Early Treatment Reduces the Cardiovascular Risk Factors in Newly Diagnosed Rheumatoid Arthritis Patients

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Objective: To investigate subclinical atherosclerosis and the effect of treatment in patients with early rheumatoid arthritis (RA).

Patients and methods: Forty patients with early RA who met the revised American College of Rheumatology (ACR) criteria and disease duration of <1 year were included in the study. Smokers and patients with classical risk factors for atherosclerosis were excluded. The serum levels of total cholesterol (TC), triglycerides, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol were determined in all patients before and after 1 year of therapy. Carotid artery intima-media thickness (IMT) and carotid plaque were measured before and after treatment. RA disease activity was measured using the 28 joint indices score (DAS-28) and clinical improvement was determined by the ACR response criteria. Forty-five age- and sex-matched nonsmoking volunteers were used as controls. All patients were treated with methotrexate and prednisone.

Results: RA patients had a baseline mild dyslipidemia characterized by a decrease in serum HDL-C levels and a high TC/HDL-C atherogenic ratio compared with controls. Both lipid parameters were significantly improved after treatment ($P < 0.01$). Common carotid artery IMTs at baseline were higher in RA patients compared with controls ($P < 0.05$). After 1 year of therapy there was a significant decrease in the IMTs ($P < 0.001$). Thirty-five patients (88%) achieved the ACR 20%, while 30 (75%) reached the ACR 50% response criteria. A significant decrease of DAS-28 was observed after treatment ($P < 0.03$).

Conclusions: The atherogenic lipid profile and subclinical atherosclerosis are features of early RA, which improved after therapy. Early intervention and control of the disease activity may reduce the risk of atherosclerosis and cardiovascular events in patients with RA.

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In the last 2 decades, premature coronary heart disease and cardiovascular (CV) disease have been recognized as major determinants of morbidity and mortality in patients with rheumatoid arthritis (RA) (1-3). The immune dysfunction of the Th1 phenotype, seen in RA, results in a chronic inflammatory state which may have implications for early atherosclerosis in these patients (4). Classical risk factors for CV disease in the general population also appear to be important in RA (5). Other risk factors implicated in CV disease manifestations in RA include the long-term use of corticosteroids, older age at RA diagnosis, long disease duration, extra-articular manifestations, persistent disease activity (6-8), and the use of all classes of nonsteroid anti-inflammatory drugs (NSAIDs) (9).

The lipid profile of patients with active and untreated RA is primarily characterized by a decrease in serum levels

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of high-density lipoprotein cholesterol (HDL-C), whereas contrasting results have been published on the serum levels of total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) (10). Importantly, the reduced HDL-C consequentially increases the TC/HDL-C ratio, which represents an atherogenic index important for CV disease development (11,12). On the other hand, case-control studies have shown that an increased intima-media thickness (IMT) of the common carotid artery is a good indicator of generalized atherosclerosis in RA patients (13,14). The increased carotid IMT may precede the development of CV events by many years. The determination of carotid IMT using ultrasound techniques provides useful and early information about atherosclerosis in subclinical stages of the disease in individuals at risk (15).

Recently, we reported that early RA patients are characterized by an atherogenic lipid profile, which improves after therapy (16). To our knowledge, no studies have been reported regarding the presence of atherosclerosis in early RA patients. Thus, in the present study we investigated the presence of subclinical atherosclerosis and the effect of treatment in patients with early RA using ultrasound techniques.

PATIENTS AND METHODS

Patients

Inclusion criteria. Forty-nine consecutive, unselected patients who were referred to the outpatient rheumatology clinic between January 2004 and September 2005 were included in the study. All patients fulfilled the American College of Rheumatology (ACR) 1987 criteria for RA (17), had early disease with a disease duration of less than 1 year, and had no prior use of disease-modifying antirheumatic drugs (DMARDs) or systemic steroids.

Exclusion criteria. Patients with a history of atherosclerosis, of prior CV events, 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 also excluded from the study. Finally, the use of NSAIDs was prohibited because of sodium retention, edema, hypertension, etc, which may alter the body mass index and other laboratory parameters.

Controls

Forty-five apparently healthy, nonsmoking volunteers also participated in the study and were used as controls. These individuals were selected from blood donors during the last 2 months of the patients' selection period and fulfilled the same exclusion criteria reported for the patient group. None of the individuals participating in the control group had a history of CV manifestations. The control group was proportionally matched for age and sex to the patient group. All controls reported no significant changes in their body weight for at least 3 months before entry to the study. Informed consent was obtained from both patients and controls and the study protocol was approved by the Institutional Ethics Committee.

Study Design

Patients were treated with methotrexate (MTX; 0.2 mg/kg/wk) and prednisone (7.5 mg/d). The dose of MTX remained stable during the study, while the dose of prednisone was tapered according to the patient's clinical response. Disease activity was determined by measuring the disease activity for 28 joint indices score (DAS-28) (18), while the clinical response was evaluated according to the ACR 20% and 50% response criteria (19). All patients were followed up every month for the first 3 months, and every 3 months thereafter for a total period of 12 months. During the follow-up period, a questionnaire concerning changes in dietary habits was carefully answered by all patients. The body weight was also measured at each visit.

Blood Sampling and Laboratory Monitoring

Overnight fasting blood samples were obtained at baseline and after 12 months of follow-up from both RA patients and controls. Serum lipids were determined within 6 hours of blood sampling. TC, triglycerides (TG), and HDL-C were determined on an Olympus AU560 Clinical Chemistry analyzer (Hamburg, Germany) as previously described (20). LDL-C was estimated using the Friedewald formula (21). Non-HDL-C levels were estimated by subtracting HDL-C from TC. Serum apolipoproteins B and A-I (apoB and apoA-I, respectively) were measured by immunonephelometry with the aid of a Behring Nephelometer BN100 and reagents (antibodies and calibrators) from Behring Diagnostics GmbH (Liederbach, Germany). C-reactive protein (CRP) and IgM rheumatoid factor were measured by nephelometry. Erythrocyte sedimentation rate (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, and urinalysis, were performed at each patient visit until the end of the study.

Common Carotid Artery Evaluation

Common carotid arteries were assessed using a B-mode ultrasound (Acuzon Phillips, Germany) with an electrical linear transducer (midfrequency, 7.5 MHz). The radiologist of the current study was blinded to RA patients and to the control group. Patients and healthy individuals were examined in a supine position with the neck extended and the chin turned away from the side being