Effect of Atorvastatin on Inflammation and Modification of Vascular Risk Factors in Rheumatoid Arthritis

AMAL M. EL-BARBARY, MANAL S. HUSSEIN, ELSAYED M. RAGEH, HALA E. HAMOUDA, AYMAN A. WAGIH, and RAGHDA G. ISMAIL

ABSTRACT. ***Objective.*** To investigate the effect of atorvastatin therapy on inflammation, disease activity, endothelial dysfunction, and arterial stiffness in patients with rheumatoid arthritis (RA).

Methods. This study included 30 patients with early RA, randomly divided into 2 groups. Group 1 (n = 15) received methotrexate (MTX; 0.2 mg/kg/week; mean (15.5 ± SD 1.3) plus prednisone (10 mg/day). Group 2 (n = 15) received MTX and prednisone with the same previous doses plus atorvastatin therapy (40 mg/day). Ten healthy individuals of similar age and sex served as controls. Disease activity, lipid profile, serum malondialdehyde (MDA), tumor necrosis factor-α (TNF-α), resistin, adiponectin, and brachial artery flow-mediated dilation (FMD) were measured before and after 6 months of treatment.

Results. Atorvastatin combined with MTX therapy significantly reduced serum total cholesterol, low-density lipoprotein cholesterol, and triglycerides, and increased high-density lipoprotein cholesterol ($p < 0.001$). Disease activity variables, serum MDA, TNF-α, resistin, adiponectin, and FMD were significantly improved by the drug combinations ($p < 0.001$).

Conclusion. Atorvastatin therapy in patients with RA reduced disease activity and conventional and novel vascular risk factors that promote the atheromatous lesion. Therapy was also associated with concomitant improvement in endothelial function. (J Rheumatol First Release Nov 1 2010; doi:10.3899/jrheum.100582)

Key Indexing Terms:
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Rheumatoid arthritis (RA) is a chronic progressive autoimmune disorder characterized by symmetric erosive synovitis and sometimes showing multisystem involvement. The longterm outcome is characterized by significant morbidity, loss of functional capacity, and increased mortality. This disease affects about 1% of the general population worldwide[1].

There is intense interest in mechanisms whereby low-grade inflammation could interact with conventional and novel vascular risk factors to promote the atheromatous lesion. Patients with RA manifested by persistent high levels of inflammation are at greater risk of developing cardiovascular disease[2].

White adipose tissue is now considered to be a dynamic endocrine organ that secretes a number of factors that are increasingly recognized to contribute to systemic and vascular inflammation[3]. Tumor necrosis factor-α (TNF-α) is one adipokine involved in systemic inflammation and is a member of a group of cytokines that stimulate the acute-phase reaction. The primary role of TNF-α is in regulation of immune cells. TNF is also able to induce apoptotic cell death, to induce inflammation, and to inhibit tumorigenesis[4].

Resistin is a recently discovered cysteine-rich adipokine of 108 amino acid and 12.5 kDa that has emerged during this decade as a promising inflammatory marker in various diseases in humans by means of its secretion in substantial quantities by mononuclear cells[5]. It is synthesized either from adipocytes or from immune cells, and exerts a proinflammatory profile in a variety of different experimental settings. Resistin has been shown to increase transcriptional events, leading to increased expression of several proinflammatory cytokines including (but not limited to) interleukin 1 (IL-1), IL-6, IL-12, and TNF-α[6].

Adiponectin has been identified as one of the "adipocytokines" that are derived only from adipose tissue, and that are abundantly present in circulating blood. Adiponectin has protective actions in the initiation and progression of atherosclerosis through its antiinflammatory and antiatherogenic effects[7].

From the Department of Rheumatology, Department of Medical Biochemistry, and Department of Cardiology, Faculty of Medicine, Tanta University, Tanta, Egypt.

A.M. El-Barbary, MD, Lecturer; M.S. Hussein, MD, Lecturer; E.M. Rageh, MD, Lecturer, Department of Rheumatology; H.E. Hamouda, Assistant Professor; A.A. Wagih, MD, Assistant Professor, Department of Medical Biochemistry; R.G. Ismail, MD, Assistant Professor, Department of Cardiology, Faculty of Medicine, Tanta University.

Address correspondence to Dr. A. El-Barbary, Department of Rheumatology and Rehabilitation, Tanta Faculty of Medicine, Elgesh Street, Egyt Tanta, 002 Egypt. E-mail: ml_barbary@yahoo.com

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It is well established that the antioxidant system is impaired in RA and reactive oxygen species (ROS) cannot be removed effectively. Because of impairment, it seems that patients with RA are exposed to lipid peroxidation, which is one of the indicators of oxidative stress[8]. Investigations also support the oxidative-stress hypothesis of atherosclerosis. Oxidative stress is the unifying mechanism for many cardiovascular disease (CVD) risk factors, which additionally supports its central role in CVD[9].

Vascular endothelial injury is the primary event in atherosclerosis, and has been associated with endothelial dysfunction[10]. This may be determined as an impaired ability of the artery to dilate in response to physical and chemical stimuli due to reduced bioavailability of nitric oxide (NO)[11]. Endothelial function can be noninvasively determined by postocclusion flow-mediated vasodilatation (FMD) of the brachial artery using high-sensitivity brachial ultrasonography[12].

Atorvastatin (ATV) is a member of the drug class known as statins, which are 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, which have demonstrated benefit in the primary and secondary prevention of cardiovascular disease by promoting reduction in plasma concentrations of low-density lipoprotein (LDL) cholesterol[13]. Some of the clinical benefits of statin therapy are the pleiotropic effects that are believed to include antiinflammatory actions, the reversal of endothelial dysfunction by prevention of LDL oxidation, and the increase of NO bioavailability[14].

We investigated the effect of atorvastatin therapy on disease activity, endothelial dysfunction, and arterial stiffness in patients with RA.

MATERIALS AND METHODS

Thirty patients with RA were selected from the Outpatient Clinic of the Physical Medicine and Rheumatology Department, Tanta University Hospitals; all fulfilled the 1987 American College of Rheumatology revised criteria for diagnosis of RA[15]. All patients had disease duration of less than 1 year with no prior use of disease-modifying antirheumatic drugs (DMARD) and/or systemic steroids. In addition, 10 healthy volunteers matched for age and sex were recruited as controls.

Exclusion criteria. Subjects excluded from the study were those with conditions that affect the lipid profile, endothelial dysfunction, and arterial stiffness, such as diabetes mellitus, hypothyroidism, liver or kidney disease, Cushing's syndrome, obesity (body mass index > 30), current smokers, history of familial dyslipidemia, myocardial infarction during the last 6 months, and any malignancy or seizure. In addition, patients receiving medications affecting lipid metabolism such as lipid-lowering drugs, oral prednisolone > 10 mg/day, beta blockers, oral contraceptives, estrogen, progestin, thyroxin, and vitamin E were excluded.

Study design. Patients with RA were randomly divided into 2 groups and the treatment was given in unblinded fashion. Group 1 (n = 15) received methotrexate (MTX; 0.2 mg/kg/week; mean total dose/wk 15.5 ± SD 1.3) plus prednisone (10 mg/day); Group 2 (n = 15) received MTX and prednisone with the same dose as Group 1 plus atorvastatin therapy (40 mg/day). The dose of MTX remained stable during the study whereas the dose of prednisone was tapered according to the patient's clinical response. But this procedure was forbidden within 4 weeks of clinical and laboratory assessment.

Approval was obtained from the Local Research Ethics Committee, and written informed consent was obtained from each participant.

Disease activity was assessed by the Disease Activity Score for 28 joints (DAS28)[16]. Components of DAS28 are erythrocyte sedimentation rate (ESR), patient-assessed global score (0–100), swollen and tender joint counts (0–28); whereas the clinical response was evaluated according to European League Against Rheumatism (EULAR) criteria to calculate the response in DAS28, that is, comparing the DAS28 from one patient at 2 different timepoints[17].

Laboratory investigations. Overnight fasting venous blood samples were taken from controls and patients before and after the recommended lines of treatment, transferred slowly into a dry sterile centrifuge tube, then centrifuged as soon as possible at 2000 g for 10 min at 4°C, and aliquots of serum were immediately stored at –70°C until the analysis.

Routine laboratory investigations included complete blood count, ESR, serum C-reactive protein (CRP), and lipid profile. Specific investigations included (1) serum TNF-α level, determined using Quantikine Human TNF-α ELISA kits (Roche Diagnostics GmbH, Mannheim, Germany)[18]; (2) serum resistin concentration, by a sandwich ELISA using the Max Human resistin ELISA kit[19]; (3) serum adiponectin concentration, using the Quantikine Human Adiponectin ELISA kit (R&D Systems, Bad Nauheim, Germany)[20]; and (4) spectrophotometric determination of serum malondialdehyde (MDA) as a marker for oxidative stress[21].

We recorded adverse events throughout the study. We performed hematology and biochemical screening for liver function, creatine kinase, and renal function at baseline and at 6 months.

Ultrasound examination of brachial artery FMD. Subjects underwent noninvasive examination of endothelium-dependent vasodilation (FMD) and endothelium-independent vasodilation (nitroglycerine-mediated dilation; NMD) of the brachial artery on the nondominant arm, according to the International Brachial Artery Reactivity Task Force guidelines[12]. FMD was expressed as the relative increase in brachial artery diameter using hyperemia, and defined as (posthyperemic diameter – basal diameter)/basal diameter × 100. The maximum FMD and NMD diameters were calculated as the average of the 3 consecutive measurements and the percentage changes in the diameters compared with baseline resting diameter, and expressed as percentage diameter variation. FMD was carried out blinded to the treatment given.

After screening, study visits were scheduled for 0 and 6 months.

Statistical analysis. Data were analyzed using SPSS software (version 11, SPSS Inc., Chicago, IL, USA). Baseline characteristics are presented as mean ± standard deviation for the continuous variables, and as frequency and percentage for discrete variables. Baseline comparisons between groups were conducted using ANOVA. Student's t test was used for paired data to examine within-group differences. ANCOVA was used for comparisons of the effect of drugs between groups. Correlation between variables was examined using Pearson's correlation coefficient. Multiple linear regression analysis was performed to investigate independent associations of several biochemical and inflammatory variables with changes in FMD. FMD changes between the end of the study and baseline were used as a dependent variable. The changes in serum lipids and biochemical variables that could affect the FMD were included as independent variables.

RESULTS

A total of 30 patients with active RA completed the study. The demographic variables and biochemical and hemodynamic characteristics of patients and controls at entry are shown in Table 1. They were 25 women and 5 men with a mean age of 53.7 ± 15.4 years in Group 1 and 54.8 ± 14.7 years in Group 2. There were no significant differences in age, sex, and mean body mass index values between patients and controls. Patients with early RA exhibited mild dyslipi-

Table 1. Baseline demographic, biochemical, and hemodynamic characteristics of subjects with rheumatoid arthritis and controls. Values represent mean ± standard deviation.

Characteristic	Control Group, n = 10	Patient Group 1, n = 15	Patient Group 2, n = 15
Age, yrs	58.5 ± 17.8	53.7 ± 15.4	54.8 ± 14.7
No. male/female	3/7	2/13	3/12
Body mass index, kg/m^2	25.8 ± 3.7	25.5 ± 3.3	25.8 ± 3.1
IgM rheumatoid factor, +/–	0/0	15/5	14/6
ESR, mm/h	8.10 ± 3.38	56.93 ± 20.81*	58.33 ± 22.02*
CRP, mg/l	3.05 ± 0.42	33.06 ± 14.13*	31.46 ± 14.33*
TC, mg/dl	177.20 ± 14.09	224.66 ± 31.12*	228.13 ± 11.75*
TG, mg/dl	91.30 ± 19.80	137.33 ± 47.31*	126.93 ± 31.97**
LDL-C, mg/dl	124 ± 16.46	142.33 ± 24.41**	142.66 ± 24.33**
HDL-C, mg/dl	54.50 ± 11.81	44.06 ± 9.12**	41.60 ± 10.85*
TC/HDL-C	3.4 ± 0.27	5.31 ± 1.38*	5.75 ± 1.44*
LDL-C/HDL-C	2.49 ± 0.81	3.40 ± 1.03*	3.56 ± 0.82*
MDA, nmol/ml	2.05 ± 0.45	4.35 ± 0.75*	4.42 ± 0.81*
Resistin, ng/ml	6.86 ± 1.31	9.17 ± 1.53*	9.37 ± 1.80*
Adiponectin, μg/ml	12.27 ± 1.83	19.81 ± 1.95*	19.21 ± 2.10*
TNF-α, pg/ml	3.71 ± 0.97	9.79 ± 3.42*	10.13 ± 2.90*
FMD, %	7.93 ± 2.31	3.93 ± 1.29*	3.72 ± 2.02*

Significance was determined using one-way analysis of variance for independent samples (ANOVA). * $p < 0.001$; ** $p < 0.05$ compared to controls. ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; TC: total cholesterol; TG: triglycerides; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; MDA: serum malondialdehyde; TNF-α: tumor necrosis factor-α; FMD: flow-mediated dilation.

demia characterized by significantly higher baseline total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG) compared to controls. In addition, high-density lipoprotein cholesterol (HDL-C) levels were significantly lower compared to controls. As a consequence, the atherogenic ratio of TC/HDL-C as well as that of LDL-C/HDL-C was significantly higher in RA patients compared to controls.

All biochemical markers including serum MDA, resistin, adiponectin, and TNF-α were significantly higher in RA patients than in controls. Endothelial function was determined by postocclusion FMD of the brachial artery, which was significantly lower in patients compared to controls.

Table 2 shows the effect of treatment on lipid profile, disease activity indicators, adipokines, and hemodynamic measures after 6 months of each drug therapy. There was a significant decrease in the disease activity variables. The reduction was more pronounced with atorvastatin therapy (Group 2) than with MTX therapy (Group 1). There were significant increases of serum levels of TC and HDL-C compared to baseline values before treatment, without significant change in the serum levels of LDL-C and TG, in Group 1 after treatment. However, there were significant reductions in TC, LDL-C, and TG levels with significant increase in HDL-C in Group 2 after treatment. Importantly, the atherogenic ratios TC/HDL-C and LDL-C/HDL-C were significantly reduced after treatment in Group 2, moreso than in Group 1.

There were significant decreases in biochemical markers including serum MDA, resistin, and TNF-α in both groups after treatment; the reduction was more pronounced in Group 2 than in Group 1. By contrast, serum levels of adiponectin were significantly increased and their levels were higher in Group 2 compared with Group 1 after treatment. In Group 2, FMD was significantly increased after treatment (from 3.72 ± 2.22% to 6.74 ± 3.78%) with no significant change in Group 1.

Moderate or good DAS28 responses (EULAR criteria) were achieved in 10 of 15 (66.6%) patients in Group 2 compared with 3 of 15 (20%) patients in Group 1 after 6 months of treatment.

As for the correlation matrix in all RA patients (n = 30), serum resistin and TNF-α were positively correlated with activity variables including DAS28, ESR, and CRP before and after treatment ($p < 0.001$). Adiponectin levels were positively correlated with these activity variables, serum resistin, and TNF-α before treatment ($p < 0.001$). However, adiponectin levels were negatively correlated with the same variables after treatment ($p < 0.001$). FMD was negatively correlated to LDL-C before and after treatment ($p < 0.001$). Moreover, we found no correlation between lipid profiles and serum MDA compared to inflammatory markers or disease activity.

We examined correlations with change over time in patients allocated to atorvastatin (Group 2); the reduction of LDL-C was found to correlate with the improvement of FMD ($r = –0.45$, $p < 0.05$). Moreover, there was significant positive correlation between the change in adiponectin

Table 2. Effect of treatment on disease activity, lipid profile, adipokines, and hemodynamics. Values represent mean ± standard deviation.

Feature	Patient Group 1		Patient Group 2		
	Baseline, n = 15	Posttreatment, n = 15	Baseline, n = 15	Posttreatment, n = 15	Significance Between Drugs, p†
TJC	11.0 ± 2.59	7.20 ± 1.61*	11.13 ± 3.13	3.8 ± 1.32*	< 0.001
SJC	6.73 ± 2.34	4.20 ± 1.78*	6.06 ± 2.60	1.53 ± 0.83*	< 0.001
VAS	54.66 ± 13.55	42.00 ± 10.82*	56.0 ± 14.78	21 ± 6.86*	< 0.001
ESR, mm/h	56.93 ± 20.81	43.60 ± 20.30*	58.33 ± 22.02	26.73 ± 8.56*	< 0.001
CRP, mg/l	33.06 ± 14.13	19.73 ± 10.84*	31.46 ± 14.33	7.20 ± 3.09*	< 0.001
DAS28	6.19 ± 0.82	5.27 ± 0.66*	6.09 ± 0.88	3.9 ± 0.45*	< 0.001
Morning stiffness, min	77.0 ± 35.79	59.33 ± 33.79*	86.0 ± 44.80	19.33 ± 10.66*	< 0.001
TC, mg/dl	224.66 ± 31.12	235.66 ± 30.93**	228.13 ± 11.75	191.80 ± 12.77*	< 0.001
TG, mg/dl	137.33 ± 47.31	137.13 ± 46.78	126.93 ± 31.97	96.60 ± 18.69*	< 0.001
LDL-C, mg/dl	142.33 ± 24.41	140.40 ± 25.70	142.66 ± 24.33	120.26 ± 14.14*	< 0.001
HDL-C, mg/dl	44.06 ± 9.12	51.73 ± 10.05*	41.60 ± 10.85	60.07 ± 9.38*	< 0.001
TC/HDL-C	5.31 ± 1.38	4.72 ± 1.11*	5.75 ± 1.44	3.26 ± 0.48*	< 0.001
LDL-C/HDL-C	3.40 ± 1.03	2.80 ± 0.79*	3.56 ± 0.82	2.06 ± 0.38*	< 0.001
MDA, nmol/ml	4.35 ± 0.75	3.44 ± 0.66*	4.42 ± 0.81	2.25 ± 0.39*	< 0.001
Resistin, ng/ml	9.17 ± 1.53	8.11 ± 1.35*	9.37 ± 1.80	7.28 ± 1.37*	< 0.001
Adiponectin, μg/ml	19.81 ± 1.95	21.61 ± 1.86*	19.21 ± 2.10	23.36 ± 2.10*	< 0.001
TNF-α, pg/ml	9.79 ± 3.42	7.95 ± 2.64*	10.13 ± 2.90	3.96 ± 1.00*	< 0.001
FMD, %	3.93 ± 1.29	4.01 ± 1.22	3.72 ± 2.02	6.74 ± 3.78*	< 0.001

* $p < 0.001$; ** $p < 0.05$ compared to baseline values. † The effect of individual treatments was determined by ANCOVA (final column). TJC: tender joint count; SJC: swollen joint count; VAS: visual analog score; DAS28: disease activity score for 28 joints; other abbreviations as in Table 1.

levels and FMD ($r = 0.64$, $p < 0.003$). In addition, the change in adiponectin levels had a significant inverse correlation with the change in TNF-α ($r = –0.77$, $p < 0.001$), serum resistin ($r = –0.70$, $p < 0.001$), and CRP level ($r = –0.45$, $p < 0.05$).

Multiple linear regression showed that the change in FMD was statistically significantly associated with the change in LDL-C ($B = 0.13$, $p = 0.032$) and adiponectin levels ($B = 0.09$, $p < 0.001$).

Regarding steroid doses during the 6-month period after withdrawal of the baseline dose, 12 of 15 (80%) patients in the MTX group (Group 1) and 11 of 15 (73.3%) patients in the atorvastatin group (Group 2) received oral prednisone 5 to 10 mg/day at different frequencies. No patient received steroid within 4 weeks of clinical and laboratory assessment.

Atorvastatin was well tolerated in the study population. Adverse events (mild gastrointestinal upset) arose with similar frequency in patients who received combined atorvastatin and MTX (Group 2) compared to patients who received MTX only (Group 1). In particular, no significant liver function or muscle abnormality was detected in those given atorvastatin.

DISCUSSION

Our study revealed increased levels of TC, LDL-C, and TG and decreased levels of HDL-C in patients with early active RA. As a consequence, the atherogenic ratio of TC/HDL-C as well as that of LDL-C/HDL-C was significantly higher compared to controls. Moreover, there was no significant correlation between lipid profile and activity or laboratory variables. These changes are associated with an increased incidence of cardiovascular disease in the general population. The available literature on lipid profiles in RA is contradictory. There have been studies reporting increased, decreased, or similar levels for TC, LDL-C, and HDL-C in comparison to controls[22,23,24,25,26,27]. The discrepancies in the lipid values observed in the various studies might be due to differences in study populations and in disease activity.

After 6 months of MTX therapy (Group 1), a significant increase in serum HDL-C levels was observed that resulted in reduction of the atherogenic ratios TC/HDL-C and LDL-C/HDL-C. This improvement was associated with a reduction in disease activity and in the acute-phase reactants. These observations indicate that active disease with a stable inflammatory response expressed by a persistently elevated CRP may be responsible for the development of early atherosclerosis in RA. Georgiadis, *et al*[28] documented effective suppression of disease activity at an early stage with MTX, and this was associated with a reduction in dyslipidemia and a decrease in mortality. Hadda, *et al*[29] stated that DMARD control the inflammation, which leads to normalization of functions of circulating cytokines like TNF-α, IL-1ß, and IL-6, which alters the function of distant tissues, including the adipose tissue, skeletal muscle, liver, etc., which leads to dyslipidemia.

We have observed significant suppression of acute-phase variables and marked reduction in disease activity with atorvastatin therapy (Group 2) as compared with MTX therapy (Group 1). Moreover, atorvastatin substantially increased the HDL-C levels, with a reduction in LDL-C, TG levels, and atherogenic ratios; this provides a direct coronary heart disease-protective pathway in RA[30]. The mechanism of the

effect of atorvastatin on the lipid profile was largely attributed to the ability of atorvastatin to impair cholesterol synthesis by inhibiting the enzyme HMG-CoA reductase, which is the rate-limiting step in cholesterol biosynthesis. This inhibition induces hepatocytes to increase their surface expression of LDL receptors, which promotes uptake and clearance of circulating LDL[31,32,33].

We demonstrated that serum concentrations of MDA were significantly increased in patients with RA compared with control subjects; this is in agreement with other studies in which higher MDA levels have been reported in patients with RA, confirming the role of oxidative stress in the pathogenesis of RA[34]. On the other hand, Olivieri, *et al*[35] reported no change in lipid peroxidation.

MDA levels showed a significant decrease in patients with RA in both groups studied, with a more significant reduction with atorvastatin therapy (Group 2). This is in agreement with findings from Akyol, *et al*[36], who reported that MDA levels in the untreated patients were significantly higher than those of treated patients due to suppression of inflammatory conditions, which drive leukocytes into the affected joint, where they become activated to produce ROS.

The marked significant reduction in MDA levels with atorvastatin treatment in Group 2 may be attributed to the antioxidant-mediated effect of atorvastatin that results from inhibition of the mevalonate pathway, leading to reduction in the synthesis of important intermediates including isoprenoids that serve as lipid attachments for intracellular signaling molecules, in particular, inhibition of small GTPase-binding proteins (Rho, Rac, Ras, and G proteins). These proteins modulate a variety of cellular processes including signaling, differentiation, and proliferation[37]. Some of the antioxidant effects of atorvastatin may be due to its metabolites, such as hydroxyl metabolites, that have direct antioxidant effects. Atorvastatin improves and preserves the level of vitamins C and E and endogenous antioxidants such as reduced glutathione[38]. Moreover, atorvastatin treatment may play a role in protecting LDL-C and HDL-C from oxidation by increasing antioxidant activity of the HDL-associated enzyme and paraoxonase 1[39].

The results of our study showed that serum TNF-α and resistin levels were significantly increased in RA patients compared with controls. Also, their levels were positively correlated with disease activity variables. Previous studies observed increased resistin levels in synovial fluid from patients with RA[40]. These authors observed the association between synovial fluid resistin levels, disease activity, and acute-phase reactants, including CRP and IL-1Ra-antagonizing IL-1ß suggests that resistin may be a significant mediator in the inflammatory process of RA[41].

In our study, TNF-α and resistin levels showed a significant decrease with MTX therapy (Group 1), but they were still higher than those of the control group. Their levels with atorvastatin therapy (Group 2) showed a more statistically significant decrease when compared to Group 1. Our study confirmed previous findings that TNF-α could induce resistin expression in human macrophages[42]. The inhibitory effect of atorvastatin on TNF-α-induced resistin expression provides additional evidence of a pleiotropic effect of statin[42]. Statin therapy may become another therapeutic strategy for controlling resistin-associated pathologic cardiovascular disease in humans[43].

As for baseline serum levels of adiponectin, levels were significantly increased in RA patients compared to controls. Our results are in accord with those of Senolt, *et al*[44] and Otero, *et al*[45], who demonstrated significantly higher adiponectin levels in RA patients compared to healthy controls. Moreover, there was a significant positive correlation between adiponectin levels and activity scores, ESR, CRP, and serum TNF-α and resistin levels, in agreement with the results of Otero, *et al*[45], who recorded the correlation between activity of RA and adiponectin levels. In contrast, Senolt, *et al*[44] concluded that adiponectin levels were not related to disease activity in RA.

Serum levels of adiponectin showed more significant increases with atorvastatin therapy (Group 2) when compared to corresponding levels with MTX therapy (Group 1). Moreover, there was a significant negative correlation between the levels of adiponectin after treatment and activity variables. The changes in adiponectin levels had a significant positive correlation with changes in FMD and an inverse correlation with the changes in TNF-α, serum resistin, and CRP. This result is in agreement with data from Nakamura, *et al*[46], who suggested that insulin-sensitizing and antiinflammatory effects of atorvastatin may be related to the increase in adiponectin levels. Further, increase in adiponectin levels may partially mediate the restoration of endothelial vasomotor function, after treatment with statin increased nitric oxide. By contrast, another study reported that simvastatin significantly decreased adiponectin levels and insulin sensitivity[47]. Bruun, *et al*[48] showed that plasma TNF-α and IL-6 levels were negatively correlated with the plasma adiponectin level in humans. By contrast, another study reported that there was no correlation between the plasma TNF-α and adiponectin levels[49].

We demonstrated that atorvastatin significantly improved endothelial function in RA to a level similar to that of healthy control subjects (an FMD > 4.5% is considered to be normal). The reduction of total LDL and increased adiponectin level was significantly correlated with the improvement of FMD, suggesting that these factors were related to the improvement in endothelial function. This result was in accord with findings of Tomas, *et al*[50], who concluded that atorvastatin has a beneficial effect on lipid profile associated with an improvement in peripheral FMD, and its improvement is related to the levels of LDL. Mäki-Petäjä, *et al*[51] have shown that both ezetimibe and simvas-

tatin reduce inflammatory markers, disease activity, and endothelial function, and concomitantly arterial stiffness was improved by both drugs.

In summary, cholesterol-reducing therapies may be beneficial for patients with RA, because they are well tolerated, improve clinical outcome, and reduce cardiovascular risk.

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