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ORIGINAL ARTICLE

Antibodies against oxidized low-density lipoprotein are associated with subclinical atherosclerosis in recent-onset rheumatoid arthritis

Hamada M. M. Sayed Ahmed · Mahmoud Youssef · Youssef M. Mosaad

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Abstract Rheumatoid arthritis (RA) patients have increased mortality largely as a result of cardiovascular diseases (CVD) that cannot be explained by traditional risk factors, suggesting that systemic inflammation may accelerate atherosclerosis. We investigated the presence of subclinical atherosclerosis in early RA (<12 months) and the possible association of RA-related risk factors. Forty patients with early RA and 40 controls matched for age, sex, and traditional risk factors for CVD were selected. Carotid US examination, assay of lipogram, C-reactive protein (CRP), and oxidized low-density lipoprotein antibodies (OxLDL-ab) were done. RA patients had significantly higher carotid intima-media thickness (cIMT) values and more plaque than the control ($P<0.001$ and $P=0.0122$, respectively). CRP and OxLDL-ab were significantly higher in RA patients than controls. Traditional risk factors and RA-related risk factors (disease duration, DAS-28, duration of treatment with steroids, erythrocyte sedimentation rate, and CRP) as well as OxLDL and cIMT were significantly higher in RA with plaques compared to those without plaques. Regression analysis identified the age of patients, CRP, and OxLDL-ab as an independent risk factor associated with the presence of atherosclerosis. Conclusion: there is increased prevalence of carotid plaques in patients with recent-onset RA compared to matched controls. The accelerated atherosclerosis is predicted by age, CRP, and oxLDL-ab. The association of plaques with elevated CRP and OxLDL-ab support the hypothesis that chronic systemic autoimmune inflammatory process is probably a driving force for premature atherosclerosis.

Keywords CRP · OxLDL-ab · Recent-onset RA · Subclinical atherosclerosis

H. M. M. S. Ahmed (✉)
Rheumatology and Rehabilitation Department,
Mansoura Faculty of Medicine, Mansoura University,
Mansoura, Egypt 35111
e-mail: dr_hamada1970@yahoo.com

M. Youssef
Internal Medicine Department, Mansoura Faculty of Medicine,
Mansoura University,
Mansoura, Egypt
e-mail: myousif200@yahoo.com

Y. M. Mosaad
Clinical Immunology Unit, Clinical Pathology Department,
Mansoura Faculty of Medicine, Mansoura University,
Mansoura, Egypt
e-mail: youssefmosaad@yahoo.com

Introduction

Rheumatoid arthritis (RA) patients have significantly increased mortality and morbidity as a result of cardiovascular disease (CVD) [1]. Increased cardiovascular morbidity and mortality in patients with RA and SLE cannot be entirely explained by traditional risk factors. However, there is increasing evidence that chronic inflammation contributes to accelerated atherogenesis [2, 3].

Chronic inflammation plays a major role in all stages of atherosclerosis, and inflammatory cells such as macrophages and lymphocytes are known to stimulate reactive oxygen species, leading to increased levels of oxidized low-density lipoproteins (OxLDL) [4]. OxLDL is antigenic in nature and autoantibodies are formed against it [5]. It would appear that measurement of oxidized low-density lipoproteins autoantibodies (OxLDL-ab) could serve as an early marker for atherosclerosis. Clinical, laboratory, and epidemiological studies suggest that immune dysregulation and systemic inflammation play important roles in the accelerated athero-

sclerosis [6]. In RA, there is a pro-inflammatory and pro-oxidative state that can accelerate atherosclerosis [7].

An approach to assessing the presence and extent of preclinical atherosclerosis is carotid ultrasonography. It is a feasible, reliable, valid, and cost-effective method detecting atherosclerosis progression [8]. Increased carotid artery intima-media thickness (cIMT) and carotid atherosclerotic plaques as measured by ultrasonography (US) have been proposed as an early manifestation of atherosclerosis [9]. Several studies have demonstrated subclinical atherosclerosis in established RA patients either by increased cIMT or the presence of carotid atherosclerotic plaque [10]. However, the study of these changes in recent-onset RA and early diagnosis of atherosclerosis in this population might trigger more aggressive prophylaxis.

Subjects and methods

RA patients

Forty patients with recent-onset RA (symptoms <12 months) were recruited from the Rheumatology and Rehabilitation Outpatient Clinics of Mansoura University Hospital. The patients were nine males and 31 females with their ages ranging from 25 to 62 years. All patients fulfilled American College of Rheumatology 1987 revised criteria for diagnosis of RA [11]. All patients have no previous history of overt atherosclerosis. Patients with angina, myocardial infarction, congestive heart failure, transient ischemic attacks, or stroke, also, patients with present or past smoking habits, patients using cholesterol-lowering drugs, and obese patients (body mass index $\geq$30 kg/m^2) were excluded before the start of the study.

Controls

Control subjects were healthy volunteers (n=40). They were nine males and 31 females, matched to RA patient's age, and CVD traditional risk factors participated in this study as controls. We also excluded subjects with present or past smoking habits.

Clinical assessment

All participants underwent a comprehensive clinical evaluation including complete history taking and full physical examination. Disease duration was determined by the length of RA symptoms. The patient evaluation included the Health Assessment Questionnaire [12] and calculation of the disease activity score using DAS-28, a validated composite score incorporating tender joint counts (out of 53) and swollen joint counts (out of 44), the erythrocyte sedimentation rate, and the patient global assessment of disease activity (100 mm visual analogue scale) [13].

Cardiovascular risk factor evaluation

Risk factors for CVD were assessed among RA patients and controls at presentation. Diabetes mellitus was classified as present if diagnosed by a physician or if patients were taking anti-diabetic medications. Family history of CVD attack or cerebrovascular attack before age 65 in first-degree relatives was determined by questionnaire. History of hypercholesterolemia and hypertension were determined by diagnosis and recording as such in medical records by a physician or use of lipid-lowering drugs or antihypertensive medication. Blood pressure was measured at first presentation.

Laboratory measurements

Blood samples were collected after an overnight fast for 12–14 h. Two milliliters of blood were delivered into citrated tube for erythrocyte sedimentation rate (ESR) determination. The separated serum was used for assay of:

1. Lipogram: Total serum cholesterol, triglycerides, and high density lipoprotein cholesterol (HDL) were measured by standard enzymatic methods. Low-density lipoprotein (LDL) was measured by Friedewald formula [14].
2. C-reactive protein assay (CRP): Quantitative assay of CRP was supplied by Turbox® CRP, Orion Diagnostica Turbox assay for CRP is a liquid phase immune-precipitation assay with nephelometric detection. Anti-serum to CRP is diluted and added to patient serum. The light scattering caused by antigen antibody complexes is measured after incubation. The resulting light scattering is directly proportional to the CRP concentration in the sample [15].
3. OxLDL-ab was done using ELISA kit. This assay is a sandwich enzyme immunoassay technique in which the plate is coated with cu++ OxLDL as an antigen. Autoantibodies in the sample and control bind specifically to the antigen. After washing, a specific peroxidase-conjugated antihuman IgG antibody detects the presence of bound antibodies. After washing, chromogen substrate is added for color development. The amount of color development is directly proportional to the concentration of oxLDL-ab [16].

Measurement of carotid intima-media thickness and plaque

Patients and healthy volunteers underwent B-mode carotid US examination using Alocka SSD 2000 machine and 7.5 MHz linear array transducer for measurement of cIMT

and detection of plaque. The subject lay in supine position, neck is extended, chin was turned contralateral to the side being examined, and scanning of carotid artery in transverse and longitudinal planes. Measurement of cIMT was made 1 cm distal to the carotid bifurcation in posterior wall, measured from end-diastolic, minimum dimension to minimize variability depending on changes of cIMT and lumen diameter during cardiac cycle [8]. Both right and left carotid arteries were examined and the mean cIMT [(right + left)/2] was taken as a measure of wall thickness of distal common carotid artery. Both extracranial carotid arterial systems were extensively scanned in multiple planes to identify plaques. cIMT values <0.9 mm indicates normal cIMT, values >0.9 mm indicates increased cIMT, while values >1.3 mm indicates atherosclerotic plaques [17].

Statistical analysis

Continuous data were expressed as mean ± standard deviation while categorical data were expressed in number and percentage. Comparison of categorical data was made by chi-square test. Comparison of continuous data between two groups was made by using Student's *t* test. Associations between clinical and laboratory variables and the plasma OxLDL-ab level were studied using multiple linear regression analysis. *K* statistics were used to determine the degree of intra-observer agreement for US diagnosis of IMT. Statistical significance was defined as a *P* value of <0.05. Analyses were performed using SPSS program, version 10 under Windows XP.

Results

Forty patients presenting with RA within 12 months of symptom onset were compared to 40-matched controls (Table 1). Patients and controls were similar regarding age, sex, and traditional risk factors for CVD. CRP and OxLDL-ab were significantly higher in RA patients than controls ($P<0.001$ and $P=0.0089$, respectively; Figs. 1 and 2). The US observer himself agreed in 76 out of 80 cases (95%, kappa value=0.881). Carotid plaques were 2.67-fold more prevalent in RA patients than controls (40% versus 15%, respectively, $P=0.0122$; Fig. 3). The cIMT was significantly thicker in RA patients than controls ($P<0.001$, Fig. 4).

RA patients with carotid plaques were significantly older in age, more hypertensive, and with higher cholesterol and HDL levels than RA patients without plaques. As regards RA characteristics, disease duration, DAS-28, ESR, CRP, and duration of treatment with steroids were significantly higher in RA patients with plaques compared to those without plaques ($P=0.0394$, $P=0.0175$, $P=0.3014$, $P<0.001$, and $P=0.0322$, respectively). Patients with plaques had significantly higher serum OxLDL-ab than those without plaques ($P=0.0256$) and thicker cIMT compared with patients who had RA without plaque ($P<0.001$, Table 2).

Multivariate analyses were carried out to determine CVD risk factors or inflammatory factors that might contribute to atherosclerosis in early RA. A positive association was shown between the plaque occurrence and age, CRP, and oxLDL (Table 3).

Table 1 Demographic, clinical, laboratory, and ultrasound data of patients with recent-onset RA and controls

	Patients with recent-onset RA ($n=40$)	Control ($n=40$)	*P*
Demographic, clinical data			
Age (years)	43.4±9.22	45.21±7.15	>0.05
Female/male ratio	9:31	9:31	NA
Hypertension (*n*, %)	8 (20%)	7 (17.5%)	>0.05
Diabetes mellitus (*n*, %)	5 (12.5%)	5 (12.5%)	NA
Family history (*n*, %)	9 (22.5%)	7 (17.5%)	>0.05
Laboratory data			
Cholesterol (mg/dl)	213.84±35.19	199.81±34.55	>0.05
Triglycerides (mg/dl)	133.11±17.8	127.21±15.81	>0.05
LDL cholesterol (mg/dl)	142.6±12.2	138.11±15.9	>0.05
HDL cholesterol (mg/dl)	58.11±8.56	61.03±10.83	>0.05
CRP (mg/dl)	7.2±2.3	5.44±1.9	**<0.001***
OxLDL-ab (U/ml)	0.19±0.05	0.16±0.05	**0.0089***
Ultrasound data			
cIMT (mm)	1.19±0.16	0.7±0.17	**<0.001***
Plaques (*n*, %)	16 (40%)	6 (15%)	**0.0122***

*P significant if <0.05

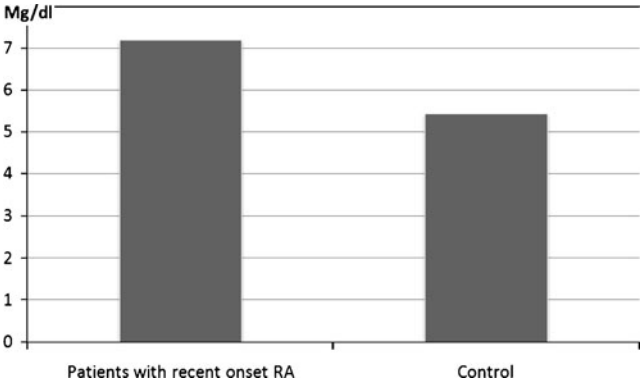

Fig. 1 The CRP in patients with recent-onset RA and in controls ($P<0.001$)

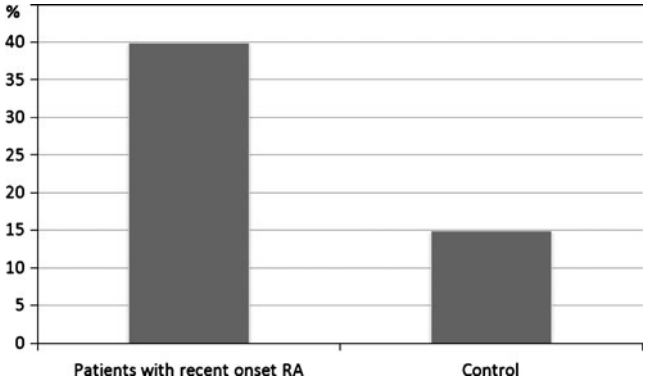

Fig. 3 Plaque occurrence in patients with recent-onset RA and control ($P=0.0122$)

Discussion

Early detection of asymptomatic atherosclerotic disease allows early intervention and possibly retards the development of symptomatic CVD. Plaque is an unequivocal manifestation of subclinical atherosclerosis and is a more potent predictor of adverse cardiovascular outcome than the increase in cIMT [18, 19].

In the present study, subclinical atherosclerosis is evidenced by occurrence of plaques in carotid ultrasound examination in patients presenting with recent-onset RA. Carotid plaques were 2.67-fold more prevalent in RA patients than controls (40% versus 15%, respectively). The current study also found that cIMT is significantly thicker in the patients than controls. The increased risk occurred independently of traditional risk factors. However, RA-related risk factors (disease duration, DAS-28, ESR, CRP, and duration of treatment with steroids) were significantly higher in RA patients with plaques compared to those without plaques. Thus, our study identified the presence of RA as a risk factor for the development of atherosclerosis as previously reported by Roman et al. [20].

However, in the study of Abu-Shakra et al. [21], the cIMT of RA patients and controls were not significantly different and thus they suggested that RA is not an independent risk factor of atherosclerosis among patients with RA. This discrepancy may be related to methodological difference and low number of RA patients which may be not enough to confirm whether or not RA is an independent risk factor for accelerated atherosclerosis.

Our data showed that patients with plaques are significantly older and with significantly longer disease duration than those without plaques. Previously, cIMT in RA patients has been shown to be related to the disease duration so that patients with prolonged RA had more atherosclerosis than patients with more recent disease onset [22]. Also, RA patients with plaques used corticosteroids for significantly longer duration than RA patients without plaques. This may be due to the atherogenic properties of steroids that are known to enhance the development of atherosclerosis, such as hypertension, dyslipidemia, and diabetes and they induce vascular injury.

Moreover, we found that serum cholestrol, LDL-cholestrol levels are significantly higher in recent-onset

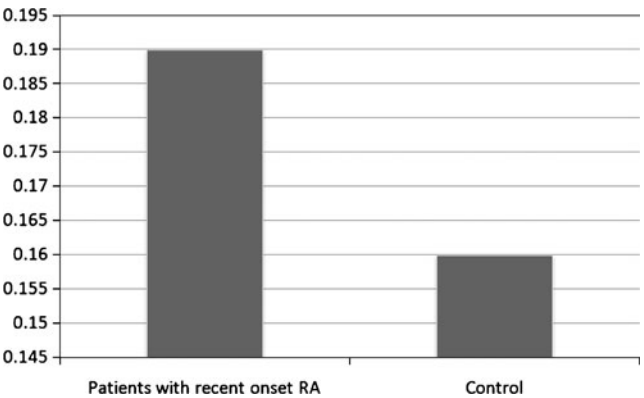

Fig. 2 The oxLDL-ab in patients with recent-onset RA and controls ($P=0.0089$)

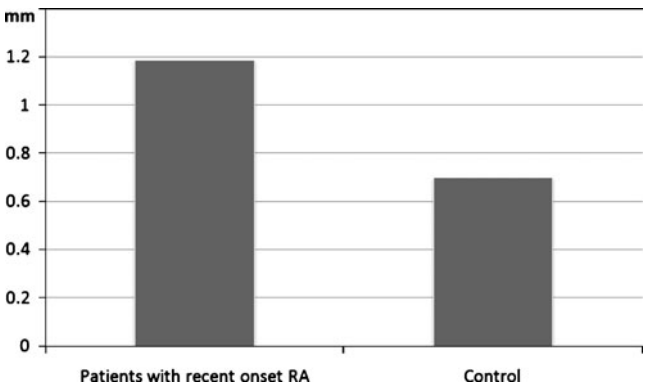

Fig. 4 cIMT in patients with recent-onset RA and control ($P<0.001$)

Table 2 CVD traditional and RA-related risk factors in early-onset RA patients with plaques and without plaques

	Recent-onset RA with plaques (n=16)	Recent-onset RA without plaques (n=24)	P
Traditional CVD risk factors			
Age (years)	41.11±7.35	46.28±6.27	**0.0071***
Female/male ratio	11:5	20:4	>0.05
Hypertension (n, %)	6 (37.5%)	2 (8.3%)	**0.0238***
Diabetes mellitus (n, %)	3 (18.8%)	2 (8.3%)	>0.05
Smoking (n, %)	2 (12.5%)	2 (8.3%)	>0.05
Family history (n, %)	4 (25%)	5 (20.8%)	>0.05
Cholesterol (mg/dl)	252.6±42.44	191.61±37.81	**<0.001***
Triglycerides (mg/dl)	138.22±21.65	131.24±18.14	>0.05
LDL cholesterol (mg/dl)	150.1±13.61	138.54±10.01	**0.0037***
HDL cholesterol (mg/dl)	60.33±8.77	56.12±8.12	>0.05
RA characteristics			
RA duration (months)	8.07±1.25	7.18±1.32	**0.0394***
Joint count	13.41±2.42	12.87±3.35	>0.05
Disease activity score (DAS-28)	5.47±1.21	4.44±1.33	**0.0175***
HAQ	0.53±0.13	0.46±0.15	>0.05
CRP (mg/dl)	9.22±2.31	5.64±1.81	**<0.001***
ESR in first hour (mm)	48.4±9.87	54.9±8.41	**0.0314***
Duration of steroid use (months)	6.88±2.12	5.17±2.54	**0.0322***
Others			
OxLDL-ab (U/ml)	0.2±0.04	0.17±0.04	**0.0256***
cIMT (mm)	1.35±0.02	0.97±0.13	**<0.001***

*P significant if <0.05, ±SD (standard deviation)

RA patients with atherosclerotic plaques than without plaques. These are similar to results of Jonsson et al. [23]. Moreover Steiner and Urowitz [24] found that RA is associated with an abnormal lipoprotein pattern and it should be managed in patients with RA to minimize the long-term risk of CVD.

DAS-28, ESR, and CRP which reflect disease activity are significantly higher in RA patients with plaques than without plaques. In support, previous studies have shown that excess CVD mortality in RA is associated with high levels of inflammatory markers as elevated CRP and elevated ESR [25, 26]. Del Rincon et al. [27] found that increased cIMT and plaques are associated with markers of systemic inflammation in patients with RA. These data indicate that chronic inflammation may have a direct role in atherosclerosis in general as well as in patients with RA [28, 29].

Chronic inflammatory disorders, such as SLE and RA, are found to be associated with an increased incidence of CVD [30, 31]. Among the inflammation markers, CRP is recently found to be a reliable predictor of CVD events [32]. The greater prevalence of atherosclerosis in RA strongly suggests the involvement of autoimmunity in the atherosclerotic process [4]. Since inflammation has been shown to predate the onset of clinical RA, the accelerated atherogenic process related to inflammation may precede RA symptom onset [33]. Thus, it is not surprising to find

Table 3 Multivariate regression analysis to identify risk factors for atherosclerotic plaques in patients with recent-onset RA

	Standardized coefficients	T	P
Age	0.432	2.961	**0.005***
Disease duration	0.227	1.968	0.057
Hypertension	0.264	01.721	0.094
DAS-28	0.085	0.746	0.461
Duration of steroid use	0.031	0.294	0.771
Serum LDL	0.08	0.688	0.496
C-reactive protein	0.3	2.622	**0.013***
OxLDL-ab (U/ml)	0.364	02.721	**0.010***

*P significant if <0.05

higher prevalence of atherosclerosis in RA patients than in controls within the first year of their disease.

Our findings indicate that OxLDL-ab is significantly higher in RA patients than in healthy subjects. OxLDL-ab is also significantly higher in RA patients with plaques than without plaques. A recent study found that among RA patients, CRP was positively correlated with OxLDL-ab. This indicates that OxLDL-ab is strongly related to the degree of inflammation and may predispose to a higher risk for CVD. It is concluded that OxLDL-ab is associated with subclinical atherosclerosis [4]. It is suggested that OxLDL-ab is predictive for the presence of atherosclerosis and that its increased serum level may function as a marker for atherosclerosis [34].

In the regression analysis, age, CRP, and oxLDL-ab emerged as the key determinants of plaque occurrence in the patients with recent-onset RA. These results are in concordance with several studies that demonstrate the association of older age in RA patients on CV mortality [26, 35]. Also, a previous study found that age and baseline CRP are the key determinants of atherosclerosis in early RA [33].

In conclusion, there is increased prevalence of carotid plaques in patients with recent-onset RA compared to matched controls. The accelerated atherosclerosis is predicted by age, CRP, and oxLDL-ab. The association of plaques with elevated CRP and OxLDL-ab support the hypothesis that chronic systemic autoimmune inflammatory process is probably a driving force for premature atherosclerosis. The presence of oxLDL-ab in early RA does not implicitly mean that RA has to be treated aggressively, but means that a potential pathway is shown which may be of importance in reducing cardiovascular risks in early RA already. Whether this means aggressive treatment or just prednisone or possibly just anti-TNF in early RA remains to be elucidated.

Submission declaration The manuscript has not been published elsewhere and has not been submitted simultaneously for publication elsewhere.

Disclosures None

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