Subclinical Atherosclerosis and Endothelial Dysfunction in Patients with Early Rheumatoid Arthritis as Evidenced by Measurement of Carotid Intima-Media Thickness and Flow-Mediated Vasodilatation: An Observational Study

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Objective: In this study, we aimed to investigate the frequency of endothelial dysfunction and subclinical atherosclerosis in early rheumatoid arthritis (RA) patients by carotid intima-media thickness (cIMT) and endothelial-dependent flow mediated vasodilatation (ED-FMD) as compared with healthy controls.

Methods: The study included 35 early RA patients (disease duration <12 months) and 35 healthy controls. Intima-media thickness of common carotid artery and ED-FMD of brachial artery were measured by high-resolution ultrasonography. Disease activity of RA was assessed by Disease Activity Score and activities of daily living were determined by Health Assessment Questionnaire–Disability Index Score.

Results: RA patients (age 38.3 ± 10.6 years) had average disease duration of 0.46 ± 0.28 years and 22 patients (62.9%) were rheumatoid factor (RF) positive (RF titer >9.56 IU/mL). There were no significant differences between age, sex, and lipid profiles of patient and control group. cIMT was significantly higher in RA patients (0.50 ± 0.16 mm) than in controls (0.44 ± 0.09 mm) ($P = 0.007$). Similarly, FMD% was significantly lower in RA patients [5.26 (2.9-10.6)] as compared with controls [10.34 (7.4-14.3)] ($P = 0.004$). Age, systolic blood pressure, tender joint count, and swollen joint count had significant correlations with patient cIMT. RF titer came out to be the major risk factor for increased cIMT of the patients.

Conclusions: Compared with controls, early RA patients have higher cIMT and lower FMD%, denoting premature atherosclerosis. Our data suggest that early determination of FMD% and cIMT may be useful tools to assess cardiovascular risk even in early RA patients.

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Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that causes significant morbidities due to synovial inflammation, joint destruction, and associated disabilities (1). Patients with RA have an increased morbidity and mortality due to cardiovascular diseases (CVD) as well (2-6). Atherosclerotic process in RA is thought to be accelerated by systemic chronic inflammation in addition to traditional CV risk factors (7-20).

Increased carotid intima-media thickness (cIMT), measured by ultrasound, is regarded as an early indicator of overall atherosclerosis and several studies on cIMT in the general population have shown a relation between increased cIMT and future cardiovascular (CV) event (21,22). Increased cIMT of established RA (disease duration >12 months) patients when compared with controls indicates premature atherosclerosis (8-11,13,14,19,23-25). Increased cIMT of patients with RA has been associated with traditional CV risk factors, including age and sex, markers of inflammation, and disease duration (7-20,23-27). However, most of the previous reports are cross-sectional studies with patients having established RA.

Endothelial dysfunction (ED), another very relevant and important sign of early atherosclerosis, can be assessed noninvasively by impairment of endothelial-dependent flow-mediated vasodilatation (ED-FMD) of peripheral arteries, measured by ultrasonography (28). Even in the general population, ED-FMD is a predictor of future CV event, it being associated with risk factors of CVD and also being reversible by cardioprotective drugs (29). Earlier studies with RA patients have been small and most of them were patient cohorts at an established stage of the disease (30-32). Several studies on ED-FMD analyzing treatment outcomes in RA could be found (33-35) but only a few studies that evaluated patients with early RA (disease duration <12 months) are so far available in the literature (32,36).

There have been several reports on the increased prevalence of subclinical atherosclerosis assessed by both cIMT and FMD methods from other countries (12, 24,30,32,36). However, there are only 2 studies on carotid IMT measurement in late RA patients from India (19,23).

We, therefore, took up the objective to assess the prevalence of subclinical atherosclerosis and endothelial dysfunction in early RA patients by measuring both cIMT and FMD% in the Indian population.

MATERIALS AND METHODS

Patients and Controls

The subjects in the present study were 35 early rheumatoid arthritis (RA) patients (29 women and 6 men) and 35 healthy controls (28 women and 7 men). The 35 consecutive patients with RA, who fulfilled the inclusion criteria, were selected from among the patients attending the "early arthritis clinic" of the Rheumatology Department at the Institute of Postgraduate Medical Education and Research, SSKM Hospital, between December 2009 and May 2010. All patients fulfilled the following inclusion criteria:

(1) Diagnosis of RA as per American College of Rheumatology (formerly, The American Rheumatism Association) 1987 criteria for RA (37),
(2) Disease duration less than 1 year, and
(3) No prior use of disease-modifying antirheumatic drugs or systemic corticosteroids.

Thirty-five healthy volunteers willing to participate in the study were recruited as controls from among the hospital staff. Written informed consent was taken from all study participants and the study protocol was approved by the institutional ethics committee.

To avoid confounding by other known risk factors for atherosclerosis, we used the following exclusion criteria for both patients and controls:

(1) Age more than 60 or less than 18 years at entry.
(2) Current or recent (within the past 3 months) pregnancy.
(3) Comorbid diseases/conditions: diabetes, obesity (body mass index ≥30), familial dyslipidemia, hypertension, coronary artery disease, cerebrovascular accident, peripheral vascular disease, hypothyroidism, renal disease (serum creatinine ≥3.0 mg/dL or creatinine clearance ≤30 mL/min), liver disease, Cushing's syndrome.
(4) Concurrent treatment with lipid-lowering drugs, beta-blockers, oral contraceptives, estrogens, progestin, thyroxin, vitamin E, steroids.
(5) Smoking.

Baseline Evaluation

Patients' assessment included duration of disease, tender joint count (TJC), swollen joint count (SJC), Health Assessment Questionnaire–Disability Index (HAQ-DI) score (38), and visual analog scale (0-100 scale). A composite Disease Activity Score (DAS28) was calculated using 4 variables: SJC (28), TJC (28), VAS (0-100 scale), and Westergren erythrocyte sedimentation rate (ESR). The low disease activity is defined by DAS28 ≤3.2, moderate disease activity as DAS28 ≈ 3.3 to 5.3, and severe disease activity as DAS28 ≥5.4 (39).

Blood Sampling and Laboratory Analysis

Overnight fasting (12 hour) blood samples were obtained at baseline from both patients and the control group. The blood samples were immediately centrifuged and the sera were collected and stored at −30°C until analyzed. All sera analysis was performed within 1 month of blood collection and storage. Serum levels of cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, and other lipid variables were determined using a semi-