in the metabolic syndrome[12]. IR is associated with atherosclerotic risk factors like hypertension, hyperlipidemia, and obesity that subsequently accelerate the development and progression of atherosclerosis[13]. Whether IR is an independent risk factor in the development of atherosclerosis remains debatable. It was reported that there was peripheral IR in RA patients related to disease activity and that it improved after tumor necrosis factor (TNF)-blocking therapy[14].

We assessed subclinical atherosclerosis by determining main carotid artery IMT and measuring carotid plaques in patients with RA, and compared that data with a control group. In addition, we investigated risk factors implicated in the development of subclinical atherosclerosis among patients with RA. We were particularly interested in the role of IR in predisposing these patients to accelerated atherosclerosis.

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MATERIALS AND METHODS

We studied 63 patients with RA and 34 control subjects. All RA subjects fulfilled the 1987 American College of Rheumatology criteria[15]. The control group consisted of age and sex matched patients with osteoarthritis (OA) who attended our outpatient rheumatology clinic. The disease duration in RA patients was at least 1 year. RA and OA patients with known atherosclerotic complications such as stroke and MI; those undergoing hemodialysis; patients with peripheral vascular disease, malignancy, or infections; and diabetic patients were excluded. All patients gave verbal informed consent. The study design was in accord with guidelines of the ethics committee at our institution.

In all patients with RA, we recorded number of tender and swollen joints, the Disease Activity Score (DAS28) calculated for each patient using the erythrocyte sedimentation rate (ESR), tender joint count (TJC, 28 joints), swollen joint count (SJC, 28 joints), and the patient's assessment of global well-being (100 mm visual analog scale). The formula for DAS28 is as follows: $(0.56 \times [\text{vTJC}]) + (0.28 \times [\text{vSJC}]) + (0.70 \times \ln\text{-ESR}) + (0.014 \times \text{VAS})$. All patients completed the Health Assessment Questionnaire (HAQ).

From all patients and controls we collected demographic, clinical, and laboratory data and family history of cardiovascular diseases. Body mass index was calculated for all patients and controls, and blood pressure was determined in supine position. Blood was obtained from all subjects in the morning after an overnight fast for measurement of total cholesterol (normal 120–200 mg/dl), high density lipoprotein (HDL) cholesterol (normal 45–65 mg/dl), low density lipoprotein (LDL) cholesterol (normal 0–130 mg/dl), triglyceride (normal 35–135 mg/dl), glucose (normal 75–115 mg/dl), insulin (normal 6–26 μU/ml), C-reactive protein (CRP; normal 0–0.5 mg/dl), and ESR. Insulin was determined using the microparticle enzyme immunoassay method (Immulite 1000; Bio-DPC, Los Angeles, CA, USA). Hypertension was defined as systolic blood pressure > 140 mm Hg and/or diastolic blood pressure > 90 mm Hg and/or patient's intake of antihypertensive medications.

IR was calculated according to the HOMA homeostasis model as [serum insulin (μU/ml) × plasma glucose (mmol/l)/22.5]. Gokcel, *et al*[16] reported that the mean HOMA-IR value in a healthy Turkish control population was 2.24. Accordingly, we used a threshold HOMA-IR value of > 2.24 for identification of IR.

The main carotid arteries of RA patients and controls were examined by B-mode ultrasonography using a linear 7.5 MHz probe in the supine position (Esaote AU4 Idea, Esaote Biomedica, Genoa, Italy). In order to visualize the IMT complex of the arteries, both right and left main carotid arteries were examined longitudinally. The IMT was measured at multiple sites more than 1 cm proximal to the common carotid artery bifurcation. Multiple IMT measurements were made by computer analysis. IMT was calculated for both left and right common carotid arteries, and the common carotid artery IMT was defined as the mean of these. The presence of a plaque was determined when there was a localized irregular thickening at least 1.5 mm thick. All measurements were performed by the same radiologist (EU), who was blinded to clinical characteristics of the subjects. Reproducibility of IMT measurements was evaluated in 13 subjects within 2 weeks of the first examination. Intraobserver variability correlation coefficient for IMT was 0.908.

Statistical analyses were conducted using the SPSS program. Results were expressed as median (interquartile range). The number of RA patients and controls yielded a statistical power of 80%. Mann-Whitney U test, chi-square, or Fisher's exact tests were used for comparisons between RA patients and controls, and also between RA patients with and those without plaques. For correlation analysis, Spearman's correlation test was used. Logistic regression was used to determine factors that had an independent effect on the presence of plaques, and multiple linear regression analysis was used to determine factors affecting carotid IMT. Duration of RA, sex, and factors found to be associated with the presence of plaques in univariate analysis that were HOMA-IR > 2.24, age, and hypertension were included for multivariate analysis.

RESULTS

The general features of patients with RA are presented in Table 1. The median age of patients was 50 (range 43–63) years, the median disease duration 6 (2–10) years, and 46% were rheumatoid factor (RF) positive. Among RA patients, 66.7% were using disease modifying antirheumatic drugs and 63.5% were using steroids.

There were no differences in age, sex, traditional atherosclerotic risk factors, or HOMA-IR levels between RA patients and controls ($p > 0.05$; Figure 1). The median carotid IMT in the RA group, 0.61 mm (range 0.56–0.74), was significantly greater than that in controls (0.54 mm, range 0.50–0.64; $p = 0.01$). In addition, RA patients showed a trend to a higher frequency of carotid plaques than controls [12 RA patients (19%) vs 2 controls (5.9%); $p = 0.10$]. Clinical features and ultrasonography results of patients and controls are shown in Table 2.

Table 1. Demographic and clinical features of 63 RA pateints. Results are expressed as median (interquartile range), unless otherwise indicated.

n (Female/male)	63 (56/7)
Age, yrs	50 (43–63)
Disease duration, yrs	6 (2–10)
Rheumatoid factor-positive, n (%)	29 (46)
Extraarticular involvement, n (%)	17 (27)
Erosive disease, n (%)	34 (54)
Current DMARD usage, n (%)	42 (66.7)
Current sulfasalazine usage, n (%)	25 (39.7)
Current methotrexate usage, n (%)	30 (47.6)
Current steroid usage, n (%)	40 (63.5)
Cumulative steroid dosage, g	0.63 (0–2)
Number of tender joints (0–28)	6 (4–10)
Number of swollen joints (0-28)	2 (0–4)
DAS28	5.04 (3.87–5.56)
HAQ score	1 (0.5–1.5)

DMARD: disease-modifying antirheumatic drug, DAS28: Disease Activity Score, HAQ: Health Assessment Questionnaire.

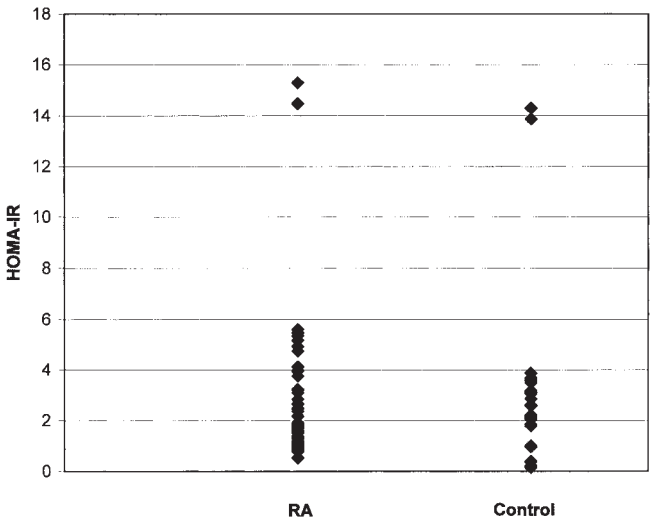

Figure 1. HOMA-IR values in RA patients and controls.

Table 2. Main clinical and ultrasonographic differences between RA pateints and controls. Results are expressed as median (interquartile range), unless otherwise indicated.

	RA	Controls	p
n (Female/male)	63 (56/7)	34 (30/4)	NS
Age, yrs	51 (43–63)	53 (50–58)	0.19
Smoking, n (%)	13 (20.6)	5 (14.7)	0.51
Hypertension, n (%)	19 (30.2)	11 (32.4)	0.82
Family history for CVD, n (%)	6 (9.5)	3 (8.8)	NS
Obesity (BMI > 30 kg/m^2), n (%)	26 (41.3)	14 (41.2)	0.99
Triglyceride, mg/dl	95 (68–120)	103 (86–159)	0.08
Total cholesterol, mg/dl	187 (163–219)	194 (176–236)	0.42
HDL cholesterol, mg/dl	52 (45–60)	49 (43–53)	0.14
LDL cholesterol, mg/dl	112 (92–138)	120 (93–143)	0.68
Insulin, μU/ml	8 (5.5–13.3)	10 (7–13.6)	0.63
HOMA-IR	1.77 (1.17–3.14)	2.4 (1.5–3.5)	0.49
IR (HOMA-IR > 2.24), n (%)	25 (39.7)	15 (44.1)	0.67
Mean carotid IMT, mm	0.61 (0.56–0.74)	0.54 (0.50–0.64)	0.01
Carotid plaque, n (%)	12 (19)	2 (5.9)	0.10

CVD: cardiovascular disease, BMI: body mass index, HDL: high density lipoprotein, LDL: low density lipoprotein, IR: insulin resistance, IMT: intima-media thickness.

It was observed that in the RA group carotid IMT had positive correlations with age (r = 0.62, p < 0.001), blood glucose concentration (r = 0.31, p = 0.016), HOMA-IR (r = 0.3, p = 0.02), and uric acid level (r = 0.45, p = 0.005). In addition, in the RA group, men had thicker carotid IMT (p = 0.023), and patients with IR had a tendency toward thicker carotid IMT (p = 0.09). In multivariate regression analysis, factors that independently affected carotid IMT were age (regression coefficient = 0.49, p < 0.001), male sex (regression coefficient = 0.28, p = 0.01), and total cholesterol level (regression coefficient = 0.26, p = 0.02). In the control group, carotid IMT had no correlation with any of the evaluated risk factors.

Compared to others, RA patients with carotid plaques were older [64.5 (range 51–69) vs 48 (42–59) yrs; p = 0.005], had thicker carotid IMT [0.75 (range 0.67–0.86) vs 0.60 (0.53–0.67) mm; p = 0.001], higher HOMA-IR level [3.6 (range 2.46–5.56) vs 1.6 (1.13–2.47); p = 0.01; Figure 2], and higher frequency of hypertension (58.3% vs 23.5%; p = 0.03) and IR (83.3% vs 29.4%; p = 0.005). The comparison of RA patients with and without plaques is shown in Table 3. Multivariate logistic regression analysis showed that factors independently associated with the presence of plaques were the presence of IR (OR 15.85, 95% CI 2.23–112.89, p = 0.006) and age (OR 1.11, 95% CI 1.02–1.21, p = 0.02). The results of multivariate analysis are shown in Table 4.

In RA patients, HOMA-IR correlated with age (r = 0.26, p = 0.04), HAQ score (r = 0.28, p = 0.04), and triglyceride (r = 0.39, p = 0.003) and cholesterol (r = 0.33, p = 0.02) levels. In the control group, HOMA-IR had a correlation with LDL level (r = 0.48, p = 0.03).

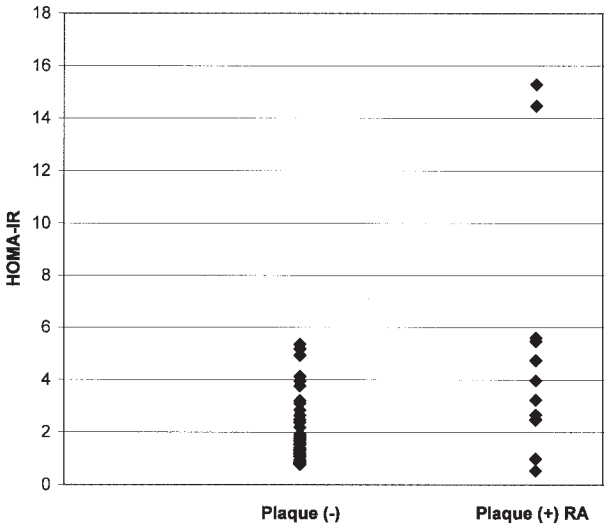

Figure 2. Individual HOMA-IR values in RA patients with and without plaque.

DISCUSSION

The frequencies of carotid IMT and carotid plaques, which are markers of subclinical atherosclerosis, were found to be increased in our patients with RA. Although contrary results have been described[17], other studies of carotid IMT and plaques reported results similar to ours[6-10]. Interestingly, in spite of increased subclinical atherosclerosis in our RA patients, the frequency of classical cardiovascular risk factors was not different from controls. Many studies have shown an increased incidence of atherosclerosis in RA[3]. Nevertheless, this cannot be explained by the presence of traditional risk factors in RA.

It is suggested that cytokines secreted into the circulation from the primary site of inflammation in RA, the synovium, accelerate atherogenesis by causing changes in the adipose tissue, skeletal muscle, liver, and vascular endothelium[2,18,19]. Synovial cytokines lead to proatherogenic changes such as IR, dyslipidemia, prooxidative effects, and endothelial dysfunction and injury[2,18]. As a result, inflammation and cytokines like TNF and interleukin 1 play major roles in the accelerated atherogenesis in RA.

In our study, multivariate analysis revealed that factors with independent effects on carotid IMT in patients with RA were age and IR. We found no association of male sex with carotid plaques in RA; however, we studied only a few male patients. Some studies have reported a significant association between inflammatory measures in RA and carotid IMT[8,20]. As our study was cross-sectional and no longitudinal data such as cumulative/mean CRP over the course of the disease were determined, we could not address this issue. Although Gonzalez-Juanatey, *et al*[10] found no correlation between current CRP level and carotid IMT in their cross-sectional study, they found that the magnitude and chronicity of the inflammatory response as measured by mean CRP correlated direct-

Table 3. Cardiovascular risk factors in RA patients with and without atherosclerotic plaque. Results are expressed as median (interquartile range), unless otherwise indicated.

	Plaque	No Plaque	p
n (female/male)	12 (11/1)	51 (45/6)	NS
Age, yrs	64.5 (51–69)	48 (42–59)	0.005
Disease duration, yrs	7 (2.5–11)	5 (2–9)	0.64
Extraarticular involvement, n (%)	5 (41.7)	12 (23.5)	0.28
Erosive disease, n (%)	7 (58.3)	27 (52.9)	0.73
Rheumatoid factor-positive, n (%)	5 (41.7)	24 (47.1)	0.74
DMARD usage, n (%)	7 (58.3)	35 (68.6)	0.51
Methotrexate usage, n (%)	5 (41.7)	25 (49)	0.65
Steroid usage, n (%)	7 (58.3)	33 (64.7)	0.75
Cumulative steroid dose, g	0.75 (0–1.9)	0.63 (0–2)	0.74
HAQ Score	1.0 (0.5–1.37)	0.5 (0.4–1.5)	0.70
DAS28	5.1 (4.7–5.6)	4.8 (3.7–5.6)	0.59
ESR, mm/h	41 (19–74)	36 (23–65)	0.72
CRP, mg/dl	2.4 (0.9–5.4)	1.3 (0.7–4)	0.55
Smoking, n (%)	1 (8.3)	12 (23.5)	0.43
Family history for CVD, n (%)	5 (9.8)	1 (8.3)	NS
Hypertension, n (%)	7 (58.3)	12 (23.5)	0.03
Obesity (BMI > 30 kg/m^2), n (%)	4 (33.3)	22 (43.1)	0.75
Triglyceride, mg/dl	75 (60–138)	98 (74–119)	0.37
Total cholesterol, mg/dl	188 (157–207)	186 (164–222)	0.90
HDL cholesterol, mg/dl	51 (41–61)	53 (45–59)	0.68
LDL cholesterol, mg/dl	118 (102–143)	112 (91–138)	0.47
Insulin, μU/ml	15 (8.5–21.8)	7.4 (5.1–11.2)	0.01
IR (HOMA-IR > 2.24), n (%)	10 (83.3)	15 (29.4)	0.001
HOMA-IR	3.6 (2.46–5.56)	1.6 (1.13–2.47)	0.005
Carotid IMT, mm	0.75 (0.67–0.86)	0.60 (0.53–0.67)	0.009

DMARD: disease-modifying antirheumatic drug, HAQ: Health Assessment Questionnaire, DAS28: Disease Activity Score, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, CVD: cardiovascular disease, BMI: body mass index, HDL: high density lipoprotein, LDL: low density lipoprotein, IR: insulin resistance, IMT: intima-media thickness.

Table 4. Results of multiple logistic regression to determine factors affecting plaque formation in pateints with RA.

	Exp (B)	95% CI	p
Sex (males vs females)	1.21	0.08–19.48	0.83
Age, yrs	1.11	1.02–1.21	0.02
RA duration, yrs	1.03	0.91–1.17	0.62
Hypertension, n (%)	3.42	0.61–19.4	0.17
HOMA-IR > 2.24	15.85	2.23–112.89	0.006

ly with the presence of subclinical atherosclerosis determined by carotid IMT in RA patients without traditional cardiovascular risk factors[20]. According to these results, longitudinal evaluation of CRP levels would be useful in predicting the development of atherosclerotic disease.

Detection of carotid artery plaques is a marker of advanced atherosclerosis. In our study, the frequency of carotid plaques in RA patients was increased. In multivariate analysis, age and IR were independent factors that significantly affected the presence of carotid plaques. The presence of plaques had no association with inflammatory measures and disease duration. The relatively short disease duration in our study may explain the negative association with carotid plaques. In contrast, one study with a longer followup yielded a strong correlation between disease duration and carotid plaques[10].

Until now, the influence of IR on subclinical atherosclerosis as measured by carotid IMT (plaque) in RA has been evaluated in only one study, in which no significant relationship was detected[21]. Increased IR is an important risk factor for cardiovascular disease. An association between IR and carotid and femoral IMT was found in patients with type 2 diabetes; and it was demonstrated that IR was an independent risk factor for atherosclerosis[13]. Basal hyperinsulinemia and increased IR have been reported in RA; and it was said that it

had an association with the degree of inflammation[22]. Nevertheless, the frequency of IR was not higher in our RA patients than in our OA group; and the frequencies of obesity in our RA and OA groups were similar. This was probably because obesity was more strongly associated with IR than inflammation. Another interesting result of our study was that in spite of similar frequencies of IR in RA patients and controls, IR was associated with carotid plaques only in the RA group. We suppose that, in contrast to the situation in OA, the interaction of chronic inflammation with IR in RA might result in a higher frequency of atherosclerosis.

In an animal model, it was shown that TNF-α played an important role in the pathogenesis of IR in RA[23]. TNF-α directly prevents insulin-related glucose uptake in skeletal muscle[24]. TNF-α blockers led to a significant decrease in HOMA-IR in RA patients with high IR[14]. Endothelial dysfunction, an early stage in the development of atherosclerosis, has also been observed in patients with RA[2]. Interestingly, IR is one of the mechanisms leading to endothelial dysfunction[2,18]. Evidence for improvement of endothelial function in RA has been demonstrated for TNF-α blockade[25,26]. However, such benefit is transient and in line with changes in systemic inflammatory levels observed in RA[26]. In addition, it was reported that methotrexate, sulfasalazine, and steroids led to an improvement in IR in RA[2,27]. Those data prove that IR in RA is associated with inflammation.

In our study of patients with RA, in addition to the correlation of HOMA-IR with variables like age and lipid levels, the correlation with the HAQ functional disability marker was also interesting. There is increasing evidence that IR is driven by inflammation. Nevertheless, there was no association between inflammatory indicators such as ESR and CRP and HOMA-IR. Our results might suggest that the IR in RA is more associated with the HAQ score, which represents the secondary disability caused by cumulative inflammation, rather than current inflammation. In addition, neither HOMA-IR nor HAQ score had any correlation with body mass index.

The first limitation of our study was that IR was not evaluated by the "gold standard" euglycemic clamp method, but by HOMA-IR. Nevertheless, the reliability of HOMA-IR in comparison with the euglycemic-hyperinsulinemic clamp has been reported[28]. Thus we used the HOMA-IR, which could be more easily used for every patient. Second, as we did not have our own control group, we used the HOMA-IR value of another Turkish group as our cutoff for the definition of IR. The third limitation was that as noted we included subjects with OA, who have inflammatory potential, as our control group. However, we believe this has no negative effect on the results because the OA patients were similar to RA patients in classical risk factors and the presence of IR. It was interesting that the frequency of RF positivity in our RA patients was low (46%); in a previous study conducted in the same region, we found a similar frequency[29]. In addition, it has been reported that RA in Turkey ran a milder course because of this reason[30].

We confirmed the presence of subclinical atherosclerosis in patients with RA with no previous history of cardiovascular disease. IR due to persistent chronic inflammation and chronically active disease may contribute to mechanisms associated with accelerated atherogenesis observed in these patients.

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