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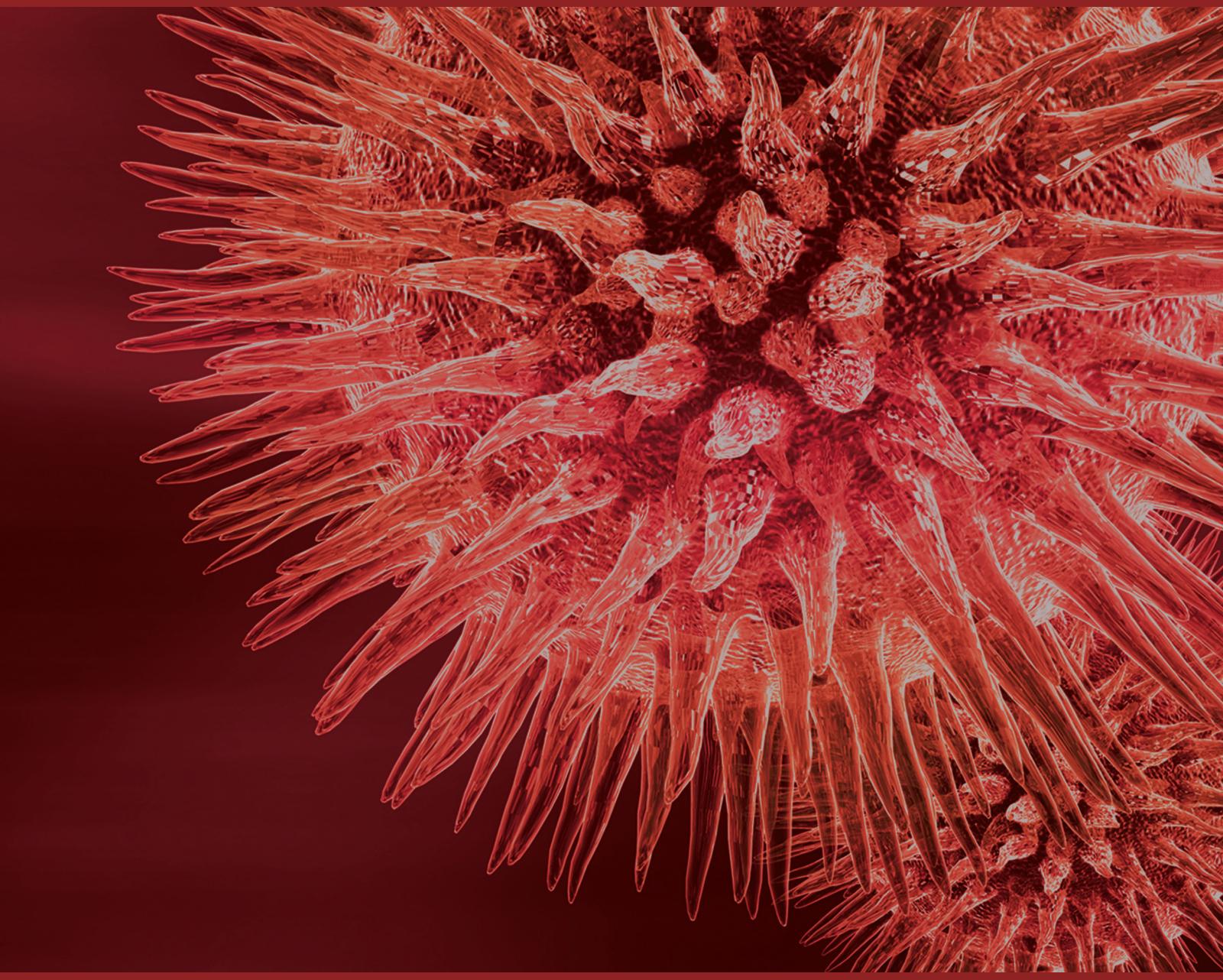
Guest Editors: Patrick H. Dessein, Anne G. Semb, Miguel A. González-Gay, and Calin D. Popa



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Editorial

Enhanced Cardiovascular Risk in Rheumatoid Arthritis: Elucidation, Assessment, and Management

Patrick H. Dessein,[1] Anne G. Semb,[2] Miguel A. González-Gay,[1,3] and Calin D. Popa[4]

[1] *Cardiovascular Pathophysiology and Genomics Research Unit, School of Physiology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg 2193, South Africa*
[2] *Preventive Cardio-Rheuma Clinic, Department of Rheumatology, Diakonhjemmet Hospital, 0370 Oslo, Norway*
[3] *Department of Rheumatology, Hospital Universitario Marques de Valdecilla, IDIVAL, 39008 Santander, Spain*
[4] *Department of Rheumatology, Radboud University Nijmegen Medical Centre, 6525 Nijmegen, Netherlands*

Correspondence should be addressed to Patrick H. Dessein; dessein@telkomsa.net

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High-grade inflammation together with its impact on traditional risk factors and genetic determinants is strongly implicated in the substantially increased risk of cardiovascular disease (CVD) and mortality experienced by patients with rheumatoid arthritis (RA) [1–4]. In view of this complexity, it should not be unexpected that adequate CVD risk assessment in RA still eludes us to date [5, 6]. This special issue in this journal was initiated with the aims of further exploring mechanisms involved in enhanced CVD risk as well as its optimal stratification and management in patients with RA.

The increased risk of ischemic heart disease, stroke, and heart failure is well established in RA [7–9]. A. K. Bacani et al. herein report that there is also a 46% increased incidence in atrial fibrillation (AF) independent of traditional AF risk factors amongst RA patients, in a study that included 831 cases and controls. Severe extra-articular disease, multiple high sedimentation rates, and COX-2 inhibitor use were associated with AF. This again illustrates the potential role of nontraditional risk factors in the increased CVD risk associated with RA.

Janus kinases (JAK) contribute to cytokine production in RA [10] and are implicated in CVD [11]. M. García-Bermúdez et al. document that JAK3 gene polymorphisms are not associated with cardiovascular events comprising ischemic heart disease, cerebrovascular disease, peripheral arterial disease, and/or heart failure, in 2136 RA patients; there were also no relationships between JAK3 gene polymorphisms and ultrasound determined carotid intima-media thickness (CIMT) or plaque amongst 539 of the participants. The current findings emphasize the need for identifying other gene polymorphisms implicated in inflammatory pathways, as potential determinants of CVD in RA. This group of researchers has previously reported that gene polymorphisms located within the MHC region as well as variations of genes outside this region can contribute to CVD in RA [3, 4].

Anti-cyclic citrullinated peptide (anti-CCP) antibodies are involved in the pathophysiology of RA [12] and are most useful in diagnosing this disease. M. V.-Del Mercado et al. show that in 82 RA patients without conventional cardiovascular risk factors, amongst a range of inflammatory markers, C-reactive protein and anti-CCP concentrations were most strongly associated with CIMT on ultrasound. The CIMT was larger in 45 anti-CCP positive patients compared to the 37 that tested negative and 62 age and sex matched healthy controls. Indeed, anti-CCP antibodies can also participate in atherogenesis amongst patients with RA [12].

Juvenile inflammatory arthritis (JIA) is a rarer disease than RA. Accordingly, data on the impact of JIA on CVD risk remain limited. E. Jednacz and L. Rutkowska-Sak compared body composition and cardiovascular risk factors as well as CIMT in 30 children with JIA and 20 age and sex matched control subjects. Lower body mass index (BMI) and BMI

centile and higher interleukin-6 concentrations were found in JIA patients. The former was likely due to increased catabolism whereas the latter is strongly associated with surrogate markers of early atherogenesis in RA [13]. Whether the findings in the present study translate into a larger incidence of cardiovascular events later in life amongst JIA patients requires further study.

Adequate traditional cardiovascular risk management is possible in RA [14] and can further reduce cardiovascular event rates to a similar extent as in non-RA subjects [15]. However, besides our current insufficient understanding of CVD mechanisms, inconsistent traditional cardiovascular risk recording by treating physicians undoubtedly contributes to the reported lack of reduction in cardiovascular event rates over the past decades in RA [5]. E. Ikdahl et al. are currently investigating means to address this shortcoming. Accordingly, they recently established a structured arthritis clinic (AC). The European League Against Rheumatism (EULAR) recommendations on CVD risk assessment [5] were implemented and medical secretaries, patients self-reporting on computer screens, rheumatology nurses, and the treating physicians are all systematically involved in this undertaking. They report that the overall rate of CVD risk factor recording is 23.6% and 59.1% in their regular rheumatology clinic (n = 612) and AC (n = 530), respectively. This improvement is encouraging but still far from optimal and indeed calls for the implementation of additional innovative strategies, as is amply discussed by the authors.

An elegant and comprehensive systematic review on the impact of biologic agents including tumor necrosis factor-α (TNF-α) blockade with adalimumab, etanercept, or infliximab on lipid metabolism in RA was recently reported [16]. In particular, adalimumab and etanercept can reduce the atherogenic index, that is, the total cholesterol-high density lipoprotein (HDL) ratio. Importantly also, infliximab use in RA was shown to enhance HDL antioxidative capacity, an effect that persisted 6 months after its initiation [17]. N. A. Rodriguez-Jimenez et al. report on their experience with etanercept in this regard. Lipid levels were measured at baseline and 4 and 24 weeks. Whereas this study is observational, its strength is that only methotrexate (n = 13) or methotrexate in combination with etanercept (n = 22) was used as disease modifying agent therapy. The investigation revealed that the addition of etanercept to methotrexate therapy results in increased HDL concentrations, which may reduce CVD risk in RA.

Whereas ~80% of cardiovascular events currently occur in poor or middle income countries, available CVD risk assessment strategies were determined based on data that were obtained in persons that belong to developed populations [18]. A. Solomon et al. systematically review reported investigations on CVD risk in African black patients with RA that belong to a developing population. Such patients were previously documented to experience marked RA activity and severity [19]. In relatively large studies, the CVD risk factor and atherosclerosis burden are now as large in African black as in white patients with RA despite an earlier epidemiological health transition stage in the former. Adequate CVD risk management should therefore be performed irrespective of population origin in RA. Even more strikingly, traditional CVD risk factors and RA characteristics were consistently unrelated to atherosclerosis amongst African black patients. This suggests that there are potential disparities in atherogenic mechanisms amongst population groups. By contrast, however, the relations of cardiovascular biomarkers including adipokines with atherosclerosis were overall similar in African black and white patients with RA. Taken together, these data support the need for population specific cardiovascular risk stratification with the consideration of vascular imaging and, potentially, the use of novel CVD risk biomarkers, particularly in African black patients with RA.

The studies reported here have implications in CVD risk and cardiovascular risk stratification and management amongst patients with RA and JIA. Equally important, the evidence reported in this special issue reinforces the need for more awareness in daily clinical practice of increased cardiovascular risk in RA and the notion that much more research is necessitated in this field.

Patrick H. Dessein
Anne G. Semb
Miguel A. González-Gay
Calin D. Popa

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Research Article

Assessment of the Body Composition and Parameters of the Cardiovascular Risk in Juvenile Idiopathic Arthritis

Ewa Jednacz and Lidia Rutkowska-Sak

Paediatric Clinic of Rheumatology, Institute of Rheumatology, Spartanska 1, 02-637 Warsaw, Poland

Correspondence should be addressed to Ewa Jednacz; ewa.jednacz@op.pl

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The study was aimed to evaluate cardiovascular risk parameters, body mass index (BMI) centiles for sex and age, and body fat percentage using the electric bioimpedance method in children with juvenile idiopathic arthritis (JIA). 30 children with JIA participated in the study. A control group included 20 children. Patients were well matched for the age and sex. The body mass and body fat percentage were determined using the segmental body composition analyser; the BMI centiles were determined. All patients had the following parameters determined: lipid profile, hsCRP, homocysteine, and IL-6. The intima media thickness (IMT) was measured. Patients with JIA had significantly lower body weight, BMI, and the BMI centile compared to the control group. The IL-6 levels were significantly higher in patients with JIA compared to the control group. There were no differences between two groups with regard to the lipid profile, % content of the fat tissue, homocysteine levels, hsCRP, and IMT. Further studies are necessary to search for reasons for lower BMI and BMI centile in children with JIA and to attempt to answer the question of whether lower BMI increases the cardiovascular risk in these patients, similarly as in patients with rheumatoid arthritis (RA).

1. Introduction

Atherosclerosis is a disease known from many years [1, 2]. There were many theories regarding the aetiology of atherosclerosis, but groundbreaking was the theory of Russel Ross, who announced that atherosclerosis is an inflammatory disease [3]. Currently, apart from commonly known risk factors predisposing to atherosclerosis development more attention has been paid to new risk factors such as acute phase proteins like CRP, proinflammatory cytokines, homocysteine, and noninvasive methods to assess the intima media thickness (IMT), the values of which correlate with the advancement of atherosclerosis.

Clinical consequences of an atherosclerotic process are present in the adult population; nonetheless, atherosclerotic lesions start to form in early childhood, even in the foetal life [4, 5]. In 2011, the American Academy of Pediatrics published extensive guidelines on lowering the cardiovascular risk in children and adolescents [6]. High and medium cardiovascular risk groups were distinguished. The medium risk group includes children with chronic inflammatory diseases such as systemic lupus erythematosus and juvenile idiopathic arthritis (JIA). JIA is the most common chronic arthropathy of the developmental age that develops with arthritis, extra-articular lesions, and systemic complications. Diagnostic criteria include a disease onset prior to the age of 16 years, duration of symptoms for at least 6 weeks, and exclusion of other causes of arthritis based on the so-called exclusion list [7]. In contrary to the population of adults with rheumatoid arthritis (RA), there is little data indicating an increased cardiovascular risk in children with JIA. Patients with RA have a shorter life expectancy compared to the general population. Cardiovascular diseases are the main causes of death in this population [8–10]. In 2009, The European League against Rheumatism (EULAR) presented its recommendations regarding screening tests for circulatory diseases in patients with RA and other forms of arthritis and according to them, RA is a disease associated with a higher risk of cardiovascular disease development [11]. Studies of recent years have provided more and more evidence that

there is a correlation between inflammatory processes in the course of RA and development of atherosclerotic lesions. The synovial membrane in RA and atherosclerotic plaques have pathological similarities. Similar mechanisms in the synovial membrane in RA and in the development of atherosclerotic plaques include T and B cells, macrophages, adhesive molecules, proinflammatory cytokines: tumor necrosis factor (TNF) alpha, interleukin 1 (IL-1), interleukin 6 (IL-6), and chemokines [12].

The study was aimed to evaluate cardiovascular risk parameters, body mass index (BMI) centiles for sex and age, and body fat percentage using the electric bioimpedance method in children with JIA.

2. Materials and Methods

2.1. Study Population. 30 children with JIA who were patients of the Paediatric Clinic of Rheumatology, Institute of Rheumatology in Warsaw, participated in the study between September 2012 and April 2013. Inclusion criteria were as follows: the age between 11 and 17 years and the diagnosis of JIA based on the criteria of the International League of Associations for Rheumatology [13]. 16 children suffered from oligoarticular and 14 from polyarticular JIA. Children took only medicines associated with JIA; they did not suffer from any other medical conditions. 22 children received methotrexate (in monotherapy or in combination treatment), 6 children sulfasalazine (in monotherapy or in combination treatment), 5 children chloroquine (in monotherapy or in combination treatment), 2 children cyclosporine A (in combination treatment), 1 child azathioprine (in combination treatment), 5 children TNF inhibitors (in combination treatment), and 8 children glucocorticosteroids (in combination treatment). Children were divided into groups depending on disease duration, below one year, 6 children (20%), and above one year, 24 children (80%), and depending on the disease activity. According to the criteria by Ringold and Wallace, an inactive disease phase was indicated by the following criteria: no joints with active arthritis, lack of fever, rash, serositis, splenomegaly, generalized lymphadenopathy associated with JIA, no signs of active uveitis; normal erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP); and no signs of active disease based on the physician global assessment of disease activity [14]. The criteria of an inactive disease phase were met by 11 children (37%) and those of an active disease by 19 children (67%). A child was diagnosed as overweight when the body mass index (BMI) indicated the value equal to or above the 85th centile and below the 95th centile for the sex and age, whereas obesity was diagnosed when the BMI was equal to or above the 95th centile [15–17]. There were no overweight or obese children in the study group.

A control group included 20 children at the age between 10 and 16 years who were patients at the Paediatric Clinic of Rheumatology and in whom rheumatologic diseases were excluded with appropriate paediatric tests. These children did not take any medicines, were not supervised by any other specialists, and were not overweight or obese.

All patients had a physical examination performed, blood samples were drawn early in the morning after overnight fasting, and anthropometric measurements and the IMT were assessed at the Paediatric Clinic of Rheumatology.

The study was approved by the Bioethics Committee at the Institute of Rheumatology in Warsaw. All parents and children provided their consent for study participation.

2.2. Anthropometric Measurements. The body mass and body fat percentage were determined using the segmental body composition analyser, TANITA BC-418 MA, using bioelectric impedance technology, according to the manufacturer's instructions. This model has 4 additional electrodes in hand grips apart from a standard platform with 4 electrodes, which provides a system of 8 electrodes. As a result, it is possible to perform a detailed assessment of separate body segments.

The BMI was determined based on the body mass and height measurements using the following formula: the body mass in kilograms divided by the height in square meters. The BMI centiles were determined using a calculator prepared based on the OLAF project (calculator's author: Anna Manerowska, Warsaw University of Technology). An additional aim of the OLAF project included preparation of standards in a form of centile charts presenting the body mass index with relation to the sex and age of children and adolescents aged 7–18 years, representative for the Polish population [18], whereas the main aim included preparation of arterial pressure standards in a form of centile charts.

2.3. Laboratory Measurements. Lipid profiles were determined using dry chemistry methods with the Vitros S 350 analysers by Ortho Clinical Diagnostics (Ortho Clinical Diagnostics Vitros S 350 Chemistry Analyzer), according to the manufacturer's instructions.

High-sensitivity C-reactive protein (hs-CRP) was determined using latex-enhanced immunoturbidimetry with the Cobas C 501 analyser, according to the manufacturer's instructions. Human CRP agglutinates with latex particles that are coated with monoclonal antibodies to human CRP. A precipitate formed is measured turbidimetrically at the wave length of 552 nm.

Homocysteine was measured immunochemically with microparticles and a chemiluminescence marker used for quantitative determination of L-homocysteine in human serum samples using the ARCHITECT i System, according to the manufacturer's instructions. IL-6 was determined using the double-bond Sandwich ELISA method that belongs to immunoenzymatic methods, using a Diagnostics Pasteur device.

2.4. Carotid Ultrasonography. The IMT was measured with a semiautomatic method using a linear transducer of the Vivid S5 device by GE Medical Systems. The intima-medial thickness of the common carotid artery 1-2 cm proximally to the bifurcation at the segment of 1 cm [19] was calculated based on automatic detection of outlines of the intima-media contours on the posterior vascular wall.

The following parameters were calculated: mean IMT, maximum IMT, minimum IMT, standard deviation of IMT

measurements, and number of successful IMT measurements. Finally, the mean IMT on the right and left was assessed. The test was performed in a supine position, with an abducted head, slightly tilted oppositely to the examined side, and preceded by a 10-minute rest.

2.5. Statistical Analysis. Continuous variables were assessed whether they were normally distributed using the Kolmogorov-Smirnov test and presented as means and standard deviations (SD) or medians and interquartile ranges (IQR: 25th and 785th), as appropriate. Comparisons between groups were made using the independent t-test, one-way ANOVA (normal distribution), Mann-Whitney U test, or Kruskal-Wallis H-tests (irregular or skewed distribution). Significance levels were adjusted for multiple comparisons using the Tukey post hoc method. A correlation between continuous variables was performed using Pearson's or Spearman's correlation coefficient (r), as appropriate. Categorical variables were expressed as frequencies and percentages, and the Fisher's exact or χ^2 tests were used for comparison.

A two-tailed P value of <0.05 was considered statistically significant. Statistical analyses were performed with SAS 9.2 (Cary, NC, USA).

3. Results

Comparison between children with JIA and the control group and the demographic, clinical, laboratory, and ultrasonographic data of patients with JIA and healthy controls are shown in Table 1. Patients were well matched for the age and sex. Patients with JIA had significantly lower body weight ($P = 0.0066$), BMI ($P = 0.0302$), and the BMI centile ($P = 0.0308$) compared to the control group. The IL-6 levels were significantly higher in patients with JIA compared to the control group ($P = 0.0137$). There were no differences between two groups with regard to the lipid profile, % content of the fat tissue, homocysteine levels, hsCRP, and IMT.

The analysis in patients with active and inactive JIA and the control group (Table 2) presents a comparison between patients with active and inactive JIA and the control group.

Patients with active JIA had higher hsCRP levels compared to patients with inactive disease ($P = 0.0154$, inactive versus active JIA: 0.0109). There were no differences between patients with active and inactive disease with regard to lipid parameters, BMI centile, % of the fat tissue, homocysteine levels, and IMT assessment. The analysis in oligoarticular and polyarticular JIA and the control group (Table 3) presents a comparison of patients with oligoarticular and polyarticular JIA and the control group. There were no significant differences between patients with oligoarticular and polyarticular JIA with regard to lipid parameters, BMI centile, % of the fat tissue, hsCRP levels, IL-6 levels, homocysteine levels, and IMT assessment.

3.1. Correlations. Table 4 presents correlations between hsCRP, IL-6, homocysteine levels, IMT and lipid parameters, BMI, and BMI centile in all studied patients with JIA. A positive correlation between the patient age and homocysteine levels was observed ($r = 0.35$; $P = 0.06$), but it was not statistically significant. A positive correlation between the homocysteine levels and LDL cholesterol levels was observed ($r = 0.22$; $P = 0.25$) and between the homocysteine levels and IL-6 levels ($r = 0.35$; $P = 0.14$), but they were not statistically significant. There were no correlations between other analysed parameters.

4. Discussion

Atherosclerosis is an inflammatory disease. Obesity is one of commonly known cardiovascular risk factors. American studies demonstrated obesity in 18% of patients with JIA [20]. In German studies 15% of children were overweight and 7% were obese [21]. In patients with RA special attention is paid to the fact that low BMI is associated with cardiovascular risk [22]. In RA patients rheumatoid cachexia is observed. It is characterised by the loss of body mass, but fat mass tends to be maintained or increased [23]. Less is known about assessing of the body composition in patients with JIA. In a longitudinal study using whole body dual X-ray absorptiometry scans the percentage of total body fat was greater in patients with JIA and total lean body mass was less in patients with JIA compared to healthy children [24, 25]. But in a study with adult patients with JIA, who were in remission or with active disease, patients with JIA had significantly less body fat than healthy controls [26]. Some researchers draw attention to the fact that JIA patients exhibit impaired nutrition and lower BMI values compared to healthy children [27, 28]. Factors associated with this fact are not clearly determined, and they may be associated with an inflammatory process, secreted cytokines, absorption disturbances, effects of medicines [29], inadequate dietary intake, and physical activity limitation [30]. Patients with systemic JIA have increased expenditure of energy [31]. In our studies patients with JIA exhibited lower BMI centiles for sex and age compared to the control group, and this difference was statistically significant, but there was no significant difference between the fat tissue percentages. We used the bioelectric impedance method as it is noninvasive, simple, and quick to perform, even though dual-energy X-ray absorptiometry (DEXA) is more accurate to assess fat mass and lean body mass. Further studies are necessary to determine whether a low BMI centile in children with JIA is associated with a cardiovascular risk, which has been demonstrated for patients with RA and low BMI.

Patients with RA have dyslipidemia defined as higher levels of total cholesterol and/or triglycerides and/or lower HDL levels. Dyslipidemia depends on the disease activity, and the higher the disease activity score (DAS) is, the lower total cholesterol levels are; however, the HDL fraction levels are reduced to a larger extent; therefore the atherogenicity index is increased [32]. Studies in children with JIA demonstrate varied results [33–35]. Some of them indicate lack of significant differences in a lipid profile compared to healthy children, and it was also observed in our study.

Endothelial dysfunction is observed at an early stage of atherosclerosis. Proinflammatory cytokines, such as IL-6,

Table 1: Characteristics of patients with JIA and control group.

	JIA group, $n = 30$	Control group, $n = 20$	P
Age, years	14,0 ± 1,8	14,4 ± 1,8	0.4301
Female	23 (76,7%)	15 (75,0%)	1.0000
Weight, kg	48,4 ± 8,6	55,5 ± 9,0	0.0066*
Height, cm	160,7 ± 8,8	166,0 ± 10,3	0.0592
BMI	18,6 ± 2,2	20,1 ± 2,3	0.0302*
BMI percentile	37,2 ± 23,6	52,9 ± 25,6	0.0308*
FAT %	19,9 ± 5,8	23,0 ± 5,5	0.0603
Total cholesterol, mg/dL	151,4 ± 25,1	153,4 ± 26,8	0.7928
Triglycerides, mg/dL	89,4 ± 38,8	92,1 ± 37,3	0.8113
LDL cholesterol, mg/dL	77,6 ± 23,6	77,6 ± 23,9	0.9996
HDL cholesterol, mg/dL	58,5 ± 13,7	57,4 ± 14,9	0.7866
hsCRP, mg/L	0,40 [0,30–1,60]	0,45 [0,30–0,70]	0.7342
IL-6, pg/mL	56,0 [0,0–272,2]	0,0 [0,0-0,0]	0.0137*
Homocysteine, μmol/L	8,9 ± 2,9	9,2 ± 2,5	0.7327
IMT, mm	0,47 ± 0,04	0,47 ± 0,04	0.9665

BMI: body mass index, % FAT: % body fat, LDL: low density lipoprotein, HDL: high density lipoprotein, hsCRP: high senstivity C-reactive protein, IL-6: interleukin 6, IMT: intima media thickness, and *statistically significant.

Table 2: Characteristics of patients with JIA according to disease activity.

	JIA inactive, $n = 11$	JIA active, $n = 19$	Control group, $n = 20$	P
Age, years	13,7 ± 1,8	14,2 ± 1,8	14,4 ± 1,8	0.5762
Female	10 (90,9%)	13 (68,4%)	15 (75%)	0.4066
Weight, kg	47,7 ± 10,2	48,7 ± 7,8	55,5 ± 9,0	0.0248 CG versus I: 0.0582 CG versus A: 0.0516
Height, cm	159,3 ± 10,3	161,5 ± 8,1	166,0 ± 10,3	0.1428
BMI	18,6 ± 2,6	18,6 ± 2,0	20,1 ± 2,3	0.0979
BMI percentile	39,6 ± 22,7	35,8 ± 24,6	52,9 ± 25,6	0.0917
FAT %	21,0 ± 5,4	19,3 ± 6,0	23,0 ± 5,5	0.1293
Total cholesterol, mg/dL	156,6 ± 27,8	148,3 ± 23,6	153,4 ± 26,8	0.6770
Triglycerides, mg/dL	92,3 ± 42,6	87,7 ± 37,5	92,1 ± 37,3	0.9266
LDL cholesterol, mg/dL	74,8 ± 21,8	79,2 ± 25,1	77,6 ± 23,9	0.8909
HDL cholesterol, mg/dL	63,4 ± 13,5	55,6 ± 13,4	57,4 ± 14,9	0.3435
hsCRP, mg/L	0,30 [0,20–0,50]	0,70 [0,40–3,90]	0,45 [0,30–0,70]	0.0154* I versus A: 0.0109
IL-6, pg/mL	0,0 [0,0–369,6]	168,4 [0,0–255,9]	0,0 [0,0-0,0]	0.0384* CG versus A: 0.0109
Homocysteine, μmol/L	8,6 ± 2,6	9,1 ± 3,0	9,2 ± 2,5	0.8191
IMT, mm	0,49 ± 0,05	0,46 ± 0,03	0,47 ± 0,04	0.1796

BMI: body mass index, FAT %: % body fat, LDL: low density lipoprotein, HDL: high density lipoprotein, hsCRP: high sensitivity lipoprotein, IL-6: interleukin 6, IMT: intima media thickness, *statistically significant, CG: control group, I: inactive, and A: active.

are involved in this process and they increase the ICAM-1 expression and CRP synthesis [36]. The administration of IL-6 to mice susceptible to atherosclerosis and to mice resistant to atherosclerosis receiving a cholesterol-rich diet resulted in atherosclerotic lesions developing only in mice susceptible to atherosclerosis [37]. The increased levels of proinflammatory cytokines are observed in RA [38], similarly in children with JIA [39]. In studies on patients with RA, IL-6 played an especially vital role in the vascular endothelial activation [40]. Our study demonstrated the increased IL-6 levels in children

Table 3: Characteristic of patients with JIA according to type of JIA and control group.

	Polyarticular, $n = 14$	Oligoarticular, $n = 16$	Control group, $n = 20$	P
Age, years	14,9 ± 1,6	13,3 ± 1,8	14,4 ± 1,8	0.0441
Female	10 (71,4%)	13 (81,2%)	15 (75,0%)	0.8427
Weight, kg	50,6 ± 7,1	46,4 ± 9,5	55,5 ± 9,0	0.0109* P versus O: 0.0083
Height, cm	163,2 ± 5,5	158,4 ± 10,7	166,0 ± 10,3	0.0665
BMI	19,0 ± 2,3	18,3 ± 2,1	20,1 ± 2,3	0.0699, P versus O: 0.0606
BMI percentile	36,5 ± 27,0	37,9 ± 21,0	52,9 ± 25,6	0.0985
FAT %	19,9 ± 6,3	19,9 ± 5,5	23,0 ± 5,5	0.1745
Total cholesterol, mg/dL	145,6 ± 26,2	156,4 ± 23,7	153,4 ± 26,8	0.5022
Triglycerides, mg/dL	78,4 ± 30,0	99,0 ± 43,8	92,1 ± 37,3	0.3293
LDL cholesterol, mg/dL	77,1 ± 25,9	77,9 ± 22,4	77,6 ± 23,9	0.9961
HDL cholesterol, mg/dL	58,2 ± 14,1	58,7 ± 13,9	57,4 ± 14,9	0.9605
hsCRP, mg/L	0,70 [0,40–3,90]	0,40 [0,25–0,55]	0,45 [0,30–0,70]	0.0962
IL-6, pg/mL	150,5 [0,0–239,6]	0,0 [0–369,6]	0 [0,0-0,0]	0.0327 CG versus P: 0.0067
Homocysteine, μmol/L	8,6 ± 2,5	9,2 ± 3,2	9,2 ± 2,5	0.8209
IMT, mm	0,46 ± 0,03	0,48 ± 0,05	0,47 ± 0,04	0.3418

BMI: body mass index, % FAT: % body fat, LDL: low density lipoprotein, HDL: high density lipoprotein, hsCRP: high sensitivity lipoprotein, IL-6: interleukin 6, IMT: intima media thickness, *statistically significant, P: polyarticular, and O: oligoarticular.

Table 4: Correlations [Pearson/Spearman correlation coeficient and P value: $r(P)$] between hsCRP, IL-6, homocysteine, IMT, and cardiovascular risk factors in children with JIA.

	JIA all patients, $n = 30$			
	hsCRP	IL-6	Homocysteine	IMT
Age	$r = 0.29$ $P = 0.13$	$r = 0.21$ $P = 0.39$	$r = 0.35$ $P = 0.06$	$r = -0.06$ $P = 0.75$
BMI	$r = 0.30$ $P = 0.10$	$r = -0.09$ $P = 0.71$	$r = 0.25$ $P = 0.19$	$r = 0.05$ $P = 0.79$
BMI percentile	$r = 0.25$ $P = 0.18$	$r = -0.11$ $P = 0.66$	$r = 0.08$ $P = 0.69$	$r = 0.05$ $P = 0.79$
Total cholesterol, mg/dL	$r = 0.24$ $P = 0.20$	$r = -0.05$ $P = 0.85$	$r = 0.28$ $P = 0.14$	$r = 0.04$ $P = 0.82$
LDL cholesterol, mg/dL	$r = 0.31$ $P = 0.10$	$r = -0.15$ $P = 0.53$	$r = 0.22$ $P = 0.25$	$r = 0.09$ $P = 0.64$
HDL cholesterol, mg/dL	$r = -0.11$ $P = 0.54$	$r = 0.19$ $P = 0.44$	$r = -0.06$ $P = 0.77$	$r = 0.07$ $P = 0.72$
hsCRP, mg/L	$r = 1.00$	$r = -0.07$ $P = 0.77$	$r = 0.32$ $P = 0.09$	$r = -0.10$ $P = 0.61$
IL-6, pg/mL	$r = -0.07$ $P = 0.77$	$r = 1.00$	$r = 0.35$ $P = 0.14$	$r = -0.27$ $P = 0.26$
Homocysteine, μmol/L	$r = 0.32$ $P = 0.09$	$r = 0.35$ $P = 0.14$	$r = 1.00$	$r = -0.21$ $P = 0.26$

JIA: juvenile idiopathic arthritis, BMI: body mass index, LDL: low density lipoprotein, HDL: high density lipoprotein, hsCRP: high sensitivity lipoprotein, IL-6: interleukin 6, and IMT: intima media thickness.

with JIA compared to the control group, and this difference was statistically significant.

As it is possible to assay the CRP levels with a high-sensitivity method, it became possible to precisely determine low CRP levels that indicate mild inflammation, assumed to contribute to atherosclerosis pathogenesis. The increased CRP levels are a risk factor for cardiovascular incidents [41]. Our study did not demonstrate differences in the hsCRP levels between children with JIA and the control group; however, there was a statistically significant difference in the hsCRP levels between patients with active and inactive disease.

The elevated homocysteine levels are an independent risk factor for brain stroke and ischaemic heart disease, and when these levels are reduced the risk becomes lower [42]. In 2004, the guidelines were published that concluded that the reference homocysteine levels should be determined for separate populations depending on many factors, such as the age, and also supplementation with folic acid and B group vitamins [43]. The studies by Gonçalves et al. did not demonstrate significantly elevated homocysteine levels compared to healthy children despite treatment with methotrexate, which was probably a result of appropriate supplementation with folic acid [35]. We obtained similar results in our study, and it might stem from the fact that the majority of patients received methotrexate, and all patients receiving methotrexate took folic acid supplementation. A positive correlation between the age and the homocysteine levels ($r = 0.35$; $P = 0.06$) was observed, but it did not reach statistical significance probably due to a low number of patients.

Moreover, positive correlations between the homocysteine levels and LDL cholesterol levels and between the homocysteine levels and IL-6 levels were observed, but they were not statistically significant probably due to a low number of patients.

In the search for noninvasive methods to assess the risk of atherosclerosis, ultrasonography is of interest as it allows determining the intima media thickness. The IMT is a factor predicting the stage of atherosclerosis and it may help assess the cardiovascular risk in asymptomatic patients with a moderate cardiovascular risk [44]. In the studies by Vlahos in children with JIA increased IMT was observed only in children with a systemic disease, and this difference was not observed for oligoarticular or polyarticular form [45]. The studies by Breda demonstrated increased IMT in children with JIA compared to healthy children [46]. Our study did not demonstrate differences in IMT between healthy children and children with JIA. It might have been caused by the fact that the study group did not include children with a systemic disease where the intensity of inflammatory lesions is especially high. Our study has some limitations. It is a cross-sectional study with a relatively low number of patients. The nutritional status assessment performed in order to compare children with JIA with the control group did not consider a diet of children, and everyday diet was not reported, but it may have a significant effect on the nutritional status. We did not consider the functional impairment status and physical activity levels in patients with JIA. Both may influence the nutritional status of the patient. When assessing patients with JIA only oligoarticular and polyarticular disease were considered, and the systemic disease was not taken into account due to a very low number of patients with this form of disease at the time of study enrollment. It is possible that differences in the IMT evaluation or in other cardiovascular risk factors might have been visible in such patients. Additionally, the results of the study were not analysed with regard to the treatment applied, and the treatment itself affects the cardiovascular risk [47].

5. Conclusions

As it was demonstrated by our study, the impaired nutritional status may be present in children with JIA. Despite a lower BMI centile the fat tissue percentage was not significantly lower in these children. Further studies are necessary to search for reasons for lower BMI centiles in children with JIA and to attempt to answer the question of whether lower BMI increases the cardiovascular risk in these patients, similarly as in patients with RA.

Further studies with large groups of patients with JIA are required in order to assess the cardiovascular risk in this population.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Serum Levels of Anticyclic Citrullinated Peptide Antibodies, Interleukin-6, Tumor Necrosis Factor-α, and C-Reactive Protein Are Associated with Increased Carotid Intima-Media Thickness: A Cross-Sectional Analysis of a Cohort of Rheumatoid Arthritis Patients without Cardiovascular Risk Factors

Mónica Vázquez-Del Mercado,[1,2] Lourdes Nuñez-Atahualpa,[3] Mauricio Figueroa-Sánchez,[3] Eduardo Gómez-Bañuelos,[1] Alberto Daniel Rocha-Muñoz,[1] Beatriz Teresita Martín-Márquez,[1] Esther Guadalupe Corona-Sanchez,[1,4] Erika Aurora Martínez-García,[1,4] Héctor Macias-Reyes,[3] Laura Gonzalez-Lopez,[5] Jorge Ivan Gamez-Nava,[6] Rosa Elena Navarro-Hernandez,[1] María Alejandra Nuñez-Atahualpa,[7] and Javier Andrade-Garduño[7]

[1] *Instituto de Investigación en Reumatología y del Sistema Músculo Esquelético, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Sierra Mojada No. 950, Colonia Independencia, 44340 Guadalajara, JAL, Mexico*
[2] *Departamento de Reumatología, Hospital Civil "Dr. Juan I. Menchaca", Universidad de Guadalajara, Salvador de Quevedo No. 750, 44100 Guadalajara, JAL, Mexico*
[3] *Hospital Civil de Guadalajara "Fray Antonio Alcalde", Universidad de Guadalajara, Hospital No. 278, 44280 Guadalajara, JAL, Mexico*
[4] *Departamento de Fisiología, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Sierra Mojada No. 950, Colonia Independencia, 44340 Guadalajara, JAL, Mexico*
[5] *Departamento de Medicina Interna-Reumatología, Hospital General Regional No. 110, Instituto Mexicano del Seguro Social, Circunvalación Oblatos No. 2212, Colonia Oblatos, 44700 Guadalajara, JAL, Mexico*
[6] *Unidad de Investigacion, Unidad Medica de Alta Especialidad, Hospital de Especialidades del Centro Médico Nacional de Occidente, Instituto Mexicano del Seguro Social, Belisario Domínguez No. 1000, Independencia Oriente, 44340 Guadalajara, JAL, Mexico*
[7] *Facultad de Medicina, Universidad Autónoma de Guadalajara, Avenida Patria 1201, Lomas del Valle, 45129 Zapopan, JAL, Mexico*

Correspondence should be addressed to Mónica Vázquez-Del Mercado; dravme@hotmail.com

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The main cause of death in rheumatoid arthritis (RA) is cardiovascular events. We evaluated the relationship of anticyclic citrullinated peptide (anti-CCP) antibody levels with increased carotid intima-media thickness (cIMT) in RA patients. *Methods*. Forty-five anti-CCP positive and 37 anti-CCP negative RA patients, and 62 healthy controls (HC) were studied. All groups were assessed for atherogenic index of plasma (AIP) and cIMT. Anti-CCP, C-reactive protein (CRP), and levels of tumor necrosis factor alpha (TNFα) and interleukin-6 (IL-6) were measured by enzyme-linked immunosorbent assay (ELISA). *Results*. The anti-CCP positive RA patients showed increased cIMT compared to HC and anti-CCP negative ($P < 0.001$). Anti-CCP positive versus anti-CCP negative RA patients, had increased AIP, TNFα and IL-6 ($P < 0.01$), and lower levels of high density lipoprotein cholesterol (HDL-c) ($P = 0.02$). The cIMT correlated with levels of anti-CCP ($r = 0.513$, $P = 0.001$), CRP ($r = 0.799$, $P < 0.001$), TNFα ($r = 0.642$, $P = 0.001$), and IL-6 ($r = 0.751$, $P < 0.001$). In multiple regression analysis, cIMT was associated with CRP ($P < 0.001$) and anti-CCP levels ($P = 0.03$). *Conclusions*. Levels of anti-CCP and CRP are associated with increased cIMT and cardiovascular risk supporting a clinical role of the measurement of cIMT in RA in predicting and preventing cardiovascular events.

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease with a major component of inflammatory process [1, 2]. The main cause of death in these patients is cardiovascular events, which lead to a decreased life expectancy by 3 to 10 years [3, 4].

Cytokines play an important role in the regulation of inflammatory process and severity and progression of RA. Macrophages and lymphocytes are considered the main mediators of inflammation as these are the main source of interleukin-6 (IL-6) and tumor necrosis factor alpha (TNFα), the two major cytokines implicated in the pathogenesis of RA [5]. IL-6 may increase the risk of atherosclerosis mediated by endothelial damage, as well as increased carotid intima-media thickness (cIMT) [6].

Anticyclic citrullinated peptide (anti-CCP) antibodies are associated with the pathogenesis, clinical expression, and cardiovascular risk in RA [7–9]. Sokolove et al. [10] demonstrated by immunohistochemistry the presence of citrullinated proteins within the damaged endothelium in atherosclerotic plaque. RA patients positive for anti-CCP or rheumatoid factor (RF) have more endothelial dysfunction [9]. So far, it has been shown that positivity of anti-CCP antibodies is associated with the increased cIMT [11–15].

The measurement of cIMT >0.6 mm is a marker of atherosclerosis and has been suggested as a surrogate marker of subclinical atherosclerotic disease [2]. The ultrasound findings of carotid tissue are considered by some authors to be a mirror of the coronary arteries' condition [16]. The cIMT is strongly correlated with cardiovascular disease (CVD) risk factors [1, 16, 17] and clinical coronary events [1, 2, 18, 19]. RA patients with values of 0.9 mm in cIMT or the presence of atherosclerotic plaques is highly related with high CVD risk [2, 20, 21].

The cIMT in RA patients has been associated with increased levels of inflammatory molecules in independent studies focused on particular markers [2, 16, 32]. Scarce studies have explored the presence of cytokine expression and anti-CCP antibodies. The aim of this work was to evaluate the relationship of levels of anti-CCP antibodies, inflammation markers, and subclinical atherosclerosis measured by cIMT in RA patients without comorbidities.

2. Methods

2.1. Study Design. It is a cross-sectional study.

2.1.1. Patients. The study population was recruited over a period of 2 years from 2010 to 2012 and included 82 patients with RA attending an outpatient rheumatology service of the Hospital Civil "Dr. Juan I. Menchaca" of the Universidad de Guadalajara, Jalisco. To be eligible for the study, patients had to be 18 years or older and to have met the American College of Rheumatology criteria (1987) and ACR/European League against Rheumatism (EULAR) 2010 [33, 34]. For the healthy control group (HC) we included blood donors without rheumatic disease matched by gender and age and were assessed by cardiovascular risk profile and family history of CVD. The exclusion criteria for both groups were previous or current smoking history, ischemic CVD, hypertension, diabetes mellitus, thyroid disease, renal impairment, malignancy, hepatic disease, and hyperlipidemia. We also excluded patients previously treated with high doses of steroids (>10 mg/day prednisone or equivalent, including intravenous administration).

2.1.2. Definition and Assessment of cIMT. The cIMT was assessed according to the recommendations defined by the Mannheim Carotid Intima-Media Thickness and Plaque Consensus (2004–2006–2011) [17]. The cIMT was measured using a high-resolution B-mode ultrasound (US) (PHILIPS, Saronno, Italy) with a 9 MHz transducer. Briefly, with the subject in the supine position in a semidark room, longitudinal scanning was performed from the common carotid artery (CCA) to the cranial entry of the internal carotid artery (ICA). The evaluated segments of the left and right carotid arteries were the CCA, carotid bifurcation (BF), and ICA. Two segments of the CCA, one from the BF, and two from the ICA were measured, providing a total of 10 measurements per individual. Mean cIMT values were calculated for each segment of the carotid arteries. Hence, five cIMT values were obtained. All measurements were performed by a single operator.

The ultrasound images and parameters were evaluated by two expert radiologists (LNA, MFS) blinded to the clinical characteristics of patients. The cIMT was determined as a double-line pattern visualized by echography on both walls of the CCA in a longitudinal image. Two parallel lines, which consist of the leading edges of two anatomical boundaries, form the lumen-intima and media-adventitia interfaces as demonstrated in a previous study [17].

2.1.3. Clinical Assessment. A structured questionnaire was applied to each patient in order to evaluate demographic and clinical variables including disease duration and treatment. The clinical evaluation was performed by trained personnel; RA disease activity was measured by disease activity score (DAS) 28 [35], erythrocyte sedimentation rate (ESR), and posteroanterior radiographs of the hands obtained at the time of recruitment. The degree of RA progression was assessed by the Steinbrocker score of the metacarpophalangeal (MCP) joints [36].

2.1.4. Anti-CCP and Other Laboratory Measurements. ESR was measured using the Wintrobe method. The CRP levels were calculated by nephelometry; total cholesterol (TC), triglycerides (Tg), high density lipoprotein cholesterol (HDL-c), and low density lipoprotein cholesterol (LDL-c) were measured by standard techniques after centrifugation of blood samples. Cardiovascular risk ratio was calculated using atherogenic index of plasma (AIP) which was defined as TC/HDL-c [37].

Venous blood samples were collected immediately at the moment of the clinical assessment. Serum was obtained by

Table 1: Comparison of ultrasound parameters between patients with rheumatoid arthritis (RA) and healthy controls (HC).

Ultrasound parameters	HC $n = 62$	RA $n = 82$	P
Common carotid artery			
Proximal third, mm ± SD	0.51 ± 0.11	0.59 ± 0.16	0.001
Distal third, mm ± SD	0.50 ± 0.13	0.66 ± 0.24	<0.001
Bulb, mm ± SD	0.58 ± 0.20	0.68 ± 0.23	0.01
Internal carotid artery			
Proximal third, mm ± SD	0.46 ± 0.12	0.60 ± 0.15	<0.001
Distal third, mm ± SD	0.43 ± 0.12	0.57 ± 0.17	<0.001
Increased carotid intima-media thickness, n (%)	9 (14.5)	35 (42.7)	0.005
Number of segments thickened, n (%)	1.53 ± 1.91	3.20 ± 2.16	<0.001
Presence of carotid plaque, n (%)	4 (6.5)	6 (7.3)	0.83

RA, rheumatoid arthritis; HC, healthy controls. Qualitative variables are expressed as frequencies (%); quantitative variables are expressed as means ± standard deviations (SD). Comparisons between proportions were computed using Chi-square or Fisher exact test. Comparisons between means were computed with unpaired Student's t-test.

centrifugation of whole blood at 2,000 rpm for 15 minutes, and aliquots with serum were stored at −70°C for no longer than 6 months and were used for the determination of anti-CCP antibodies, IL-6, and TNFα by enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Bender MedSystem).

2.1.5. Statistical Analysis. Variables were tested for normality using the Kolmogorov-Smirnov test. Normally distributed values are presented as means with standard deviations (SD), or percentages as appropriate. Between-group differences were estimated by independent-sample Student's t-test and ANOVA test. Chi-square test (or Fisher's exact test) was used for comparing categorical variables. Pearson's correlation coefficient was calculated for cIMT, DAS28, CRP, levels of anti-CCP, IL-6, and TNFα. Risk of abnormal cIMT (>0.6 mm) in patients was quantified by an odds ratio (OR) with a 95% confidence interval. Multiple linear regression analysis was performed to assess independent associations between cIMT, clinical evaluation, and laboratory measurement. All data were analyzed using SPSS 16.0 software (SPSS Inc, Chicago, IL), considering a two-tailed level of $P < 0.05$ to be statistically significant for univariate and multivariate analysis.

2.1.6. Ethical Approval. This protocol was approved by the IRB Committee with the register 1068/10 of the Hospital Civil "Dr. Juan I. Menchaca" of the Universidad de Guadalajara, following Helsinki declaration.

3. Results

Since our main objective was to detect an increased cIMT suggesting subclinical atherosclerosis in RA subjects, the cIMT was assessed by high-resolution B-mode US in 62 HC, 45 RA patients anti-CCP positive, and 37 RA patients anti-CCP negative.

3.1. RA Patients Had Increased cIMT. The US assessment of the carotid artery between HC and patients with RA is shown in Table 1. Remarkably, the increased thickness of cIMT and carotid segments was significant between HC and RA ($P \leq 0.01$), but not in the presence of carotid plaques ($P = 0.83$). The segments measured by US were thicker in CCA, bulb, and ICA in RA patients. The mean value of cIMT was higher among the RA anti-CCP positive patients when compared with the anti-CCP negative group and HC, $P < 0.001$ (Figure 1). The OR of an increased cIMT (>0.6 mm) in RA patients was 5.68 (95% CI 2.12–15.24, $P < 0.001$) compared to HC. An OR of 4.83 (95% CI 2.27–9.81, $P < 0.001$) was obtained when comparing RA anti-CCP positive versus RA anti-CCP negative.

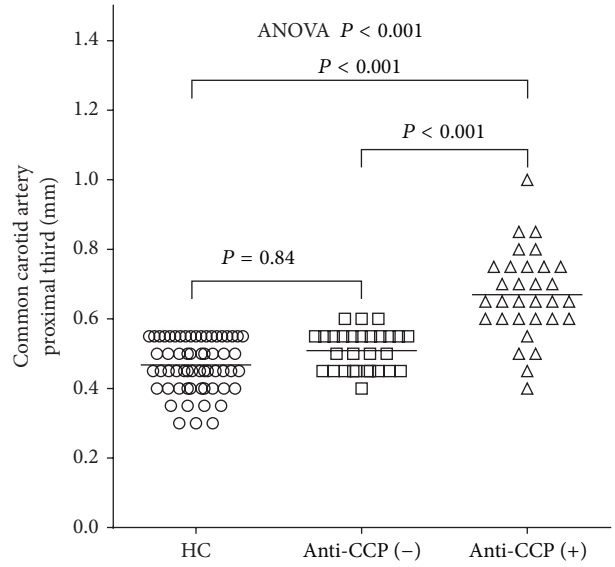

Figure 1: Carotid intima-media thickness (cIMT) in patients with rheumatoid arthritis (RA) classified by anti-CCP antibodies, compared with healthy controls (HC). Horizontal bars indicate the median. ANOVA P values indicate the significance of the overall trend while comparisons between groups are compared by Scheffé's post hoc test.

Table 2: Characteristics and comparison of RA subgroups according to anti-CCP antibodies.

Variable	RA patients		P
	Anti-CCP (−) $n = 37$	Anti-CCP (+) $n = 45$	
Age, years ± SD	41.59 ± 11.41	44.09 ± 12.73	0.36
Disease duration, years ± SD	5.44 ± 7.69	4.90 ± 6.85	0.75
DAS28, units ± SD	1.43 ± 0.95	3.14 ± 0.44	0.05
Remission (<2.6)	19 (51.35)	16 (33.3)	0.06
Hands' Steinbrocker stage, III or IV, *n* (%)	0	7 (15.6)	0.01
Lipid profile			
TC, mg/dL	175.42 ± 39.74	203.02 ± 54.53	0.02
Tg, mg/dL	143.19 ± 61.70	165.51 ± 63.14	0.05
HDL-c, mg/dL	50.60 ± 16.68	42.98 ± 11.01	0.02
LDL-c, mg/dL	106.57 ± 30.28	103.49 ± 24.25	0.63
VLDL-c, mg/dL	28.72 ± 11.64	27.44 ± 12.97	0.66
AIP: TC/HDL-c	3.78 ± 1.34	5.11 ± 2.10	0.002
Low risk, *n* (%)	29 (78.4)	20 (44.5)	
Moderate risk, *n* (%)	7 (18.9)	15 (33.3)	0.006
High risk, *n* (%)	1 (2.7)	10 (22.2)	
Serologic profile			
ESR, mm/h	21.74 ± 3.16	27.09 ± 4.96	0.07
RF, IU/mL	111.86 ± 331.47	136.74 ± 201.57	0.73
CRP, mg/L	3.75 ± 2.00	11.47 ± 7.92	<0.001
TNFα, pg/mL	40.93 ± 3.14	66.78 ± 11.98	0.003
IL-6, pg/mL	20.92 ± 12.49	82.73 ± 29.87	<0.001
DMARDs			
Methotrexate, *n* (%)	31 (83.8)	45 (100)	0.04
Chloroquine, *n* (%)	22 (59.46)	32 (71.1)	0.22
Sulfasalazine, *n* (%)	9 (24.3)	9 (20.0)	0.79
Azathioprine, *n* (%)	6 (16.2)	8 (17.8)	1.00
Corticosteroids, *n* (%)	3 (8.1)	2 (4.4)	0.65

Anti-CCP, anticyclic citrullinated peptide antibodies; RA, rheumatoid arthritis; DAS28, disease activity score; TC, total cholesterol; Tg, triglycerides; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; VLDL-c, very low density lipoprotein cholesterol; AIP, atherogenic index of plasma; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; CRP, C-reactive protein; TNFα, tumor necrosis factor alpha; IL-6, interleukin-6; DMARDs, disease-modifying antirheumatic drugs.

Qualitative variables are expressed as frequencies (%); quantitative variables are expressed as means ± standard deviations (SD). Comparisons between proportions were computed using Chi-square or Fisher exact test. Comparisons between means were computed with unpaired Student's t-test.

3.2. Increased Cardiovascular Risk Is Associated with Clinical and Laboratory Characteristics in RA Patients. The clinical and laboratory findings in the RA study groups are summarized in Table 2. In comparison between anti-CCP negative ($n = 37$) versus anti-CCP positive ($n = 45$) patients, the anti-CCP positive had higher DAS28 (1.43 ± 0.95 versus 3.14 ± 0.44 units, $P = 0.05$) with a Steinbrocker radiological stage III or IV (0 versus 15.6%, $P = 0.01$).

Higher concentrations of serum lipids were found in anti-CCP positive compared to anti-CCP negative patients. However, we could not find differences between RA and HC in lipid profile (data not shown). Anti-CCP positive patients had a moderate cardiovascular risk according to the AIP. Levels of RF, ESR, CRP, TNFα, and IL-6 were increased in the RA anti-CCP positive group. When treatment was evaluated in these RA patients, the use of methotrexate was more frequent in anti-CCP positive patients ($P = 0.04$).

3.3. Correlations between cIMT and Clinical and Laboratory Characteristics in RA Patients. There was a correlation coefficient (r) ≥ 0.3 between age, DAS28, and Tg. In contrast, the correlation coefficients between the cIMT and AIP, TC, CRP, TNFα, and IL-6 were ≥0.600 (Table 3).

3.4. Multivariate Analysis. To determine whether demographic, clinical, and serological variables were potential confounders or effect modifiers, we carried out a univariate linear regression analysis to determine which were most significantly associated with cIMT. Variables with a P value of 0.2 or less were chosen for inclusion in further multivariate

Table 3: Correlation coefficients between cIMT and characteristics of evaluated the groups.

Baseline variable	cIMT (mm)	
	r	P
Age, years	0.587	<0.001
Disease duration, years	0.018	0.88
DAS28, units	0.350	0.05
TC, mg/dL	0.720	0.002
Tg, mg/dL	0.397	0.001
HDL-c, mg/dL	−0.595	0.02
LDL-c, mg/dL	0.332	0.007
VLDL-c, mg/dL	0.267	0.03
AIP: TC/HDL-c	0.716	0.001
ESR, mm/h	−0.137	0.38
RF, IU/mL	0.214	0.04
CRP, mg/L	0.799	<0.001
TNFα, pg/mL	0.642	0.001
IL-6, pg/mL	0.751	<0.001
Anti-CCP, U/mL	0.513	0.001

cIMT, carotid intima-media thickness; RA, rheumatoid arthritis; DAS28, disease activity score; TC, total cholesterol; Tg, triglycerides; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; VLDL-c, very low density lipoprotein cholesterol; AIP, atherogenic index of plasma; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; CRP, C-reactive protein; TNFα, tumor necrosis factor alpha; IL-6, interleukin-6; anti-CCP, anticyclic citrullinated peptide antibodies.

Table 4: Multiple linear regression analysis of cIMT with selected clinical features.

Independent variables	cIMT					
	Model 1		Model 2		Model 3	
	β	P	β	P	β	P
Age, years	0.002	0.09	0.005	0.12	0.001	0.71
Disease duration, years	−0.002	0.44	−0.008	0.24	−0.004	0.29
CRP, mg/L	0.006	0.05	0.008	0.05	0.008	<0.001
Anti-CCP, U/mL	0.001	0.005	0.001	0.009	0.001	0.03
RF, IU/mL	—	—	0.005	0.93	0.003	0.43
DAS28, units	—	—	−0.019	0.20	−0.046	0.08
TNFα, pg/mL	—	—	—	—	0.001	0.67
IL-6, pg/mL	—	—	—	—	0.003	0.05
R^2	0.87	<0.001	0.86	<0.001	0.89	<0.001

cIMT, carotid intima-media thickness; CRP, C-reactive protein; anti-CCP, anticyclic citrullinated peptide antibodies; RF, rheumatoid factor; DAS28, disease activity score; TNFα, tumor necrosis factor α, IL-6, interleukin-6; R^2, multiple coefficient of determination; β, standard regression coefficient.

analyses. The results of multivariate linear regression analysis of clinical variables associated and the measurement of cIMT are shown in Table 4. After adjustment for age and disease duration, the variables associated with an increase in cIMT were CRP ($P = 0.05$) and anti-CCP ($P = 0.005$) (Model 1); after inclusion of RF and DAS28 score in Model 2, only CRP ($P = 0.05$) and anti-CCP ($P = 0.009$) were positively associated with cIMT. No significant relationships were identified with other clinical variables. When we considered TNFα and IL-6 levels in Model 3, the variables that remained associated with cIMT were CRP ($P < 0.001$) and anti-CCP ($P = 0.03$). If we excluded the anti-CCP levels from the model, this variable by itself is responsible for no clinical association with the rest of parameters included, which may be interpreted as a cardiovascular risk factor to be evaluated along with cIMT.

4. Discussion

The cardiovascular risk in RA increases with cIMT, suggesting that the pathophysiological mechanisms that underlie the progression of carotid injury in RA may differ from the general population. In order to exclude the influence of other comorbidities in the development of cardiovascular risk in RA patients, we decided to apply strict exclusion criteria for the present study, excluding obesity, smoking, hypertension, diabetes, and other comorbidities like thyroid, liver, and renal disease. Thus, we were able to discriminate the influence of other independent risk factors previously reported for increased cIMT, such as age > 65 years old (OR 3.7), male gender (OR 1.9), smokers (OR 2.2), hypertension (OR 5.0), and diabetes (OR 2.4) [12, 38, 39]. In our study, RA was an

independent cardiovascular risk factor associated with a 4-fold risk for increased cIMT, in conjunction with anti-CCP antibody levels with an OR of 4.8 (95% CI 2.27–9.85).

Although the biological role of anti-CCP is controversial, citrullinated proteins have been identified in various tissues affected in RA, such as lung tissue, vascular endothelium, endocardium, and oral mucosa [10, 40, 41]. López-Longo et al. [42] found that anti-CCP antibodies are associated with increased risk of ischemic heart disease. Also an association of anti-CCP antibodies with endothelial dysfunction has been described in RA patients [42, 43].

Despite several reports about anti-CCP and cIMT in RA (Table 5), only in few the association between anti-CCP antibodies and subclinical atherosclerosis has been evaluated. Notwithstanding, this association has only been evaluated from a "qualitative" point of view and not taking into account the effect of the serum levels of anti-CCP antibodies. In this study we demonstrated by multiple linear regression analysis, an independent association between serum levels of anti-CCP antibodies and cIMT after adjustment for age, gender, and disease activity. According to our results, for every unit of anti-CCP antibodies, there would be an increment of 0.001 mm in the cIMT (β coefficient for anti-CCP in multiple regression analysis, Table 4). These findings suggest a possible role of anti-CCP antibodies in the pathogenesis of atherosclerosis in RA, but also the relevance of their role in the prediction of cardiovascular risk in this group of patients.

In the present study, we reported that RA patients with high levels of anti-CCP antibodies have a poor clinical prognosis and subclinical cardiovascular risk, based on increased cIMT, CRP, and high levels of proinflammatory molecules such as TNFα and IL-6. Serum TNFα and IL-6 were strongly correlated with cIMT (Table 3) [44]. Furthermore, the anti-CCP positive patients had a more atherogenic lipid profile characterized by lower HDL-c and a high AIP (Table 2).

It is well known that cIMT reflects the integrity of coronary arteries [16, 45]. In this scenario we might suggest that our RA patients have subclinical atherosclerosis given that we found a greater proportion of affected carotid segments, 3 : 1, when compared with HC [43].

It is important to highlight that, unlike the present study, carotid plaques have been more commonly observed in RA patients versus matched HC. Gonzalez-Juanatey et al. [46] reported a higher frequency of carotid plaques in RA without comorbidities (34%, $n = 16$) versus HC (15%, $n = 7$), $P = 0.031$. RA patients with carotid plaques were older than HC and had longer disease duration, higher cIMT, and more frequently extra-articular manifestations.

An important issue related to the development of atherosclerosis in RA patients is to look for the causes of endothelial dysfunction. In this context, proinflammatory cytokines such as IL-6 and TNFα have been correlated with cIMT [47].

On the other hand, one point that should be addressed as possible contributor to accelerated atherosclerosis is the genetic background. In this context, HLA-DRB1*0404 is related with increased CVD risk and high levels of anti-CCP antibodies [48–50].

Genes for proinflammatory cytokines such as IL-6 and TNFα are recognized as inducers of systemic and local manifestations of RA. The contribution of IL-6-174 GG genotype in the development of severe endothelial dysfunction by flow-mediated endothelium-dependent vasodilatation in patients with RA was reported by Palomino-Morales et al. [51].

In addition, the allele A of TNFα polymorphism −308G>A (rs1800629) has been associated with a higher risk of CVD in RA patients who are carriers of at least one copy of the shared epitope [52]. These results highlight the potential implication of TNFα in the mechanisms associated with CVD in RA, as well as the improvement in CVD risk in patients treated with TNFα blockers. Gonzalez-Juanatey et al. [53] showed that short term therapy with adalimumab improved the endothelial dependent vasodilatation as well as acute phase reactants, disease activity, and AIP. On the other hand, Gonzalez-Gay et al. [54] showed that infliximab infusion was able to decrease proinflammatory cytokines such as resistin in RA patients, measured before and after (120 minutes) infliximab infusion. Also, they showed the reduction in acute phase reactants such as ESR, platelet count, and CRP when compared from disease diagnosis to time of the study.

We found an association between CRP levels and cIMT. This observation is in accordance with a previous report by Gonzalez-Gay et al. [55] in a retrospective study of RA patients without comorbidities, treated with at least one of disease-modifying antirheumatic drugs (DMARDs) during 5 years. They found a positive correlation between the maximum observed CRP (during follow-up) and current cIMT ($r = 0.37$, $P < 0.009$). This phenomenon was also observed in patients with CRP > 10 mg/L ($r = 0.316$, $P = 0.031$).

Finally, in our multivariate analysis, higher levels of CRP and levels of anti-CCP antibodies remained associated with the cIMT, independent of age and disease duration, suggesting that the possible damage to vascular endothelium in the carotid arteries is a subclinical but active process in RA. In our study, anti-CCP antibodies explained up to 80% of the variability in the cIMT; this observation has not been previously shown in studies regarding atherosclerosis and RA; we consider this observation as a strength of our study (Table 4).

One caveat of our study is the cross-sectional design, so we cannot establish a biological explanation enough to sustain the link of anti-CCP antibodies and endothelial damage; so far the anti-CCP antibodies are only considered as a clinical marker of disease. We cannot rule out the influence of cumulative disease activity measured by DAS28 and CRP in the development of subclinical atherosclerosis given the cross-sectional nature of our study.

Further studies are needed to evaluate the possible relationship between serum levels of anti-CCP and future cardiovascular events and assess whether these markers are predictive of a worse CVD outcome. A longitudinal cohort study of anti-CCP positive RA patients, measuring levels of proinflammatory cytokines (IL-6 and TNFα), may be necessary to determine if these markers are predictive of a worse clinical outcome and comorbidities such as CVD.

Table 5: Published studies relating CVD risk factors and cIMT in RA.

Reference (author, year)	Study groups and design	CVD risk factors present in studied patients	Anti-CCP/IL-6/TNFα	Conclusions
del Rincón et al. (2003) [16]	Cross-sectional RA (n = 204) HC (n = 102)	Age ≥40 yrs old	No	ESR, CRP, and RF being associated with the increased cIMT in RA patients
Gerli et al. (2005) [22]	Cross-sectional RA (n = 101) HC (n = 75)	Systemic hypertension, dyslipidemia, type 2 DM, current smokers, and family history of CVD	No	Smoking increasing the cIMT in RA patients
Hannawi et al. (2007) [23]	Cross-sectional RA (n = 40) HC (n = 40)	Current smokers	No	Higher cIMT in RA than HC; cIMT correlating with DAS28 and CRP; atherosclerotic plaques being more frequent in RA
Ciftci et al. (2008) [24]	Cross-sectional RA (n = 30) HC (n = 52)	None	No	Increased cIMT in RA versus HC; correlation between cIMT and time of evolution
Stamatelopoulos et al. (2009) [25]	Cross-sectional RA (n = 84) HC (n = 84) Type 2 DM (n = 48)	None	No	Increased cIMT in RA versus HC
Ristić et al. (2010) [26]	Cross-sectional RA (n = 42) HC (n = 32)	Current smokers	Anti-CCP	Higher cIMT in RA smokers; negative correlation with time on treatment; positive correlation with FR and ESR
Ahmed et al. (2010) [27]	Cross-sectional Early RA (n = 40) HC (n = 40)	None	No	DAS28, ESR, CRP, disease duration, steroids use, and ox-LDL associated with the presence of plaque
Södergren et al. (2010) [4]	Cross-sectional RA (n = 79) HC (n = 44)	Current smokers, family history of CVD	No	Higher cIMT in RA versus HC
El-Barbary et al. (2011) [28]	Cross-sectional RA (n = 100) HC (n = 100)	None	IL-6 TNFα Anti-CCP Anti-MCV	Positive correlation between anti-MCV with changes in cIMT, not with anti-CCP
Ajeganova et al. (2012) [29]	Prospective cohort RA	None	No	Higher cIMT associated with CRP
Targońska-Stepniak et al. (2011) [30]	Cross-sectional RA (n = 74) HC (n = 31)	Type 2 DM, Systemic hypertension	Anti-CCP	Higher cIMT associated with age, anti-CCP, erosions, and extra-articular manifestations
Akrout et al. (2012) [31]	Cross-sectional RA (n = 34) versus HC (n = 34)	None	No	Higher cIMT in RA than control; higher AIP in RA and lower HDL

Table 5: Continued.

Reference (author, year)	Study groups and design	CVD risk factors present in studied patients	Anti-CCP/IL-6/TNFα	Conclusions
Vázquez-Del Mercado Mónica (Present study)	Cross-sectional RA ($n = 60$) versus HC ($n = 62$)	None	Anti-CCP IL-6 TNFα	Levels of anti-CCP and CRP associated with the cIMT in RA in multiple linear regression

CVD, cardiovascular disease; DM, diabetes mellitus; RA, rheumatoid arthritis; HC, healthy controls; cIMT, carotid intima-media thickness; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; CRP, C-reactive protein; TNFα, tumor necrosis factor α; IL-6, interleukin-6; anti-CCP, anticyclic citrullinated peptide antibodies; ox-LDL, oxidized low density lipoprotein; anti-MCV, antimutated citrullinated vimentin; DAS28, disease activity score.

5. Conclusion

We provide evidence that levels of anti-CCP and CRP are not only markers of poor clinical prognosis in RA but also evidence of increased cIMT that correlate with the AIP in these patients. Additional research with controlled cohorts is needed to confirm these results.

Abbreviations

Anti-CCP: Anticyclic citrullinated peptides
cIMT: Carotid intima-media thickness
AIP: Atherogenic index of plasma
TNFα: Tumor necrosis factor alpha
IL-6: Interleukin-6
HC: Healthy control
DAS28: Disease activity score 28
HDL-c: High density lipoprotein cholesterol
CRP: C-reactive protein
RA: Rheumatoid arthritis
CVD: Cardiovascular disease
RF: Rheumatoid factor
ESR: Erythrocyte sedimentation rate
CCA: Common carotid artery
MCP: Metacarpophalangeal joints
US: Ultrasound
ICA: Internal carotid artery
BF: Carotid bifurcation
TC: Total cholesterol
Tg: Triglycerides
LDL-c: Low density lipoprotein cholesterol
SD: Standard deviations
OR: Odds ratio
Anti-MCV: Antimutated citrullinated vimentin
DMARDs: Disease-modifying antirheumatic drugs.

Conflict of Interests

The authors declare that there is no conflict of interests.

Authors' Contribution

Lourdes Nuñez-Atahualpa and Mauricio Figueroa-Sánchez performed and interpreted the carotid ultrasound and data analysis. Esther Guadalupe Corona-Sanchez, Beatriz Teresita Martín-Márquez, Erika Aurora Martínez-García, and Rosa Elena Navarro-Hernandez carried out the assays and participated in drafting the paper. Mónica Vázquez-Del Mercado conceived the study and participated in its design and coordination. Mónica Vázquez-Del Mercado, Laura Gonzalez-Lopez, and Jorge Ivan Gamez-Nava were responsible for the classification and clinical evaluation of RA patients. Alberto Daniel Rocha-Muñoz, Eduardo Gómez-Bañuelos, Héctor Macias-Reyes, and Mónica Vázquez-Del Mercado carried out the analysis and interpretation of data. Mónica Vázquez-Del Mercado, Eduardo Gómez-Bañuelos, María Alejandra Nuñez-Atahualpa, and Javier Andrade-Garduño wrote the final version of the paper. All authors read and approved the final paper.

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Research Article

Lack of Association between *JAK3* Gene Polymorphisms and Cardiovascular Disease in Spanish Patients with Rheumatoid Arthritis

Mercedes García-Bermúdez,[1] Raquel López-Mejías,[2] Fernanda Genre,[2] Santos Castañeda,[3] Alfonso Corrales,[2] Javier Llorca,[4] Carlos González-Juanatey,[5] Begoña Ubilla,[2] José A. Miranda-Filloy,[6] Trinitario Pina,[2] Carmen Gómez-Vaquero,[7] Luis Rodríguez-Rodríguez,[8] Benjamín Fernández-Gutiérrez,[8] Alejandro Balsa,[9] Dora Pascual-Salcedo,[9] Francisco J. López-Longo,[10] Patricia Carreira,[11] Ricardo Blanco,[2] Javier Martín,[1] and Miguel A. González-Gay[2,12]

[1] *Institute of Parasitología and Biomedicina López-Neyra, IPBLN-CSIC, 18016 Granada, Spain*
[2] *Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Disease, Rheumatology Division, Hospital Universitario Marqués de Valdecilla, IDIVAL, Avenida de Valdecilla s/n, 39008 Santander, Spain*
[3] *Rheumatology Department, Hospital Universitario La Princesa, IIS-Princesa, 28006 Madrid, Spain*
[4] *Department of Epidemiology and Computational Biology, School of Medicine, University of Cantabria, and CIBER Epidemiology and Public Health (CIBERESP), IDIVAL, 39011 Santander, Spain*
[5] *Cardiology Division, Hospital Universitario Lucus Augusti, 27003 Lugo, Spain*
[6] *Division of Rheumatology, Hospital Universitario Lucus Augusti, 27003 Lugo, Spain*
[7] *Department of Rheumatology, Hospital Universitario Bellvitge, 08907 Barcelona, Spain*
[8] *Department of Rheumatology, Hospital Clínico San Carlos, 28040 Madrid, Spain*
[9] *Department of Rheumatology, Hospital Universitario La Paz, 28046 Madrid, Spain*
[10] *Department of Rheumatology, Hospital General Universitario Gregorio Marañón, 28007 Madrid, Spain*
[11] *Department of Rheumatology, Hospital Universitario 12 de Octubre, 28041 Madrid, Spain*
[12] *Cardiovascular Pathophysiology and Genomics Research Unit, School of Physiology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg 2000, South Africa*

Correspondence should be addressed to Miguel A. González-Gay; miguelaggay@hotmail.com

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Rheumatoid arthritis (RA) is a polygenic disease associated with accelerated atherosclerosis and increased cardiovascular (CV) mortality. JAK/STAT signalling pathway is involved in autoimmune diseases and in the atherosclerotic process. JAK3 is a highly promising target for immunomodulatory drugs and polymorphisms in *JAK3* gene have been associated with CV events in incident dialysis patients. Therefore, the aim of this study was to assess the potential role of *JAK3* polymorphisms in the development of CV disease in patients with RA. 2136 Spanish RA patients were genotyped for the rs3212780 and rs3212752 *JAK3* gene polymorphisms by TaqMan assays. Subclinical atherosclerosis was evaluated in 539 of these patients by carotid ultrasonography (US). No statistically significant differences were found when each polymorphism was assessed according to carotid intima-media thickness values and presence/absence of carotid plaques in RA, after adjusting the results for potential confounders. Moreover, no significant differences were obtained when RA patients were stratified according to the presence/absence of CV events after adjusting for potential confounders. In conclusion, our results do not confirm association between *JAK3* polymorphisms and CV disease in RA.

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory rheumatic disease associated with an increased risk for cardiovascular (CV) events and CV-related deaths compared with the general population [1]. Evidence indicates that RA is an independent risk factor for premature heart disease [2]. This process can be partly explained by traditional CV risk factors [3], magnitude, and severity of a chronic inflammatory response [4], and genetic factors located inside [4] and outside the Human Leukocyte Antigen (HLA) region [5–8].

Janus kinases (JAKs) play a pivotal role in cytokine receptor signalling since they phosphorylate and activate signal transducer and activator of transcription (STAT) proteins. Several of these JAK-controlled cytokine receptor pathways are intimately involved in the initiation and progression of RA disease pathogenesis, autoimmune type-1 diabetes, systemic lupus erythematosus, and other autoimmune diseases [9–11]. The JAK/STAT pathway is a widely expressed intracellular signal transduction pathway, fundamentally important for T lymphocyte differentiation and function [12, 13]. This is of particular relevance since CD4+ T helper type 1 (TH1) cells are believed to promote atherosclerotic lesions and acute coronary syndromes, while T helper type 2 (TH2) cells likely serve an inhibitory or modulatory role [14, 15]. Furthermore, this signalling pathway controls important inflammatory processes in vascular cells, and its activation is involved in atherosclerosis and hypertension [16, 17].

JAK3 is the only Jak family member that associates with just one cytokine receptor, the common γ (γc) chain, which is exclusively used by the receptors for IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 [11]. Although JAK1, JAK2, and Tyk2 are expressed ubiquitously, JAK3 expression is restricted to hematopoietic lineage cells [18]. The genes encoding the JAK family members are located on three separate chromosomes. The *JAK1* and *JAK2* genes are located on human chromosomes 1p31.3 and 9p24. In contrast, the gene coding for JAK3 is located on human chromosome 19p13.1 [18].

Different genetic variants located in the *JAK3* gene have been associated with some inflammatory disorders including the development of CV events in incident dialysis patients [19]. Interestingly, tofacitinib, a molecule that inhibits JAK3 and JAK1 and to a lesser extent JAK2, has shown robust and sustained efficacy in patients with RA [20].

Taking into account all these considerations, the main purpose of this study was to determine, for the first time whether *JAK3* gene variants in RA patients are associated with the presence of subclinical atherosclerosis and CV events.

2. Patients and Methods

2.1. Patients and Study Protocol. A set of 2136 Spanish patients with RA were included in the present study. Blood samples were obtained from patients recruited from Hospital Lucus Augusti (Lugo), Hospital Marqués de Valdecilla (Santander), Hospital de Bellvitge (Barcelona), Hospital Clínico San Carlos, Hospital La Paz, Hospital La Princesa, Hospital Gregorio Marañón, and Hospital 12 de Octubre (Madrid). A subject's written consent was obtained in all the cases. The Ethics Committees of the corresponding hospitals approved the purpose of the work. All the patients fulfilled the 1987 American College of Rheumatology (ACR) and the 2010 classification criteria for RA [21, 22]. Patients were assessed for rs3212780 and rs3212752 *JAK3* gene variants. In addition, carotid intima-media thickness (cIMT) and presence/absence of carotid plaques were determined by carotid ultrasonography (US) in 539 of these patients.

Information on the main demographic data, clinical characteristics, CV risk factors, and CV events of patients enrolled in the study is shown in Table 1. Additionally, the 18% of these patients had experienced CV events, 75.2% were women and the mean age at the time of disease onset was 50.8 years. Definitions of CV events and traditional CV risk factors were established as previously described [4].

2.2. Genotyping. DNA from patients was obtained from peripheral blood using standard methods.

Table 1: Demographic characteristics of the RA patients.

Clinical features	% (n/N)
Patients	2136
Main characteristics	
Age at the time of disease onset (years, mean ± SD)	50.8 ± 14.8
Follow-up (years, mean ± SD)	11.6 ± 8.3
Percentage of women	75.2
Rheumatoid factor positive*	69.1 (1430/2071)
Anti-CCP antibodies positive	59.1 (1063/1799)
Shared epitope positive	62.6 (762/1217)
Erosions	55 (902/1640)
Extra-articular manifestations**	31.1 (511/1640)
Cardiovascular risk factors	
Hypertension	38.5 (810/2102)
Diabetes mellitus	12.4 (261/2102)
Dyslipidemia	36.0 (757/2102)
Obesity	18.1 (381/2102)
Smoking habit	24.5 (517/2102)
Patients with cardiovascular events	17.9 (384/2136)
Ischemic heart disease	8.4 (180/2136)
Heart failure	5.9 (126/2136)
Cerebrovascular accident	5.2 (112/2136)
Peripheral arteriopathy	2.4 (52/2136)

RA: rheumatoid arthritis; n: number of patients; SD: standard deviation; Anti-CCP antibodies: anti-cyclic citrullinated peptide antibodies.
*At least two determinations were required for analysis of this result.
**Extra-articular manifestations of the disease (if RA patients experienced at least one of the following manifestations: nodular disease, Felty's syndrome, pulmonary fibrosis, rheumatoid vasculitis, or secondary Sjögren's syndrome) [4].

Table 2: Differences in genotype and allele frequencies of *JAK3* polymorphisms between RA patients with or without cardiovascular (CV) events.

SNP	1/2	Subgroup	Genotype, *N* (%)				Allele test	
			1/1	1/2	2/2	MAF	*P**	OR [95% CI]*
rs3212780	G/**A**	Without CV events	909 (52.51)	688 (39.75)	134 (7.74)	0.28		
		With CV events	191 (50.26)	160 (42.11)	29 (7.63)	0.29	0.51	0.93 [0.75–1.06]
rs3212752	T/**C**	Without CV events	1547 (88.30)	203 (11.59)	2 (0.11)	0.06		
		With CV events	349 (90.88)	34 (8.85)	1 (0.26)	0.05	0.35	0.81 [0.52–1.26]

RA: rheumatoid arthritis. CV: cardiovascular. SNP: single nucleotide polymorphisms. MAF: minor allele frequency. OR: odds ratio. CI: confidence interval.
*Adjusted for sex, age at the time of ultrasonography study, follow-up time, and traditional CV risk factors (hypertension, diabetes mellitus, dyslipidemia, obesity, and smoking habit) by logistic regression.

The rs3212780 and rs3212752 *JAK3* polymorphisms were genotyped with TaqMan predesigned single-nucleotide polymorphism genotyping assays in a 7900 HT Real-Time polymerase chain reaction (PCR) system, according to the conditions recommended by the manufacturer (Applied Biosystems, Foster City, CA, USA). Negative controls and duplicate samples were included to check the accuracy of genotyping.

2.3. Carotid US Examination. Measurement of the cIMT and presence/absence of carotid plaques were performed in 539 patients from Lugo and Santander by carotid US. Patients from Santander were assessed using a commercially available scanner, Mylab 70, Esaote (Genoa, Italy) equipped with 7–12 MHz linear transducer and the automated software guided technique radiofrequency—Quality Intima Media Thickness in real-time (QIMT, Esaote, Maastricht, Holland)—was used [23, 24]. Patients from Lugo were assessed using high-resolution B-mode ultrasound, Hewlett Packard SONOS 5500, with a 10 MHz linear transducer as previously reported [25]. cIMT was measured at the far wall of the right and left common carotid arteries, 10 mm from the carotid bifurcation, over the proximal 15 mm-long segment. cIMT was determined as the average of three measurements in each common carotid artery. The final cIMT was the largest average cIMT (left or right). The plaque criteria in the accessible extracranial carotid tree (common carotid artery, bulb, and internal carotid artery) were focal protrusion in the lumen at least cIMT >1.5 mm, protrusion at least 50% greater than the surrounding cIMT, or arterial lumen encroaching >0.5 mm, according to Mannheim consensus criteria [26]. The carotid plaques were counted in each territory and defined as no plaque, unilateral plaque, or bilateral plaques [23, 24, 27]. Agreement between the two US methods in patients with RA was previously reported [27]. Two experts with high experience and close collaboration in the assessment of subclinical atherosclerosis in RA from Santander (AC) and Lugo (CGJ) performed the studies.

2.4. Statistical Analysis. All genotype data were checked for deviation from Hardy-Weinberg equilibrium (HWE) using http://ihg.gsf.de/cgi-bin/hw/hwa1.pl.

cIMT values are displayed as mean and standard deviation (SD). The association between genotypes and alleles of each polymorphism and cIMT values was tested using unpaired *t*-test to compare between 2 groups and one-way analysis of variance (ANOVA) to compare among more than two groups. Comparisons of means was adjusted for sex, age at the time of US study, follow-up time and traditional CV risk factors (hypertension, diabetes mellitus, dyslipidemia, obesity, and smoking habit) as potential confounders using analysis of covariance (ANCOVA).

Differences in the genotypic and allelic frequencies of each polymorphism according to the presence/absence of carotid plaques and CV events were calculated by χ^2 or Fisher tests when necessary (expected values below 5). Strength of associations were estimated using odds ratios (OR) and 95% confidence intervals (CI). Results were adjusted for sex, age at the time of US study, and traditional CV risk factors (hypertension, diabetes mellitus, dyslipidemia, obesity, and smoking habit) by logistic regression.

Statistical significance was defined as $P < 0.05$. All analyses were performed with STATA statistical software 12/SE (Stata Corp., College Station, TX, USA).

3. Results

The *JAK3* rs3212780 and rs3212752 genotype distribution were in Hardy-Weinberg equilibrium.

As shown in Table 2, no differences were observed when genotype and allele frequencies from patients with or without CV events were compared for rs3212780 and rs3212752 gene variants. Results from an adjusted logistic regression model did not show statistically significant association between rs3212780 or rs3212752 gene polymorphisms and the risk of CV events.

As shown in Table 3, no statistically significant differences were found when each polymorphism was assessed according to the evaluation of the cIMT in RA patients, after adjusting the results for sex, age at the time of US study and traditional CV risk factors (hypertension, diabetes mellitus, dyslipidemia, obesity, and smoking habit) as potential confounders. Similarly, no statistically significant differences were detected when each polymorphism was evaluated according to the presence/absence of carotid plaques in RA, after adjusting the results for potential cofounder factors specified above (Table 3).

Taking into account the implication of *JAK3* in inflammatory diseases and the relevant role of C-reactive protein (CRP) in inflammation, we assessed the potential association

Table 3: Association between *JAK3* polymorphisms and carotid intima-media thickness (cIMT) and presence/absence of carotid plaques in RA patients.

*JAK*3	Genotypes/alleles	cIMT mm		Presence versus absence of carotid plaques	
		Mean ± SD	P^*	OR [95% CI]**	P^{**}
rs3212780	GG (n = 285)	0.73 ± 0.17		Ref.	
	GA (n = 210)	0.73 ± 0.17		1.13 [0.79–1.61]	0.51
	AA (n = 44)	0.77 ± 0.22	0.38	1.54 [0.80–2.96]	0.20
	G (n = 780)	0.73 ± 0.17			
	A (n = 298)	0.74 ± 0.19	0.56	1.19 [0.91–1.56]	0.50
rs3212752	TT (n = 477)	0.73 ± 0.18		Ref.	
	TC (n = 60)	0.74 ± 0.17	0.17	0.61 [0.35–1.05]	0.15
	CC (n = 0)	—	—	—	—
	T (n = 1014)	0.74 ± 0.17			
	C (n = 60)	0.74 ± 0.17	0.17	0.62 [0.37–1.06]	0.15

RA: rheumatoid arthritis. cIMT: Carotid intima-media thickness. SD: standard deviation. OR: Odds Ratio. CI: confidence interval.
*Adjusted for sex, age at the time of ultrasonography study, follow-up time, and traditional CV risk factors (hypertension, diabetes mellitus, dyslipidemia, obesity, and smoking habit) using analysis of covariance (ANCOVA).
**Adjusted for sex, age at the time of ultrasonography study, follow-up time, and traditional CV risk factors (hypertension, diabetes mellitus, dyslipidemia, obesity, and smoking habit) by logistic regression.

Table 4: Association between *JAK3* polymorphisms and CRP levels in RA patients.

*JAK*3	Genotypes/alleles	CRP mg/L Mean ± SD	P^*
rs3212780	GG (n = 311)	15.2 ± 25.9	0.58
	GA (n = 234)	13.5 ± 20.1	
	AA (n = 58)	17.8 ± 30.6	
	G (n = 856)	14.9 ± 24.4	0.99
	A (n = 350)	14.9 ± 24.1	
rs3212752	TT (n = 534)	14.7 ± 24.4	0.97
	TC (n = 72)	14.5 ± 23.7	
	CC (n = 2)	6.6 ± 7.2	
	T (n = 1140)	14.7 ± 24.3	0.95
	C (n = 76)	14.1 ± 23.2	
Haplotypes	GT (820)	14.7 ± 24.3	0.92
	AT (304)	15.4 ± 24.9	
	AC (41)	13.1 ± 17.7	
	GC (31)	16.7 ± 30.1	

CRP: C-Reactive Protein; RA: rheumatoid arthritis; SD: standard deviation.
*Adjusted for potential confounder factors.

between *JAK3* polymorphisms and CRP levels in a representative subgroup of patients in whom CRP information was available. As shown in Table 4, we did not disclose a relationship between CRP levels neither with *JAK3* genotypes and alleles nor haplotypes.

Finally, we also evaluated whether there were differences in cIMT values and presence/absence of carotid plaques between patients positive and negative for rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide antibodies (anti-CCP) in relation to *JAK3* gene polymorphisms. We performed this study in a subgroup of patients in whom carotid ultrasound and clinical and laboratory data were available. In this regard, no significant results were obtained in any of the analyses (Tables 5, 6, 7, 8, 9, and 10).

4. Discussion

CV disease is the main cause of death in patients with RA [4]. Therefore, a better understanding of the mechanisms involved in this disorder has become of main importance. During the last years, several genetic markers have been involved in CV disease susceptibility and progression in patients with RA [4–8].

JAK3 is a potential target for immunomodulatory drugs since it is involved in key inflammatory pathways in both autoimmune and CV diseases. In accordance, several pharmaceutical companies have reported JAK inhibitors in various stages of clinical development [28], and some clinical trials are ongoing to monitor the efficacy and safety of JAK3 inhibitor tofacitinib [29, 30].

JAK3 polymorphisms have been associated with CV events in incident dialysis patients [19]. Because of that, in this study we analyzed two well-known polymorphisms rs3212780 and rs3212752 located in the *JAK3* gene. To the best of our knowledge, this is the first study performed to evaluate the potential influence of *JAK3* polymorphisms in the risk of CV disease and subclinical atherosclerosis in an RA cohort. However, we did not observe any statistically significant differences when each polymorphism was assessed according to cIMT values and presence or absence of carotid plaques in RA. Besides an absence of association with subclinical atherosclerosis, we did not observe significant differences when RA patients were stratified according to the presence or absence of CV events. The discrepancy observed between our results and the ones obtained in incident dialysis patients [19] may be explained by the fact that both populations displayed very different characteristics. In this regard, and in contrast to the population described by Sperati et al. [19], the vast

Table 5: Association between cIMT values and *JAK3* polymorphisms in RA patients stratified according to anti-CCP status.

Subgroup	*JAK*3	Genotypes/alleles	cIMT (mm) Mean ± SD	P^*
Anti-CCP positive	rs3212780	GG (n = 137)	0.73 ± 0.17	0.55
		GA (n = 97)	0.73 ± 0.18	
		AA (n = 21)	0.77 ± 0.23	
		G (n = 371)	0.73 ± 0.17	0.50
		A (n = 139)	0.74 ± 0.19	
	rs3212752	TT (n = 224)	0.73 ± 0.17	0.25
		TC (n = 31)	0.77 ± 0.18	
		CC (n = 0)	—	
		T (n = 479)	0.73 ± 0.18	0.27
		C (n = 31)	0.77 ± 0.18	
	Haplotypes	GT (n = 355)	0.73 ± 0.17	0.53
		AT (n = 124)	0.74 ± 0.19	
		AC (n = 15)	0.73 ± 0.21	
		GC (n = 16)	0.77 ± 0.17	
Anti-CCP negative	rs3212780	GG (n = 127)	0.71 ± 0.16	0.78
		GA (n = 102)	0.73 ± 0.17	
		AA (n = 22)	0.77 ± 0.19	
		G (n = 356)	0.72 ± 0.16	0.53
		A (n = 146)	0.74 ± 0.17	
	rs3212752	TT (n = 225)	0.72 ± 0.17	0.53
		TC (n = 24)	0.73 ± 0.15	
		CC (n = 0)	—	
		T (n = 474)	0.72 ± 0.17	0.54
		C (n = 24)	0.73 ± 0.15	
	Haplotypes	GT (n = 342)	0.72 ± 0.16	0.79
		AT (n = 132)	0.75 ± 0.18	
		AC (n = 14)	0.73 ± 0.17	
		GC (n = 10)	0.73 ± 0.11	

cIMT: carotid intima-media thickness; anti-CCP: anti-cyclic citrullinated peptide; RA: rheumatoid arthritis; SD: standard deviation.
*Adjusted for potential confounder factors.

Table 6: Association between cIMT values and *JAK3* polymorphisms in RA patients stratified according to RF status.

Subgroup	*JAK*3	Genotypes/alleles	cIMT (mm) Mean ± SD	P^*
RF positive	rs3212780	GG (n = 192)	0.73 ± 0.16	0.41
		GA (n = 132)	0.73 ± 0.17	
		AA (n = 26)	0.79 ± 0.25	
		G (n = 516)	0.73 ± 0.16	0.42
		A (n = 184)	0.75 ± 0.19	
	rs3212752	TT (n = 312)	0.74 ± 0.17	0.52
		TC (n = 38)	0.73 ± 0.17	
		CC (n = 0)	—	
		T (n = 662)	0.73 ± 0.17	0.54
		C (n = 38)	0.73 ± 0.17	
	Haplotypes	GT (n = 498)	0.73 ± 0.16	0.67
		AT (n = 164)	0.75 ± 0.19	
		AC (n = 20)	0.72 ± 0.19	
		GC (n = 18)	0.74 ± 0.14	
RF negative	rs3212780	GG (n = 116)	0.73 ± 0.16	0.95
		GA (n = 93)	0.74 ± 0.17	
		AA (n = 20)	0.76 ± 0.15	
		G (n = 325)	0.73 ± 0.16	0.84
		A (n = 133)	0.74 ± 0.16	
	rs3212752	TT (n = 203)	0.73 ± 0.17	0.20
		TC (n = 24)	0.78 ± 0.16	
		CC (n = 0)	—	
		T (n = 430)	0.73 ± 0.17	0.21
		C (n = 24)	0.78 ± 0.16	
	Haplotypes	GT (n = 312)	0.73 ± 0.17	0.40
		AT (n = 118)	0.74 ± 0.17	
		AC (n = 15)	0.76 ± 0.16	
		GC (n = 9)	0.81 ± 0.16	

cIMT: carotid intima-media thickness; RA: rheumatoid arthritis; RF: rheumatoid factor; SD: standard deviation.
*Adjusted for potential confounder factors.

majority of our RA patients were not on dialysis due to end stage renal disease as the final stage of a chronic kidney disease. Additionally, the population assessed in that study was very heterogeneous, including both black and white individuals.

Nevertheless, even though our results are negative, we feel that these negative data are of potential interest and they may be of help to establish future lines of research. Further studies aimed at determining the potential influence of polymorphisms located in genes implicated in the inflammatory pathways on the risk of CV disease in RA are warranted.

5. Conclusion

Our results do not confirm association between *JAK3* polymorphisms and CV disease in RA.

Disclosure

Dr. Javier Martín and Dr. Miguel A. González-Gay shared senior authorship in this study.

Conflict of Interests

The authors declare that they have no conflict of interests.

Authors' Contributions

Mercedes García-Bermúdez, Raquel López-Mejías, and Fernanda Genre carried out genotyping, participated in the design of the study and data analysis and helped to draft the paper. Santos Castañeda and Benjamín Fernández-Gutiérrez have been involved in the acquisition and interpretation of data and in revising it critically for important intellectual content. Alfonso Corrales and Carlos González-Juanatey performed the carotid US examination and they have been

Table 7: Association between presence/absence of carotid plaques and *JAK3* polymorphisms in anti-CCP positive RA patients.

Subgroup	Presence of carotid plaques	*JAK3*	Genotypes/alleles	*n* (%)	Presence of carotid plaques	*JAK3*	Genotypes/alleles	*n* (%)	*P**	OR* [95% CI]
Anti-CCP positive	Yes	rs3212780	GG	76 (57.1)	No	rs3212780	GG	60 (49.6)	—	Ref.
			GA	44 (33.1)			GA	53 (43.8)	0.07	0.57 [0.14–1.03]
			AA	13 (9.8)			AA	8 (6.6)	0.72	1.21 [0.42–3.47]
			G	196 (73.7)			G	173 (71.5)	—	Ref.
			A	70 (26.3)			A	69 (28.5)	0.42	0.83 [0.53–1.29]
		rs3212752	TT	118 (88.7)		rs3212752	TT	104 (85.9)	—	Ref.
			TC	15 (11.3)			TC	17 (14.0)	0.36	0.67 [0.29–1.56]
			CC	—			CC	—	—	—
			T	251 (94.4)			T	225 (93.0)	—	Ref.
			C	15 (5.6)			C	17 (7.0)	0.38	0.69 [0.31–1.55]
		Haplotypes	GT	188 (70.1)		Haplotypes	GT	164 (67.8)	—	Ref.
			AT	63 (23.7)			AT	61 (25.2)	0.59	0.88 [0.55–1.40]
			AC	7 (2.6)			AC	8 (3.3)	0.24	0.49 [0.15–1.58]
			GC	8 (3.0)			GC	9 (3.7)	0.81	0.88 [0.29–2.59]

Anti-CCP: anti-cyclic citrullinated peptide; RA: rheumatoid arthritis; OR: odds ratio; CI: confidence interval.
*Adjusted for potential confounder factors.

Table 8: Association between presence/absence of carotid plaques and *JAK3* polymorphisms in anti-CCP negative RA patients.

Subgroup	Presence of carotid plaques	*JAK3*	Genotypes/alleles	*n* (%)	Presence of carotid plaques	*JAK3*	Genotypes/alleles	*n* (%)	*P**	OR* [95% CI]
Anti-CCP negative	Yes	rs3212780	GG	59 (45.7)	No	rs3212780	GG	69 (57.5)	—	Ref.
			GA	57 (44.2)			GA	43 (35.8)	0.20	1.50 [0.81–2.80]
			AA	13 (10.1)			AA	8 (6.7)	0.72	1.21 [0.41–3.65]
			G	175 (67.8)			G	181 (75.4)	—	Ref.
			A	83 (32.2)			A	59 (24.6)	0.32	1.26 [0.79–2.00]
		rs3212752	TT	119 (93.0)		rs3212752	TT	104 (87.4)	—	Ref.
			TC	9 (7.0)			TC	15 (12.6)	0.23	0.53 [0.19–1.47]
			CC	—			CC	—	—	—
			T	247 (96.5)			T	223 (93.7)	—	Ref.
			C	9 (3.5)			C	15 (6.3)	0.24	0.55 [0.21–1.48]
		Haplotypes	GT	169 (66.0)		Haplotypes	GT	173 (72.7)	—	Ref.
			AT	78 (30.0)			AT	50 (21.0)	0.16	1.42 [0.87–2.30]
			AC	5 (2.0)			AC	9 (3.8)	0.16	0.40 [0.11–1.45]
			GC	4 (1.6)			GC	6 (2.5)	0.93	1.06 [0.26–4.43]

Anti-CCP: anti-cyclic citrullinated peptide; RA: rheumatoid arthritis; OR: odds ratio; CI: confidence interval.
*Adjusted for potential confounder factors.

Table 9: Association between presence/absence of carotid plaques and *JAK3* polymorphisms in RF positive RA patients.

Subgroup	Presence of carotid plaques	*JAK3*	Genotypes/alleles	*n* (%)	Presence of carotid plaques	*JAK3*	Genotypes/alleles	*n* (%)	*P**	OR* [95% CI]
RF positive	Yes	rs3212780	GG	105 (57.1)	No	rs3212780	GG	86 (52.4)	—	Ref.
			GA	63 (34.2)			GA	68 (41.5)	0.08	0.64 [0.39–1.05]
			AA	16 (8.7)			AA	10 (6.1)	0.96	1.02 [0.41–2.56]
			G	273 (74.2)			G	240 (73.2)	—	Ref.
			A	95 (25.8)			A	88 (26.8)	0.30	0.82 [0.56–1.19]
		rs3212752	TT	170 (92.4)		rs3212752	TT	139 (84.8)	—	Ref.
			TC	14 (7.6)			TC	25 (15.2)	0.08	0.50 [0.24–1.07]
			CC	—			CC	—	—	—
			T	354 (96.2)			T	303 (92.4)	—	Ref
			C	14 (3.8)			C	25 (7.6)	0.09	0.52 [0.25–1.10]
		Haplotypes	GT	265 (72.0)		Haplotypes	GT	229 (69.8)	—	Ref.
			AT	89 (24.2)			AT	74 (22.6)	0.60	0.90 [0.61–1.33]
			AC	6 (1.6)			AC	14 (4.3)	0.06	0.33 [0.11–1.10]
			GC	8 (2.2)			GC	11 (3.4)	0.63	0.78 [0.28–2.15]

RF: rheumatoid factor; RA: rheumatoid arthritis; OR: odds ratio; CI: confidence interval.
*Adjusted for potential confounder factors.

Table 10: Association between presence/absence of carotid plaques and *JAK3* polymorphisms in RF negative RA patients.

Subgroup	Presence of carotid plaques	*JAK3*	Genotypes/alleles	*n* (%)	Presence of carotid plaques	*JAK3*	Genotypes/alleles	*n* (%)	*P**	OR* [95% CI]
RF negative	Yes	rs3212780	GG	57 (46.0)	No	rs3212780	GG	60 (57.7)	—	Ref.
			GA	55 (44.3)			GA	37 (35.6)	0.13	1.64 [0.86–3.14]
			AA	12 (9.7)			AA	7 (6.7)	0.58	1.39 [0.4–4.40]
			G	169 (68.1)			G	157 (75.5)	—	Ref.
			A	79 (31.9)			A	51 (24.5)	0.20	1.36 [0.84–2.22]
		rs3212752	TT	111 (90.2)		rs3212752	TT	91 (88.3)	—	Ref.
			TC	12 (9.8)			TC	12 (11.7)	0.45	0.69 [0.26–1.80]
			CC	—			CC	—	—	—
			T	234 (95.1)			T	194 (94.2)	—	Ref.
			C	12 (4.9)			C	12 (5.8)	0.46	0.71 [0.28–1.79]
		Haplotypes	GT	163 (66.3)		Haplotypes	GT	150 (72.8)	—	Ref.
			AT	71 (28.9)			AT	44 (21.4)	0.16	1.43 [0.86–2.40]
			AC	8 (3.3)			AC	7 (3.4)	0.71	0.79 [0.23–2.66]
			GC	4 (1.6)			GC	5 (2.4)	0.71	0.76 [0.18–3.14]

RF: rheumatoid factor; RA: rheumatoid arthritis; OR: odds ratio; CI: confidence interval.
*Adjusted for potential confounder factors.

involved in the acquisition, interpretation of data, and coordination and helped to draft the paper. Javier Llorca carried out the analysis and interpretation of the data. Begoña Ubilla, José A. Miranda-Filloy, Trinitario Pina, Carmen Gómez-Vaquero, Luis Rodríguez-Rodríguez, Alejandro Balsa, Dora Pascual-Salcedo, Francisco J. López-Longo, Patricia Carreira, and Ricardo Blanco participated in the acquisition and interpretation of data and helped to draft the paper. Javier Martín and Miguel A. González-Gay have made substantial contributions to conception and design of the study, acquisition of data, and coordination and helped to draft the paper and have given final approval of the version to be published. Mercedes García-Bermudez, Raquel López-Mejías and Fernanda Genre had equal contribution.

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Research Article

EULAR Task Force Recommendations on Annual Cardiovascular Risk Assessment for Patients with Rheumatoid Arthritis: An Audit of the Success of Implementation in a Rheumatology Outpatient Clinic

Eirik Ikdahl,[1] Silvia Rollefstad,[1] Inge C. Olsen,[1] Tore K. Kvien,[2] Inger Johanne Widding Hansen,[3] Dag Magnar Soldal,[3] Glenn Haugeberg,[3] and Anne Grete Semb[1]

[1] *Preventive Cardio-Rheuma Clinic, Department of Rheumatology, Diakonhjemmet Hospital, P.O. Box 23 Vinderen, 0319 Oslo, Norway*
[2] *Department of Rheumatology, Diakonhjemmet Hospital, P.O. Box 23 Vinderen, 0319 Oslo, Norway*
[3] *Department of Rheumatology, Hospital of Southern Norway Trust, P.O. Box 416, 4604 Kristiansand, Norway*

Correspondence should be addressed to Eirik Ikdahl; e-ikdahl@diakonsyk.no

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Objective. EULAR recommendations for cardiovascular disease (CVD) risk management include annual CVD risk assessments for patients with rheumatoid arthritis (RA). We evaluated the recording of CVD risk factors (CVD-RF) in a rheumatology outpatient clinic, where EULAR recommendations had been implemented. Further, we compared CVD-RF recordings between a regular rheumatology outpatient clinic (RegROC) and a structured arthritis clinic (AC). *Methods*. In 2012, 1142 RA patients visited the rheumatology outpatient clinic: 612 attended RegROC and 530 attended AC. We conducted a search in the patient journals to ascertain the rate of CVD-RF recording. *Results*. The overall CVD-RF recording rate was 40.1% in the rheumatology outpatient clinic, reflecting a recording rate of 59.1% in the AC and 23.6% in the RegROC. The odds ratios for having CVD-RFs recorded for patients attending AC compared to RegROC were as follows: blood pressure: 12.4, lipids: 5.0-6.0, glucose: 9.1, HbA1c: 6.1, smoking: 1.4, and for having all the CVD-RFs needed to calculate the CVD risk by the systematic coronary risk evaluation (SCORE): 21.0. *Conclusion*. The CVD-RF recording rate was low in a rheumatology outpatient clinic. However, a systematic team-based model was superior compared to a RegROC. Further measures are warranted to improve CVD-RF recording in RA patients.

1. Introduction

The mortality gap between patients with rheumatoid arthritis (RA) and the general population is expanding, a process that is primarily driven by cardiovascular disease (CVD) [1]. Although inflammation has been shown to be a key component in the development of CVD in RA patients [2], there is also a high prevalence of traditional CVD risk factors (CVD-RF) in this patient group [3–6]. Indeed, it has been clearly documented in the general population that if CVD-RFs are identified early and treated successfully, many deaths from CVD may be prevented [7]. Such data are however not available for patients with RA.

The 2010 European League Against Rheumatism (EULAR) task force recommendations for CVD risk management [8], and a more recent updated evidence review [9], propose annual CVD risk assessment of RA patients. Age, gender, and smoking status are already a part of the traditional disease monitoring in the rheumatology setting and thus, as stated by the EULAR task force, a complete CVD risk assessment can easily be incorporated into a routine visit to monitor RA by measuring blood pressure (BP) and adding nonfasting lipids to regular laboratory tests. However, implementation of evidence-based CVD prevention recommendations into clinical practice can be

challenging [10, 11] and evidence-practice gaps are persisting [12].

Recording of CVD-RFs is a cornerstone in CVD risk assessments. Therefore, our aim was to evaluate the rate of CVD-RF recording in a rheumatology outpatient clinic that had implemented the recommendations on annual CVD risk assessment for RA patients. Furthermore, we wanted to compare the rate of CVD-RF recording in an arthritis clinic (AC), which is a novel clinical model where CVD-RF recording was performed in a structured, interdisciplinary manner versus a regular rheumatology outpatient clinic (RegROC) that did not include a specific approach to CVD-RF recording.

2. Patients and Methods

2.1. Patient Population. In 2012, 1142 patients diagnosed with RA fulfilling the ACR/EULAR 2010 criteria [13], visited the rheumatology outpatient clinic of the Hospital of Southern Norway. This outpatient clinic had established an AC, which was a structured clinical model for rheumatic joint disease monitoring. In the AC, work flow was divided into a treatment line with clearly defined work tasks for all health personnel (medical secretaries, nurses, and physicians) involved in the rheumatology consultation. There were no specific inclusion criteria into the AC, and allocation to this clinical model was based solely on the treating outpatient clinic rheumatologist's subjective evaluation of a patient's rheumatic disease. Due to capacity restrictions, only about half of the patients visiting this rheumatology outpatient clinic could be allocated to the AC. Patients who were not invited to the AC attended RegROC consultations.

2.2. Recording of CVD-RFs. In 2011, the rheumatology outpatient clinic of the Hospital of Southern Norway implemented the 2010 EULAR recommendations which stated that RA patients should have annual CVD risk assessments. The CVD risk assessment included the recording and evaluation of lipids (total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), and triglycerides (TG)), fasting glucose, glycated haemoglobin (HbA1c), and blood pressure (BP). Also, comorbidity, smoking status, medication, and history of CVD were recorded by patient self-reporting on computer screens.

In the AC, work tasks related to annual CVD-RF recording were structured as follows: (1) medical secretaries ordered lipid measurements, fasting glucose, and HbA1c as part of routine rheumatology laboratory tests, (2) patient self-reporting on computer screens was performed in the waiting room, prior to the rheumatology consultation, (3) BP measurement was incorporated into the traditional rheumatology nurse consultation, and (4) physicians assessed CVD risk from data available in the patient journal.

The rheumatology outpatient clinic's standard of annual CVD risk assessment was also applied to RA patients attending RegROC consultations, although various work tasks in CVD-RF recording and assessment in this clinical model were not designated to specific personnel.

2.3. Evaluation of Recording of CVD-RFs. We conducted a thorough search for CVD-RFs in the patient journals of all the 1142 RA patients, including recordings of BP measurements, cardioprotective medication, CVD comorbidity, and smoking status from any rheumatology consultation conducted in 2012. Regarding laboratory measurements (lipids, fasting blood glucose, and HbA1c), we allowed the measurements to be recorded at any time in the span of ±2 weeks of any rheumatology consultation in 2012.

Subsequently, we divided the 1142 RA patients attending the rheumatology outpatient clinic into two groups, those attending the RegROC and those attending the AC, and compared the rate of CVD-RF recording between the two clinical models.

The systematic coronary risk evaluation (SCORE) is a composite algorithm including age, sex, total cholesterol, systolic BP, and smoking status and provides a 10-year risk estimate for a fatal coronary event [14]. In the absence of national guidelines, EULAR recommends the use of the SCORE algorithm for CVD risk assessment [15]. Accordingly, we considered the patient journal to have a complete CVD-RF profile when the variables included in the SCORE algorithm were recorded.

Finally, to evaluate if an allocation bias to either clinic based on the patients' CVD risk profile existed, we compared the levels of the various CVD-RFs in patients attending the AC versus patients attending RegROC.

2.4. Statistics. The data are presented as crude data and the results are expressed as mean ± SD and median (IQR) for normally and non-normally distributed characteristics, respectively. Mann-Whitney U test was used for comparison of the data. The odds ratio [OR with 95% confidence interval (95% CI)] for the CVD-RF being recorded was calculated by logistic regression adjusting for age and gender. Data analyses were performed using IBM SPSS version 20.

3. Results

3.1. Rate of CVD-RF Recording. The evaluation of CVD-RF recording in the rheumatology outpatient clinic, as well as in the two clinical models, AC and RegROC, is presented in Table 1. Figure 1 shows the recording rate for the various CVD-RFs. For the 1142 RA patients attending the rheumatology outpatient clinic at the Hospital of Southern Norway in 2012, the total rate of recording of CVD-RFs was 40.1% and only 26.9% ($n = 307$) of the patients had a complete CVD-RF profile. More specifically, the recording rates for the various CVD-RFs were BP: 50.4%, the various lipids: 41.3–47.0%, fasting blood glucose: 30.7%, HbA1c: 33.7%, smoking status: 66.2%, cardioprotective medication: 22.0%, and CVD comorbidities: 20.2%.

For patients attending the AC, the total CVD-RF recording rate was 59.1%, and the corresponding rate for patients attending RegROC consultations was 23.6%. The odds ratio (OR) for the recording of specific CVD-RFs in patients attending the AC ($n = 530$) versus patients attending RegROC was consistently significant for all CVD-RFs

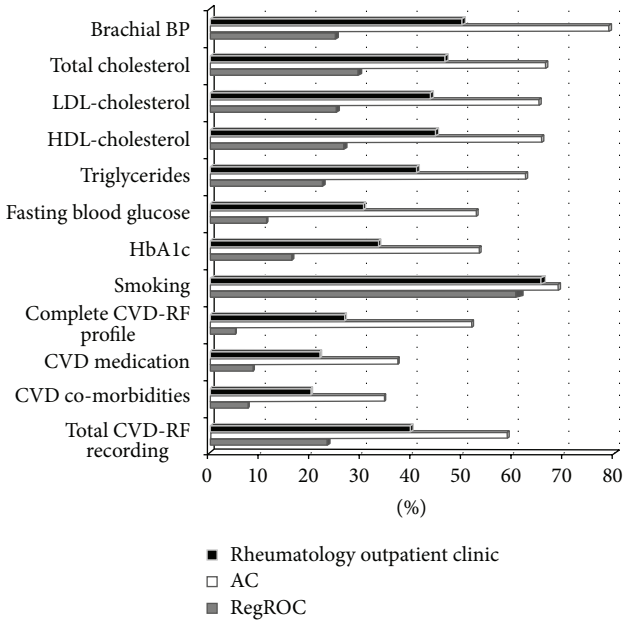

Figure 1: Recording rate of cardiovascular risk factors, medication, and co-morbidity. ROC: rheumatology outpatient clinic of the Hospital of Southern Norway, RegROC: regular rheumatology outpatient clinic, AC: arthritis clinic, BP: blood pressure, LDL: low-density lipoprotein, HDL: high-density lipoprotein, HbA1c: glycated haemoglobin, CVD-RF: Cardiovascular disease risk factor, complete CVD-RF profile: age, sex, total cholesterol levels, smoking status and systolic blood pressure, CVD: cardiovascular disease, CVD medication: antihypertensives and statins, CVD co-morbidities: hypertension, angina pectoris, acute myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, cerebrovascular accident, and premature familiar cardiovascular disease.

(Table 1). Finally, the OR for having a complete CVD-RF profile was 21.0 (95% CI = 14.0; 31.3).

3.2. Level of Recorded CVD-RFs. When comparing the levels of CVD-RFs in patients attending consultations in the AC versus those attending the RegROC (Table 2), we found a significant age and gender difference ($P = 0.05$ and $P = 0.002$, resp.). However, no significant differences concerning BP, lipids, fasting blood glucose, HbA1c, use of cardioprotective medication, presence of CVD comorbidity, the Modified Health Assessment Questionnaire (MHAQ) score, disease duration, or the estimated risk of future coronary events (calculated by SCORE) were revealed between patients attending consultations in the AC and RegROC.

4. Discussion

The implementation of effective CVD-RF recording and CVD risk assessment in daily clinical rheumatological practice is an important first step in the process of augmenting the prevention of CVD in RA patients. We have shown that the overall CVD-RF recording was poor in a rheumatology outpatient clinic despite having a standard of annual CVD risk assessment in line with EULAR recommendations. However, the effectiveness of CVD-RF recording was enhanced when patients attended a structured clinical model with clearly defined work tasks, such as the AC.

Nevertheless, even in the AC, the CVD-RF recording was far from complete. In a study from 9 European countries, Ludt et al. [16] reported an impressive rate of CVD-RF recording in 3723 high CVD risk patients from the general (non-RA) population; 92.5% had BP, 83.9% had cholesterol, 75.5% had glucose, and 77.3% had smoking status recorded in their patient journals. When comparing our results to these findings, we conclude that the implementation of systematic, team-based model for RA patients, and CVD-RF recording remained suboptimal. Accordingly, we argue that further measures are necessary to optimize the rate of CVD-RF recording in rheumatology outpatient clinics. In this regard, orchestrated efforts to implement guidelines and recommendations have been shown to be more effective than single strategies [17]. Educating health personnel may be an important measure in such implementation schemes [17, 18]. Indeed, it has been shown that education meetings (conferences, workshops, seminars, symposia, and courses for health professionals) and educational outreach visits by trained persons to health professionals can increase the uptake of recommended care by as much as 10% and 21%, respectively [12, 19]. We advocate that future attempts to implement CVD-RF recording and CVD risk assessment should be undertaken as a part of orchestrated efforts including campaigns and lectures/meetings on CVD risk and CVD-RF for rheumatic health personnel.

Rheumatology nurses played an important role in CVD-RF recording in the AC. The role of nurse-based consultations in rheumatology outpatient clinics has increasingly been acknowledged as they have been shown to bring added value to patients' outcomes at a lower price [20, 21]. Indeed, a recently published study by Primdahl et al. showed that CVD-RF recording in RA patients can be achieved in a 30-minute nursing consultation in addition to the patients' normal follow-up visits [6]. Furthermore, in diabetes clinics, nurse consultations focusing on CVD risk are common and beneficial effects on CVD-RF levels have been reported [22, 23]. Unfortunately, providing all RA patients with an additional 30-minutes consultation to screen for CVD-RFs would result in high cost and be time-consuming. On the contrary, incorporating the CVD-RF screening into traditional rheumatology consultations would be more cost-efficient [24]. However, these important observations concerning the role of the nurse in CVD risk management should undoubtedly be taken into consideration when designing optimal and feasible strategies for CVD prevention in RA patients.

Smoking status, a disease variable that has traditionally been a part of clinical rheumatological practice, was the only CVD-RF that was nearly as effectively recorded in the RegROC as in the AC. This finding underlines the importance of a structured approach to the implementation of disease variables and work processes that are not part of the traditional rheumatology practice, in this case CVD-RF recording.

Table 1: Cardiovascular risk factors recorded in patients attending a rheumatology outpatient clinic.

Risk factor recorded in the patient journal n (%)	ROC (n = 1142)	AC (n = 530)	RegROC (n = 612)	OR* (95% CI)	AC versus RegROC P value*
Blood pressure	576 (50.4)	421 (79.4)	155 (25.3)	12.36 (9.27, 16.48)	<0.001
Total cholesterol	537 (47.0)	354 (66.8)	183 (29.9)	5.02 (3.89, 6.48)	<0.001
LDL-cholesterol	503 (44.1)	347 (65.5)	156 (25.5)	5.87 (4.53, 7.62)	<0.001
HDL-cholesterol	515 (45.1)	350 (66.0)	165 (27.0)	5.59 (4.31, 7.23)	<0.001
Triglycerides	472 (41.3)	333 (62.8)	139 (22.7)	6.02 (4.63, 7.82)	<0.001
Fasting blood glucose	351 (30.7)	281 (53.0)	70 (11.4)	9.11 (6.71, 12.35)	<0.001
HbA1c	385 (33.7)	284 (53.6)	101 (16.5)	6.10 (4.62, 8.04)	<0.001
Smoking	756 (66.2)	378 (69.3)	378 (61.8)	1.44 (1.12, 1.85)	0.05
Complete risk profile included in the SCORE algorithm	307 (26.9)	276 (52.1)	31 (5.1)	20.97 (14.04, 31.33)	<0.001
Cardioprotective medication	251 (22.0)	198 (37.4)	53 (8.7)	6.31 (4.52, 8.82)	<0.001
CVD comorbidities	231 (20.2)	184 (34.7)	47 (7.7)	6.43 (4.53, 9.14)	<0.001

*Adjusted for age and gender.
ROC: rheumatology outpatient clinic of the Hospital of Southern Norway, RegROC: regular rheumatology outpatient clinic, AC: arthritis clinic, OR: odds ratio, CI: confidence interval, CVD: Cardiovascular disease, LDL: low-density lipoprotein, HDL: high-density lipoprotein, HbA1c: glycated haemoglobin, complete risk profile: complete lipid values (total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides), smoking, and blood pressure, SCORE: systematic coronary risk evaluation, cardioprotective medication: antihypertensives and statins, and CVD comorbidities: hypertension, angina pectoris, acute myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, cerebrovascular accident, and premature familiar cardiovascular disease.

Considering the low recording rate of cardioprotective medication and presence of CVD comorbidity, we may not have the statistical power to fully exclude the possibility that the patients in the AC had a higher CVD burden that lead to an increased focus on CVD-RF recording in these patients. However, as the AC was primarily a clinical model for rheumatologic disease evaluation, we argue that such allocation bias is not likely. Moreover, as we did not have information concerning the time spent to assess and manage patients in the two clinical models, there is a potential that there was more time per patient in the AC than in the RegROC, which may have improved the feasibility of CVD-RF recording in the AC. A further potential limitation to our study lies in that it did not include rheumatology disease activity measures. Nevertheless, as we found no significant differences in MHAQ or disease duration between AC and RegROC, we can presumably rule out the possibility that the differences in CVD-RF recording rates in the AC and RegROC were biased by more frequent CVD-RF recording in RA patients with higher disease related disability and longer disease duration.

This audit provides an insight into the success rate of implementation of guidelines and recommendations on CVD risk management into the speciality of rheumatology. Furthermore, we have highlighted the important elements that may optimize the implementation of such schemes. However, as this audit reflects what occurs in one institution in Norway, one might raise questions concerning the generalizability of our results. More elaborate studies and projects are therefore warranted to further uncover the optimal approach to implementation of CVD risk management into the field of rheumatology.

5. Conclusion

We conclude that the overall CVD-RF recordings were low in a rheumatology outpatient clinic. Despite the increased rate of CVD-RF recording in a structured team-based model compared to a regular clinic; it was still suboptimal. There is a huge unmet need for systems improving CVD-RF recording, which is the first step in the management of the high CVD risk in patients with RA.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Table 2: Traditional CVD risk factors, medication, and CVD comorbidities.

	AC group (n = 530)	RegROC (n = 612)	P value
Sex (male) n (%)	151 (29.2)	208 (34.3)	0.05
Age years (median, IQR)	62.0 (53.0–70.0)	66.0 (52.8–70.0)	0.002
Disease duration in years (median, IQR)	7.0 (3.0–17.0)	7.0 (3.0–15.0)	0.10
MHAQ (mean ± SD)	0.47 ± 0.47	0.51 ± 0.53	0.13
CVD risk factors (mean ± SD)			
Total cholesterol (mmol/L)	5.55 ± 1.19	5.42 ± 1.20	0.24
LDL-c (mmol/L)	3.32 ± 1.03	3.21 ± 1.00	0.27
HDL-c (mmol/L)	1.66 ± 0.50	1.69 ± 0.51	0.64
Triglycerides (mmol/L)	1.40 ± 0.74	1.49 ± 0.87	0.32
Systolic BP (mmHg)	137.2 ± 19.3	137.1 ± 20.1	0.96
Diastolic BP (mmHg)	82.1 ± 9.3	82.7 ± 11.1	0.49
Fasting glucose (mmol/L)	5.71 ± 1.64	5.75 ± 1.60	0.85
HbA1c (%)	5.71 ± 0.85	5.74 ± 0.83	0.79
Smoking n (%)[†]	61/367 (16.6)	56/378 (14.8)	0.50
CVD risk assessment (mean ± SD)			
10-year risk calculated by SCORE in %	4.00 ± 4.5	3.71 ± 3.48	0.64
CVD medication/comorbidities: n/N (%)[†] n: patients using medication/having CVD N: patients with medication/CVD recorded			
Statins	54/198 (27.3)	12/53 (22.6)	0.50
Antihypertensives	56/198 (28.3)	14/53 (26.4)	0.79
Hypertension	48/184 (26.1)	10/47 (21.3)	0.50
Angina pectoris	4/184 (2.2)	1/47 (2.1)	0.98
AMI	4/184 (2.2)	0/47 (0)	0.31
PCI/CABG	6/184 (3.3)	1/47 (2.1)	0.69
CVA	5/184 (2.7)	4/47 (8.5)	0.07
Premature familiar CVD	36/184 (19.6)	4/47 (8.5)	0.07

[†]Presented as the fraction and percent in patients who had cardiovascular risk factors recorded.
RegROC: regular rheumatology outpatient clinic, AC: arthritis clinic, MHAQ: Modified Health Assessment Questionnaire, CVD: Cardiovascular disease, AMI: acute myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft surgery, CVA: cerebrovascular accident, CVD: cardiovascular disease, LDL-c: low-density lipoprotein cholesterol, HDL-c: high-density lipoprotein cholesterol, BP: blood pressure, HbA1c: glycated haemoglobin, and SCORE: systematic coronary risk evaluation.

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Research Article

Increased Incidence of Atrial Fibrillation in Patients with Rheumatoid Arthritis

A. Kirstin Bacani,[1] Cynthia S. Crowson,[1,2] Véronique L. Roger,[2,3] Sherine E. Gabriel,[1,2] and Eric L. Matteson[1,2]

[1]*Division of Rheumatology, Department of Internal Medicine, Mayo Clinic, Rochester, MN 55905, USA*
[2]*Department of Health Sciences Research, Mayo Clinic, Rochester, MN 55905, USA*
[3]*Division of Cardiology, Department of Internal Medicine, Mayo Clinic, Rochester, MN 55905, USA*

Correspondence should be addressed to Cynthia S. Crowson; crowson@mayo.edu

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Objective. To investigate the incidence of atrial fibrillation (AF) among patients with rheumatoid arthritis (RA) compared to the general population. *Methods*. A population-based inception cohort of Olmsted County, Minnesota, residents with incident RA in 1980–2007 and a cohort of non-RA subjects from the same population base were assembled and followed until 12/31/2008. The occurrence of AF was ascertained by medical record review. *Results*. The study included 813 patients with RA and 813 non-RA subjects (mean age 55.9 (SD:15.7) years, 68% women in both cohorts). The prevalence of AF was similar in the RA and non-RA cohorts at RA incidence/index date (4% versus 3%; $P = 0.51$). The cumulative incidence of AF during follow-up was higher among patients with RA compared to non-RA subjects (18.3% versus 16.3% at 20 years; $P = 0.048$). This difference persisted after adjustment for age, sex, calendar year, smoking, and hypertension (hazard ratio: 1.46; 95% CI: 1.07, 2.00). There was no evidence of a differential impact of AF on mortality in patients with RA compared to non-RA subjects (hazard ratio 2.5 versus 2.8; interaction $P = 0.31$). *Conclusion*. The incidence of AF is increased in patients with RA, even after adjustment for AF risk factors. AF related mortality risk did not differ between patients with and without RA.

1. Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease associated with an increased risk of cardiovascular disease and premature mortality [1, 2]. The primary research focus in vascular disease in patients with RA has been on coronary heart disease. Recent publications have examined the relationship between atrial fibrillation (AF) and RA with variable results [3, 4]. We examined the incidence, prevalence, and mortality impact of AF in a population-based inception cohort of patients with RA and a comparator population from the same community.

2. Methods

2.1. Study Population. The population of Olmsted County, Minnesota, is well-suited for investigation of the epidemiology of RA and AF because comprehensive medical records on all residents are available through a record linkage system. The potential of this data system for use in population-based studies has been described [5].

An inception cohort of all cases of RA diagnosed between January 1, 1980, and December 31, 2007 ($n = 813$), among Olmsted County residents ≥18 years of age was assembled as described [6]. Incidence date was defined as the earliest date at which the patient fulfilled at least 4 of the 7 American College of Rheumatology 1987 classification criteria for RA [7]. All cases were followed up longitudinally through their entire medical records until death, migration, or 12/31/2008. A comparison cohort of Olmsted County residents without RA with similar age, sex, and calendar year was identified. The index date for each non-RA subject was defined as the RA incidence date of the corresponding patient with RA.

The medical records of each cohort were electronically crossmatched with a database of electrocardiogram (ECG)

Table 1: Characteristics of 813 patients with rheumatoid arthritis (RA) and 813 subjects without RA.

Characteristic	RA (n = 813)	Non-RA (n = 813)	P value
Age at incidence/index, years, mean ± SD	55.9 ± 15.7	55.9 ± 15.7	0.9
Sex, female, n (%)	556 (68%)	556 (68%)	0.9
Race, white, n (%)	761 (94%)	771 (96%)	0.1
Body mass index at incidence/index, kg/m^2, mean ± SD	27.8 ± 6.0	27.7 ± 6.0	0.8
Smoking status at incidence/index, n (%)			0.002
Never	364 (45%)	435 (54%)	
Current	178 (22%)	144 (18%)	
Former	271 (33%)	234 (29%)	
Diabetes mellitus at incidence/index, n (%)	79 (10%)	67 (8%)	0.3
Hypertension at incidence/index, n (%)	307 (38%)	275 (34%)	0.1
Coronary heart disease at incidence/index, n (%)	87 (11%)	89 (11%)	0.9
Heart failure at incidence/index, n (%)	23 (3%)	23 (3%)	0.9
Length of follow-up, years, mean ± SD	9.6 ± 6.9	10.9 ± 7.2	—

data. Since all ECG data were obtained during clinical care, it was not available for all patients or at specified intervals. AF was defined as the date that AF was first noted on an ECG. Cardiovascular risk factor and outcome data have been collected in both cohorts as described [8] including cigarette smoking status (current, former, or never); presence of dyslipidemia, hypertension, or diabetes mellitus; personal history of coronary heart disease (presence of angina pectoris, coronary artery disease, myocardial infarction, or coronary revascularization procedures (e.g., coronary artery bypass graft or angioplasty)); height and weight measurements at baseline and computed body mass index (BMI); and family history of coronary heart disease (defined as presence of coronary heart disease in first-degree relatives at age <65 years for females and <55 years for males). Outcomes included mortality, coronary heart disease (as defined for personal history), and heart failure (defined by Framingham criteria) [9].

2.2. Statistical Analysis. Descriptive statistics (percentages, mean, etc.) were used to summarize the characteristics of each cohort and comparisons between cohorts were performed using Chi-square and rank sum tests. The cumulative incidence of AF adjusted for the competing risk of death was estimated [10]. Patients with AF prior to RA incidence/index date were removed from these analyses because they were not at risk of developing AF. Cox proportional hazard models were used to examine the association between potential risk factors and the development of AF. Dichotomous time-dependent covariates were used to represent risk factors that developed during follow-up; patients were considered unexposed until the time when the risk factor developed and then they changed to exposed. A sensitivity analysis was performed to examine the possibility that differences in ECG testing rates might influence cumulative incidence results. A subset of ECG tests was randomly selected for patients with RA to mimic the testing rate in patients without RA for the sensitivity analysis.

3. Results

The study population consisted of 813 patients with RA and 813 subjects without RA. There were 556 (68%) women, and the mean age (SD) at RA incidence/index date was 55.9 (15.7) years. The average length of follow-up was 9.6 (6.9) years among the patients with RA and 10.9 (7.2) years among the non-RA subjects. Cardiovascular risk factors at RA incidence date/index date were similar in both cohorts except for a higher prevalence of smokers among the RA patients compared to the non-RA subjects (P = 0.002; Table 1).

There was no difference in the prevalence of AF at RA incidence/index date among patients with RA compared to non-RA subjects (number, %) (n = 33, 4% versus n = 28, 3%), P = 0.51. During follow-up, 89 patients with RA and 73 non-RA subjects developed AF. The cumulative incidence of AF during follow-up was marginally higher among patients with RA (18.3% at 20 years; 95% confidence interval (CI): 14.2, 22.3) compared to non-RA subjects (16.3% at 20 years; 95% CI: 12.3, 20.2; P = 0.048; Figure 1). This difference corresponded to a hazard ratio (HR) of 1.60 (95% CI: 1.17, 2.18) adjusted for age, sex, and calendar year of RA incidence/index date. This difference persisted after additional adjustment for current smoking status and development of hypertension (HR: 1.46; 95% CI: 1.07, 2.00). Additional potential risk factors for development of AF in patients with RA are summarized in Table 2.

Across calendar year of follow-up, the rate of AF increased among non-RA subjects (6% per year; P = 0.002 adjusted for age and sex). Among patients with RA, the increase in AF was less pronounced (3% per year; P = 0.070). However, there was no statistically significant difference

Figure 1: Cumulative incidence of atrial fibrillation in patients with rheumatoid arthritis (RA; solid line) compared to non-RA subjects (dashed line), prevalent atrial fibrillation removed ($P = 0.048$).

between trends ($P = 0.20$ for interaction between calendar year of follow-up and RA/non-RA). The rate of ECG testing decreased over calendar time for both cohorts. The RA cohort had a consistently higher rate of ECG testing compared to the non-RA cohort (77.9 ECGs per 100 person-years (py) in RA compared to 62.7 ECGs per 100 py in non-RA; rate ratio = 1.24; $P < 0.001$). This difference persisted when the analysis was limited to patients without cardiovascular disease (by censoring patients when they developed cardiovascular disease) (HR: 1.83; 95% CI: 1.20, 2.78). In a sensitivity analysis, when ECGs for patients with RA were randomly chosen to mimic the ECG testing rates in patients without RA, the number of RA patients with AF was only reduced by 3. This reduction resulted in a smaller difference in the cumulative incidence of AF between groups (17.9% in RA versus 16.3% in non-RA at 20 years; $P = 0.088$); however, the age, sex, and calendar year adjusted results still demonstrated a significant increase in AF among the RA compared to the non-RA (HR: 1.59; 95% CI: 1.16, 2.18).

During follow-up, 229 patients with RA and 163 non-RA subjects died. AF was associated with mortality in both cohorts (HR 2.5; 95% CI: 1.8, 3.3 in RA and HR 2.8; 95% CI: 1.9, 4.0 in non-RA). There was no evidence that AF had a different impact on mortality among patients with RA compared to non-RA subjects (interaction $P = 0.31$). Similarly, there was no evidence that AF exerted a differential effect on the development of coronary heart disease (interaction $P = 0.79$) or heart failure (interaction $P = 0.66$) in patients with RA compared to non-RA subjects.

Table 2: Risk factors for atrial fibrillation at rheumatoid arthritis (RA) incidence among 813 patients with RA in 1980–2007.

Characteristic	Hazard ratio (95% CI)
At rheumatoid arthritis incidence	
ESR at RA incidence, per 10 mm/hour increase	1.10 (0.99, 1.22)
Rheumatoid factor positive	1.35 (0.88, 2.08)
Current smoker	1.29 (0.78, 2.13)
Former smoker	1.00 (0.63, 1.57)
Family history of coronary heart disease	1.16 (0.72, 1.89)
At rheumatoid arthritis incidence or during follow-up (time-dependent)	
Comorbid condition	
Hypertension	2.01 (0.72, 5.59)
Diabetes mellitus	1.39 (0.86, 2.24)
Dyslipidemia	0.77 (0.48, 1.25)
Coronary heart disease	1.53 (0.96, 2.45)
Obesity (BMI $\geq 30\,kg/m^2$)	1.33 (0.87, 2.04)
Underweight (BMI $< 20\,kg/m^2$)	1.51 (0.88, 2.58)
Alcohol abuse	1.87 (0.92, 3.81)
Rheumatoid arthritis disease characteristics	
Rheumatoid nodules	1.42 (0.91, 2.22)
Erosive or destructive RA	1.29 (0.84, 1.98)
Severe extra-articular RA*	**3.29 (1.98, 5.48)**
Large joint swelling	1.48 (0.85, 2.57)
ESR > 60 mm/hr on 3 occasions	**2.04 (1.19, 3.50)**
Major joint arthroplasty	1.45 (0.92, 2.26)
Medications	
Methotrexate	1.46 (0.93, 2.28)
Hydroxychloroquine	0.91 (0.59, 1.41)
Other DMARDs**	1.35 (0.83, 2.18)
Biologic agent	1.34 (0.57, 3.15)
Corticosteroids	1.40 (0.87, 2.27)
Cox-2 inhibitor	**1.73 (1.10, 2.73)**
ASA (≥6 tabs/day for ≥3 mo)	1.03 (0.63, 1.70)
NSAID	0.96 (0.49, 1.90)

*Pericarditis, pleuritis, Felty's syndrome, major cutaneous or other organ vasculitis, neuropathy, scleritis, episcleritis, retinal vasculitis, or glomerulonephritis.
**Disease modifying antirheumatic drug includes gold, sulfasalazine, azathioprine, cyclophosphamide, cyclosporine, D-penicillamine, or leflunomide.
ASA: acetylated salicylates; BMI: body mass index; CI: confidence interval; ESR: erythrocyte sedimentation rate (Westergren); NSAID: nonsteroidal anti-inflammatory drug.

4. Discussion

Our study examined the occurrence of AF in a systematic manner in a population-based cohort of RA patients and found that the prevalence of AF was not different among patients with RA compared to non-RA subjects. The cumulative incidence of AF was increased in patients with RA compared to non-RA subjects. Over the observation period, the incidence of AF increased among non-RA subjects and increased to a lesser extent among patients with RA. Finally, AF was not more strongly associated with mortality in patients with RA than in patients without RA.

Lindhardsen et al. reported the incidence of AF and stroke among patients with RA in a Danish national registry [3] identifying patients by ICD codes, prescription data, and

hospital admission data. The study reported an overall 40% higher incidence of AF in patients with RA compared to the general population and did not adjust for all cardiovascular risk factors. We found that patients with RA have a slightly increased risk of developing AF that persists after adjusting for smoking and hypertension.

Kim et al. reported an increased incidence of hospitalization for AF in patients with RA compared to non-RA patients using data from a commercial insurance plan [4]. After adjusting for risk factors including diabetes, cardiovascular disease, medications, and healthcare utilization, the risk of AF was no longer increased among patients with RA compared to non-RA subjects and compared to patients with osteoarthritis.

Coronary heart disease is a known contributor to the excess mortality experienced by patients with RA. In the general population, coronary heart disease is a risk factor for development of AF, and AF is an independent predictor of increased mortality [11]. Our study accounted for cardiovascular risk factors and found that AF was equally associated with mortality both in patients with RA and non-RA subjects. Chronic inflammation may play a role in the development of AF [12–14]; some of our findings may reflect this possibility. A potential association between diastolic dysfunction and AF has been described, and patients with RA are known to have increased prevalence of diastolic dysfunction [13, 14]. Other identified potential risk factors for the development of AF among patients with RA include severe extra-articular RA, multiple sedimentation rates >60 mm/hour, and use of cox-2 inhibitors.

Strengths of our study include our population-based incident cohort comprised of patients who fulfill standardized criteria for RA, the long-term follow-up, and the record linkage system which permits capture of nearly all of the cases of RA in the community and minimizes referral bias. Occurrence of AF was recorded based on a cardiologist's interpretation of electrocardiogram data and included both inpatient and outpatient occurrences of AF.

Potential limitations of our study include that it was retrospective and that the population of Olmsted County, Minnesota, is predominantly Caucasian; however, the results are in general applicable to other patient populations [15]. Also, our data collection method did not enable categorizing AF into paroxysmal, persistent, or permanent or excluding postoperative AF.

5. Conclusions

In addition to the well-known increased risk for coronary heart disease in patients with RA, these patients also have an increased risk for AF. The mechanisms underlying this risk, including possibly diastolic dysfunction, require further elucidation.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Clinical Study

Modifications in Lipid Levels Are Independent of Serum TNF-α in Rheumatoid Arthritis: Results of an Observational 24-Week Cohort Study Comparing Patients Receiving Etanercept Plus Methotrexate or Methotrexate as Monotherapy

Norma Alejandra Rodriguez-Jimenez,[1] Carlos E. Garcia-Gonzalez,[2] Karina Patricia Ayala-Lopez,[3] Benjamin Trujillo-Hernandez,[4] Erika Anita Aguilar-Chavez,[2,5] Alberto Daniel Rocha-Muñoz,[1] Jose Clemente Vasquez-Jimenez,[4] Eva Olivas-Flores,[6] Mario Salazar-Paramo,[7] Esther Guadalupe Corona-Sanchez,[8] Monica Vazquez-Del Mercado,[9] Evangelina Varon-Villalpando,[10] Adolfo Cota-Sanchez,[2] Ernesto German Cardona-Muñoz,[1] Jorge I. Gamez-Nava,[11] and Laura Gonzalez-Lopez[12,13]

[1] *Programa de Doctorado en Farmacologia, Centro Universitario de Ciencias de la Salud (CUCS), Universidad de Guadalajara (U de G), Guadalajara, JAL, Mexico*
[2] *Hospital de Especialidades, Centro Medico Nacional de Occidente, Instituto Mexicano del Seguro Social (IMSS), Guadalajara, JAL, Mexico*
[3] *Departamento de Anestesiología, Hospital Regional de Zona 1, IMSS, Aguascalientes, AGS, Mexico*
[4] *Centro Universitario de Investigaciones Biomédicas, Universidad de Colima, Colima, COL, Mexico*
[5] *Programa de Becarios en Investigacion en Salud, Unidad de Medicina Familiar 2, IMSS, Guadalajara, JAL, Mexico*
[6] *Departamento de Anestesiología, Hospital General Regional 180, IMSS, Tlajomulco, JAL, Mexico*
[7] *Division de Investigacion en Salud, UMAE, Hospital de Especialidades, Centro Medico Nacional de Occidente, IMSS, Mexico*
[8] *Departamento de Fisiologia, CUCS, U de G, Guadalajara, JAL, Mexico*
[9] *Coordinacion de Posgrado, CUCS, U de G, Guadalajara, JAL, Mexico*
[10] *Departamento de Patologia Clinica, Hospital General Regional 110, IMSS, Guadalajara, JAL, Mexico*
[11] *Unidad de Investigacion en Epidemiologia Clinica, Hospital de Especialidades, Centro Medico Nacional de Occidente, IMSS, Guadalajara, JAL, Mexico*
[12] *Departamento de Medicina Interna-Reumatologia, Hospital General Regional 110, IMSS, 44716 Guadalajara, JAL, Mexico*
[13] *Programa de Doctorado en Salud Publica, CUCS, U de G, 44340 Guadalajara, JAL, Mexico*

Correspondence should be addressed to Laura Gonzalez-Lopez; dralauragonzalez@prodigy.net.mx

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Objective. To compare the modifications in lipids between patients with rheumatoid arthritis (RA) receiving etanercept plus methotrexate (ETA + MTX) versus methotrexate (MTX) and their relationship with serum levels of tumor necrosis factor-alpha (TNF-α). *Methods.* In an observational cohort study, we compared changes in lipid levels in patients receiving ETA + MTX versus MTX in RA. These groups were assessed at baseline and at 4 and 24 weeks, measuring clinical outcomes, total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, and TNF-α. *Results.* Baseline values for lipid levels were similar in both groups. HDL-C levels increased significantly only in the ETA + MTX group (from 45.5 to 50.0 mg/dL at 4 weeks, a 10.2% increase, $P < 0.001$, and to 56.0 mg/dL at 24 weeks, a 25.1% increase, $P < 0.001$), while other lipids underwent no significant changes. ETA + MTX also exhibited a significant increase in TNF-α (44.8 pg/mL at baseline versus 281.4 pg/mL at 24 weeks, $P < 0.001$). The MTX group had no significant changes in lipids or TNF-α. Significant differences in HDL-C between groups were observed at 24 weeks ($P = 0.04$) and also in TNF-α ($P = 0.01$). *Conclusion.* HDL-C levels increased significantly following treatment with ETA + MTX, without a relationship with decrease of TNF-α.

1. Introduction

Cardiovascular disease constitutes the main cause of death for patients with long disease duration in rheumatoid arthritis (RA) [1]. A recent study observed that patients with RA have at least a 1.6-fold increased risk for acute myocardial infarction and ischemic stroke compared with controls [2], whereas the frequency of dyslipidemia in RA may range from 28 to 49% [3, 4]. Dyslipidemia is influenced by a multiplicity of factors, including activity and disease duration, comorbidity, and pharmacological therapies, particularly with corticosteroids [5]. Although, some differences are reported across the results of studies evaluating the lipid profiles in RA, some researchers have observed an increase in the levels of low-density lipoprotein cholesterol (LDL-C) in patients with RA compared with controls [6]; other groups have failed to identify these differences [7]. However, yet other studies have observed lower levels of high-density lipoprotein cholesterol (HDL-C) in patients with RA [6–8]. Currently low levels of HDL-C are considered an independent risk factor for the development of cardiovascular disease [9]. Therefore, some authors consider improvement of levels of this lipoprotein as an outcome measure within the therapeutic goals of dyslipidemia treatments [10].

Tumor necrosis factor-alpha (TNF-α) exerts a multiplicity of effects that are not only related to disease activity. This cytokine also participates in increasing cardiovascular risk factors, including hepatic synthesis of C-reactive protein (CRP) and decreasing of HDL-C levels [11]. Whether or not the blocking of proinflammatory effects induced by TNF-α due to anti-TNF agents in RA would offer benefits in modifying the abnormal lipid profiles should be considered. Etanercept (ETA) is a dimeric fusion protein consisting of two extracellular domains of the human p75 TNF receptor linked with the Fc portion of a type 1 human immunoglobulin. Relevantly, this anti-TNF agent blocks not only TNF-α but also lymphotoxin-α, a cytokine that exerts proatherogenic properties in animal models [12]. However, it remains unknown whether ETA exerts significant clinical effects on the lipid profile when compared with methotrexate (MTX). A systematic review of 24 observational studies evaluated changes in lipid profile in patients with RA treated with diverse anti-TNF agents [13]. This review included only six studies of patients treated with ETA, and these results were mixed with results from patients treated with other anti-TNF agents [13]. Therefore, this review reported wide variability in lipid profile changes following ETA therapy; these effects cannot be attributed to a particular anti-TNF-α agent. In an interesting work, Jamnitski et al. assessed changes in lipid profile in patients with RA receiving ETA as unique anti-TNF agent, although this study was performed without a comparison group; therefore, the effects of potential confounders cannot be excluded [14].

Thus, a lack of comparative studies evaluating the effects of ETA on the lipid profiles of patients with RA renders it uncertain whether modifications in these lipids (if they exist) are related to changes in TNF-α serum levels induced by this anti-TNF agent. Thus, we performed a comparative study evaluating the modifications in lipid levels in patients with RA treated with ETA plus MTX versus patients receiving MTX as monotherapy and elucidating when these changes are related or not with modifications in serum levels of TNF-α.

2. Patients and Methods

2.1. Study Design. This 6-month prospective cohort study included consecutive patients with RA from an outpatient rheumatology clinic at a secondary-care hospital (Hospital General Regional 110, of the Instituto Mexicano del Seguro Social) in Guadalajara, Mexico. Patients were included if they were adults (≥18 years of age), met 1987 American College of Rheumatology (ACR) criteria for RA, had an active disease defined by disease activity score (DAS 28) > 3.2, and had not received treatment for least 3 months with synthetic disease-modifying antirheumatic drugs (DMARD) or therapy with biological agents. Patients were excluded for the following reasons: pregnancy, treatment with immunosuppressive drug such as cyclophosphamide or azathioprine, receiving prednisone or the equivalent at doses of >10 mg/day, having active infections at the time of study inclusion, receiving antimalarial drugs, and receiving other biological agents or hypolipidemic drugs (statins or fibrates) in the 3 months prior to entry into the study or during the study. Also excluded were patients with comorbidity associated with abnormalities in the lipid profile (such as hypothyroidism, diabetes mellitus, chronic renal failure, nephrotic syndrome, or hepatopathy). We did not exclude smokers or patients with metabolic syndrome (except if they had diabetes mellitus).

2.2. Criteria for Treatment Arm Assignment. According to the Mexican guidelines of the treatment for RA used in our hospital, the patients may receive as first option MTX as monotherapy or may initiate a combined therapy with

MTX plus a biological agent (usually an anti-TNF agent) specially if the patient is considered with inadequate therapeutic response after at least 3 months of monotherapy with MTX or another DMARD [15]. Therefore, the rheumatologists in the clinical visit decided to institute a therapeutic strategy independently of this study. The strategies that the rheumatologists decided to initiate were one of the following treatments: ETA + MTX (first group): these patients received ETA 25 mg subcutaneously twice weekly plus MTX 10 to 15 mg per week administered orally for 24 weeks, or MTX (second group), as monotherapy, received this drug at a dosage of 10–15 mg weekly administered orally for 24 weeks. All of the dosages of these drugs remained stable throughout the study.

2.3. Clinical Assessment and Followup. A structured questionnaire was administered to the patients to evaluate demographic and clinical variables including disease duration, smoking, and comorbidities. Patients were assessed by the same trained researcher at baseline (time of initial prescription) and at 4 and 24 weeks for the following variables: (a) disease activity according to disease activity score (DAS 28), (b) functioning according to Health Assessment Quest-Disability Index (HAQ-DI), and (c) visual analogue scales (VAS, 0–100 mm) for morning stiffness, pain severity, and disease activity assessed by the physician.

During the study, patients received oral nonsteroidal anti-inflammatory drugs (NSAID) and acetaminophen or, if required, diclofenac intramuscularly as adjuvant treatment for joint pain and inflammation. We recommended to all patients the regular practice of exercise and a diet low in fat.

2.4. Lipid Profiling and Serum TNF-α Level Measurement. A venous blood sample was obtained at baseline, at 4 and 24 weeks, to determine levels of total cholesterol, triglycerides, HDL-C, and LDL-C. These lipid levels were assessed with commercial kits using the VITROS-800 machine. All measurements were performed at our hospital's central laboratory. Normal reference values are the following: total cholesterol < 240 mg/dL, triglycerides < 160 mg/dL, HDL-C > 35 mg/dL, and LDL-C < 150 mg/dL. A patient was considered with dyslipidemia when the values of total cholesterol, triglycerides, or LDL-C were above normal values or when HDL-C levels were below reference values.

Also at baseline, 4 weeks, and 24 weeks, a second blood sample was taken and serum was obtained in order to measure TNF-α levels. These levels were quantified by enzyme-linked immunoassay (ELISA) using a commercial kit (Quantikine).

Rheumatoid factor (RF) titers and CRP were measured at all visits by nephelometry.

2.5. Statistical Analysis. Quantitative variables are expressed as means ± standard deviations (SD), and qualitative variables are expressed as numbers and percentages. Unpaired Student's t-tests were utilized for baseline comparisons of quantitative variables between groups (ETA + MTX versus MTX as monotherapy) and chi-square tests (or Fisher exact tests if required) were employed for comparisons of qualitative variables between groups. Correlations between lipid levels and disease activity, HAQ-DI, TNF-α serum levels, CRP concentrations, and RF titers were computed using Pearson correlation coefficients (r). Paired Student's t-tests were utilized for within-group comparisons of absolute changes in lipid levels, TNF-α levels, and clinical characteristics expressed as quantitative variables at 4 and 24 weeks relative to baseline. Unpaired Student's t-tests were performed for comparisons of differences in the relative change of lipid levels and serum TNF-α levels at 4 weeks and 24 weeks between ETA + MTX and MTX as monotherapy groups. Significance was set at a P value of ≤0.05. All analyses were performed with SPSS ver. 8.0 statistical software.

3. Results

Thirty-five patients were included in the study, 22 of whom received ETA + MTX and 13 MTX as monotherapy. There were no statistical differences in the majority of the variables at baseline, including gender, body mass index (BMI), proportion of smokers, or comorbidity (Table 1). Age was significantly higher in the ETA + MTX group than in the MTX group (47.4 ± 8.3 years versus 40.6 ± 10.8 years, resp.; $P = 0.04$). There was a trend toward longer disease duration in ETA + MTX patients versus MTX patients, although this difference did not reach statistical significance (12.3 ± 6.7 years versus 8.2 ± 6.0 years, resp.; $P = 0.08$). Other clinical characteristics including the DAS 28 score, the HAQ-DI score, morning stiffness, pain severity, and disease activity as assessed by the physician did not differ between groups at baseline (Table 1). There were no significant baseline differences between the two groups in lipid levels, CRP levels, and RF titers. Frequency of dyslipidemia at baseline in the ETA + MTX group was similar to that of the MTX group (59 versus 54%, resp.; $P = 0.76$) (Table 1). There was a trend toward higher baseline TNF-α levels in patients receiving ETA + MTX compared with patients receiving MTX as monotherapy, although this difference did not reach statistical significance (129.14 ± 207.70 pg/mL versus 42.36 ± 23.46 pg/mL resp.; $P = 0.08$).

Table 2 depicts the results of the Pearson correlations at baseline among TNF-α levels, clinical variables, lipid levels, RF titers, and CRP concentrations, employing the total pool of patients ($n = 35$). Although a trend was observed between higher TNF-α levels and severity of disease activity as assessed by the physician, this correlation did not achieve statistical significance ($r = 0.304$, $P = 0.07$). TNF-α serum levels did not correlate with clinical variables, RF titers, or levels of CRP, total cholesterol, triglycerides, HDL-C, or LDL-C.

We carried out within-group comparisons between baseline values and measurements taken at 4 and 24 weeks in selected clinical variables, CRP levels, and RF levels (Table 3). The ETA + MTX group experienced significant improvement at 4 and 24 weeks versus baseline in DAS-28 score ($P < 0.001$), HAQ-DI score ($P < 0.001$), and disease activity as assessed by the physician ($P < 0.001$). The group receiving

Table 1: Comparison of baseline characteristics between the etanercept + methotrexate (ETA + MTX) group and the MTX as monotherapy group.

Clinical characteristics	Total $n = 35$	ETA + MTX $n = 22$	MTX $n = 13$	P
Females, n (%)	32 (91)	20 (91)	12 (92)	0.88
Age, years	44.9 ± 9.7	47.4 ± 8.3	40.6 ± 10.8	0.04
Body mass index, kg/m^2	25.0 ± 3.3	24.7 ± 3.4	25.5 ± 3.2	0.49
Smoking, n (%)	12 (34)	7 (32)	5 (39)	0.68
Duration of RA, years	10.8 ± 6.6	12.3 ± 6.7	8.2 ± 6.0	0.08
DAS-28 score	6.3 ± 0.9	6.2 ± 0.8	6.5 ± 1.1	0.47
HAQ-DI score	1.45 ± 0.56	1.45 ± 0.52	1.51 ± 0.64	0.78
Morning stiffness, mm (VAS)	62 ± 20	63 ± 19	61 ± 23	0.85
Severity of pain, mm (VAS)	67 ± 19	66 ± 16	69 ± 24	0.65
Disease activity, by physician, mm (VAS)	61 ± 16	61 ± 15	60 ± 17	0.91
Total cholesterol, mg/dL	181.5 ± 40.2	187.9 ± 38.1	170.6 ± 42.7	0.22
High total cholesterol levels, n (%)	12 (34)	7 (32)	5 (38)	0.73
Triglycerides, mg/dL	141.8 ± 67.4	150.4 ± 75.1	127.4 ± 51.5	0.34
High triglycerides levels, n (%)	14 (40)	9 (41)	5 (38)	0.89
HDL-C, mg/dL	46.7 ± 13.0	48.1 ± 15.6	44.3 ± 6.8	0.34
Low HDL-C levels, n (%)	8 (23)	6 (27)	2 (15)	0.68
LDL-C, mg/dL	100.7 ± 30.9	100.7 ± 25.8	100.5 ± 39.2	0.99
High LDL-C levels, n (%)	7 (20)	3 (14)	4 (31)	0.38
Dyslipidemia, n (%)	20 (57)	13 (59)	7 (54)	0.76
TNF-α, pg/mL	96.91 ± 169.26	129.14 ± 207.70	42.36 ± 23.46	0.08
Rheumatoid factor, U/mL	421.23 ± 633.92	501.59 ± 752.79	309.97 ± 422.72	0.42
C-reactive protein, mg/L	29.97 ± 46.31	20.08 ± 30.02	43.67 ± 61.11	0.17

HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TNF-α: tumor necrosis factor-alpha; VAS: visual analogue scale; RA: rheumatoid arthritis; DAS-28: disease activity score; HAQ-DI: Health Assessment Quest-Disability Index. Quantitative variables are presented as mean ± standard deviation (SD); qualitative variables are presented in number (%); comparisons between proportions utilized Fisher exact test; comparisons between means were calculated with unpaired Student's t-tests.

MTX as monotherapy also significantly improved in DAS-28 score at 4 ($P = 0.01$) and 24 weeks ($P < 0.001$), HAQ-DI at 4 ($P < 0.001$) and 24 weeks ($P < 0.001$), and VAS for disease activity at 4 ($P = 0.001$) and 24 weeks ($P = 0.001$). No significant differences were detected in RF titers at 4 and 24 weeks in the ETA + MTX group, whereas the group receiving MTX as monotherapy exhibited a significant decrease in RF titers. In data not shown in the table, none of the patients who were smokers at baseline stopped smoking or decreased their smoking habit.

Treatment effects on lipid profile and TNF-α levels were determined for both groups (Table 4). A within-group comparison of ETA + MTX patients revealed a significant increase in HDL-C levels at 4 ($P = 0.02$) and at 24 weeks ($P = 0.009$) compared with baseline (Table 4). Remarkably, we observed an increase in TNF-α levels in this group at 4 ($P = 0.03$) and at 24 weeks ($P = 0.007$) compared with baseline, while we detected no significant changes in lipid levels or TNF-α levels in the group receiving MTX as monotherapy.

Regarding differences in relative change between the two groups, the MTX as monotherapy group had a significant increase in total cholesterol levels compared with the ETA + MTX group at 24 weeks ($P = 0.04$) (Table 4), while the ETA + MTX group had significantly higher HDL-C levels than the MTX group at 24 weeks ($P = 0.04$) (Table 4). We detected no other statistically significant changes in lipid levels between the two treatment groups. The ETA + MTX group exhibited significantly higher TNF-α levels than MTX group at 4 ($P = 0.02$) and at 24 weeks ($P = 0.01$) (Table 4).

4. Discussion

The results of the present study show that utilization of the ETA + MTX combined therapy significantly increased HDL-C levels with respect to baseline in patients with RA, although this effect was not associated with significant improvement in other lipids. Patients receiving MTX as monotherapy exhibited no significant changes in these lipid levels. Additionally, improvement in HDL-C levels in patients treated with ETA + MTX was not related to decreases in serum TNF-α levels.

Wide variability in the frequency of dyslipidemia has been observed in RA ranging from 28 to 49% of patients depending on the study [3, 4]. We observed abnormalities in lipid levels in more than one-half of our patients, an observation that is in agreement with previous reports that this prevalence increases during episodes of disease activity [16, 17].

Table 2: Correlations (r) between baseline tumor necrosis factor-alpha (TNF-α) serum levels and selected variables.

Characteristic	TNF-α (pg/mL) $n = 35$	
	r	P
Age	−0.041	0.81
Disease duration	0.058	0.74
Joint tenderness count	0.079	0.65
Joint swelling count	0.035	0.84
DAS-28 score	0.061	0.72
HAQ-DI score	0.247	0.15
Disease activity (physician)	0.304	0.07
Total cholesterol	0.031	0.86
Triglycerides	−0.131	0.45
HDL-C	−0.114	0.51
LDL-C	−0.227	0.19
Rheumatoid factor	0.255	0.16
C-reactive protein	−0.089	0.63

HDL-C: high-density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; DAS-28: disease activity score; HAQ-DI: Health Assessment Quest-Disability Index; disease activity was assessed by the physician using a visual analogue scale (VAS) from 0 to 100 mm. Joint swelling or tenderness counts were taken from 28 joints. Correlations were computed with Pearson correlation test.

A major consequence of dyslipidemia is the development of atherosclerosis and its complications. In this context, Roman et al. reported that 44% of their patients with RA displayed atherosclerotic plaques on carotids compared with only 15% of controls [18]. Additionally, Gonzalez-Juanatey et al. identified an increase in subclinical atherosclerosis assessed by an increase in carotid intima-media wall thickness and carotid plaques in patients with RA, particularly in those with longer disease duration and more extra-articular manifestations [19].

It has been suggested that only a small subset of patients with RA with dyslipidemia are adequately treated with hypolipemic therapy. Maradit-Kremers et al. reported that only 7–15% of their patients with RA and dyslipidemia received hypolipemic treatment in their cohort [4]. Lipid profiles in RA may be affected by several variables, such as comorbidities and drugs used for treatment. Corticosteroids may contribute to dyslipidemia and cardiovascular complications [20], while antimalarials may improve lipid profiles [21]. However, the effects of other antirheumatic drugs, such as MTX, on lipid levels are not consistent across the different studies. In one study Georgiadis et al. observed a significant increase after 1 year in total cholesterol and HDL-C levels in patients with early RA who were treated with MTX at stable doses [22]. However, that study was limited by the absence of a comparison group, and the effects of potential confounding factors cannot be excluded.

Several studies have evaluated changes in lipids levels associated with the use of anti-TNF-α agents, including infliximab, adalimumab, and ETA. However, contradictions in the observations complicate their interpretation. Popa et al. [23] and Tam et al. [24] reported significant modifications in levels of total cholesterol and triglycerides in patients with RA receiving infliximab, but Bosello et al. [25] and Peters et al. [26] did not find significant changes in lipid levels after treatment with infliximab. Studies using adalimumab have also shown contradictory results [23, 27, 28]. Popa et al. [23] and Gonzalez-Juanatey et al. [27] identified an improvement in levels of total cholesterol and HDL-C in patients with RA treated with adalimumab but the lipid profiles reported by Wijbrandts et al. [28] did not changed significantly with this anti-TNF agent. Anti-TNF agents also have shown effects on endothelial function. Gonzalez-Juanatey et al. observed the effects of adalimumab on endothelial function in patients with RA refractory to DMARD. These authors observed a significant increase in flow-mediated endothelium-dependent vasodilation after 2 weeks and 12 months of adalimumab therapy [29]. However, these authors failed to find significant differences in lipid levels and atherogenic index with treatment with adalimumab [29]. These data underscore the fact that anti-TNF alpha benefits on cardiovascular diseases are produced by multiple mechanisms independently of modifications in the lipid profile.

Although eight studies have assessed the modifications in lipid profiles in patients with RA using ETA [14, 30–36], the results are controversial. Jamnitski et al. observed a significant increase in total cholesterol and triglycerides after 1 year of treatment with ETA [14], whereas Garcês Da Gama et al. observed, in a mixture group compounded by RA patients, ankylosing spondylitis patients, and psoriatic arthritis patients, an increase in HDL-C concentration after the administration of ETA [30], and Seriolo et al. observed, in independent studies, a significant increase in total cholesterol and HDL-C [31–33]. On the other hand, three independent studies performed by del Porto et al., Soubrier et al., and Senel et al. did not observe a change in lipid values in their patients treated with ETA [34–36]. The majority of these studies are limited in their ability to attribute their results to this anti-TNF agent due to the presence of potential confounders. Nearly all of these investigations included patients treated with other anti-TNF-α agents; therefore, the statistical analyses performed combined the results to detect the possible modifications of anti-TNF-α agents as a group, rather than seeking to identify specific drug effects [32–34]. From these studies, Garcês Da Gama et al. [30] separately analyzed patients treated with ETA and treated with infliximab, although they mixed in their results with those of patients with RA, psoriatic arthritis, and ankylosing spondylitis. In the study of Jamnitski et al. [14] are evaluated the benefits on the lipid profile in a cohort of patients with RA treated with ETA, but this study lacked a comparison group and did not separately analyze the results in patients treated exclusively with ETA and patients treated with ETA + DMARD combination. Given that some DMARD, such as antimalarials, may improve lipid levels [21], considering the effects of DMARD on changes in lipid profile is required. Therefore, we evaluated the effects of ETA + MTX versus MTX alone on lipid profile without including other anti-TNF-α agents or other DMARD except for MTX. Additionally, it is relevant to consider that from eight investigations

Table 3: Within-group comparisons over time of changes in selected clinical variables, C-reactive protein levels (CRP), and rheumatoid factor titers.

Characteristic	ETA + MTX			MTX		
	Baseline ($n = 22$)	4 weeks ($n = 22$)	24 weeks ($n = 22$)	Baseline ($n = 13$)	4 weeks ($n = 13$)	24 weeks ($n = 13$)
DAS-28 score	6.2 ± 0.8	3.8 ± 1.6‡	3.6 ± 1.4‡	6.5 ± 1.1	5.5 ± 1.3**	4.9 ± 1.2‡
HAQ-DI score	1.45 ± 0.52	0.57 ± 0.43‡	0.57 ± 0.50‡	1.51 ± 0.64	1.13 ± 0.61‡	0.86 ± 0.47‡
Disease activity (physician)	61 ± 15	29 ± 17‡	25 ± 16‡	60 ± 17	43 ± 24†	41 ± 17†
Rheumatoid factor, U/mL	501.59 ± 752.79	458.77 ± 669.78	1386.57 ± 4465.90	309.97 ± 422.72	138.95 ± 186.08	84.68 ± 172.53*
CRP, mg/L	20.08 ± 30.02	14.82 ± 17.72	41.58 ± 91.04	43.67 ± 61.11	23.19 ± 26.89	28.92 ± 43.14

ETA + MTX: etanercept plus methotrexate group; MTX: methotrexate as monotherapy group; DAS-28: disease activity score; HAQ-DI: Health Assessment Quest-Disability Index. Quantitative variables are expressed as mean ± standard deviation (SD). Intragroup comparisons were performed with the Student's t-test. $^{*}P = 0.03$, $^{**}P = 0.01$, $^{\dagger}P = 0.001$, and $^{\ddagger}P < 0.001$.

performed with the aim to evaluate the effects of ETA on the lipid profile in RA, only three [32–34] utilized a comparison group, with this group being a requirement for evaluating the magnitude effect. Therefore, in order to assess effectively whether the effect of ETA + MTX on lipid levels is relevant, we included, as comparison group, patients receiving treatment with MTX as monotherapy. Interestingly, some studies have reported the effects of other biological agents different from anti-TNF inhibitors in patients with RA refractory to anti-TNF agents. In this context, rituximab has shown a short-term increase of LDL-C and total cholesterol when compared with base line values. However, these early differences observed at week 2 did not remain at month 6 [37]. On the other hand, the effect of interleukin-6 (IL-6) receptor blockade with tocilizumab has been associated with an increase of total cholesterol, LDL-C, and HDL-C [38].

The positive effects of anti-TNF agents entertain multiple advantages in lipid profiles of patients with RA. In RA, the frequency of metabolic syndrome is around 33% [39] with no previous events of cardiovascular disease. Some adipokines participate in the pathogenesis of atherosclerosis and are also mediators of inflammation; among these, leptin and adiponectin are highly relevant in RA. Leptin is a proinflammatory cytokine produced by adipocytes, with these being potent stimuli for its production of some cytokines such as TNF-α and IL-1β. This adipokine exerts several effects on atherosclerosis, such as inducing endothelial dysfunction, increasing oxidative stress, increasing platelet aggregation, and stimulating the migration, proliferation, and hypertrophy of smooth muscle cells on the vascular wall [40]. Adiponectin has, instead, some opposite effects on leptin; adiponectin possesses anti-inflammatory properties, and also high levels are associated with antiatherogenic effects, increasing insulin sensitivity. Low adiponectin levels are associated with the presence of metabolic syndrome, dyslipidemia, and higher plasma glucose, contributing to the development of atherosclerosis [40]. Gonzalez-Gay et al. describe an association between CRP levels and adiponectin concentrations [41]. These adiponectin circulating concentrations also correlated negatively with triglyceride/HDL-C ratios, total cholesterol/HDL-C ratios, and high fasting plasma glucose levels, independent of CRP levels and BMI. However, these authors did not observe significant changes in adiponectin concentrations after infliximab infusion, being the adiponectin preinfusion strongly correlated with adiponectin postinfusion. Two independent studies, the first performed by Nagashima et al. and the second by Lewicki et al., observed in RA patients treated with anti-TNF agents that adiponectin levels increased significantly with the treatment [42, 43].

While we observed that HDL-C levels increased significantly in the ETA + MTX group at week 4 of treatment and this increase remained until the end of month 6, the HDL-C levels of patients who received MTX as monotherapy did not increase significantly during followup. This response of ETA in increasing HDL-C levels was also observed by Gonzalez-Juanatey et al. [27] in patients with RA, psoriatic arthritis, or ankylosing spondylitis who were treated with ETA, but not in patients treated with infliximab, attributing these findings to possible differences in the mechanism of action of ETA on lymphotoxin-α. Our findings support their observations, although we exclusively evaluated patients with RA. In other studies, Seriolo et al. observed an increase in HDL-C levels following the use of anti-TNF-α drugs for RA [31–33], but they did not make explicit whether this increase was observed only in patients receiving ETA or if it was also observed in patients treated with other anti-TNF agents included in their study (infliximab or adalimumab). The intrinsic mechanism by which ETA may increase levels of HDL-C is not well understood, although it may involve ETA blocking the expression of lymphotoxin-α. Lymphotoxin-α has been observed to possess proatherogenic properties in animal models. Absence of lymphotoxin-α is associated with a decrease in total cholesterol levels and an increase in HDL-C levels [12].

We failed to detect a correlation between baseline TNF-α serum levels and lipid profile, and we also observed an unexpected dissociation between modifications in HDL-C levels and changes in TNF-α levels; these findings suggest that other mechanisms independent of TNF-α blocking may contribute to the beneficial effects obtained with ETA + MTX on HDL-C levels. Other mechanisms that may affect dyslipidemia in patients with RA include genetic and environmental factors. Among genetic factors, several polymorphisms have been reported to be associated with dyslipidemia and cardiovascular diseases in RA. Vallvé et al. observed, in patients with

Table 4: Within- and between-group comparisons of relative changes (%) in lipid profile and tumor necrosis factor-alpha (TNF-α) serum level at 4 and 24 weeks.

Characteristics	ETA + MTX ($n = 22$)			MTX ($n = 13$)			Comparison between groups (Δ relative change)
	Mean ± SD	Absolute change	Relative change (%)	Mean ± SD	Absolute change	Relative change (%)	P
Total cholesterol, mg/dL							
Baseline	187.9 ± 38.1	—	—	170.6 ± 42.7	—	—	0.22
4 weeks	178.5 ± 38.6	−9.4	5.0	172.8 ± 32.7	+2.2	1.3	0.18
24 weeks	182.7 ± 44.8	−5.2	2.8	188.9 ± 33.0	+18.3	10.7	0.04
Triglycerides, mg/dL							
Baseline	150.4 ± 75.1	—	—	127.4 ± 51.6	—	—	0.34
4 weeks	141.8 ± 57.4	−8.5	5.7	129.3 ± 51.9	+1.9	1.5	0.96
24 weeks	151.3 ± 61.2	+0.9	0.6	151.8 ± 74.2	+24.5	19.2	0.62
HDL-C, mg/dL							
Baseline	48.1 ± 15.6	—	—	44.4 ± 6.9	—	—	0.34
4 weeks	52.0 ± 15.8**	+3.9	8.2	45.5 ± 9.8	+1.2	2.6	0.22
24 weeks	57.1 ± 13.9†	+9.0	18.7	47.1 ± 9.7	+2.7	6.1	0.04
LDL-C, mg/dL							
Baseline	100.7 ± 25.9	—	—	100.5 ± 39.2	—	—	0.99
4 weeks	99.7 ± 30.0	−1.0	1.0	101.1 ± 31.6	+0.6	0.6	0.40
24 weeks	97.3 ± 44.7	−3.4	3.4	109.6 ± 27.9	+9.0	9.0	0.24
TNF-α, pg/mL							
Baseline	129.14 ± 207.7	—	—	42.36 ± 23.5	—	—	0.88
4 weeks	219.7 ± 228.6*	+90.6	70.2	33.9 ± 12.9	−8.3	19.8	0.02
24 weeks	337.4 ± 205.9‡	+208.2	161.2	50.7 ± 24.1	+8.2	19.6	0.01

ETA + MTX: etanercept plus methotrexate; MTX: methotrexate as monotherapy; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SD: standard deviation. Absolute change is the difference at 4 or 24 weeks versus baseline; relative change is the percentage change at 4 or 24 weeks versus baseline values. Δ: relative change between groups is a comparison of the differences in relative change (%) at 4 and 24 weeks between groups. The P values for the Δ calculations were obtained with unpaired Student's t tests. Intragroup comparisons between 4 and 24 weeks versus baseline were calculated with paired Student's t-tests.

*$P = 0.03$, **$P = 0.02$, †$P = 0.009$, and ‡$P = 0.007$.

RA, an association between TNF-α-1031 T/C genetic polymorphisms and LDL particles with greater susceptibility to oxidation [44]. Park et al. observed that the APOM C-1065A polymorphism is associated with higher risk for developing dyslipidemia in RA, because reduced HDL cholesterol levels were influenced by the APOM genotype [45]. Rodríguez-Rodríguez et al. observed an association between the TNFA rs1800629 (G > A) gene polymorphism and predisposition to cardiovascular complications in RA, including ischemic heart disease, cerebrovascular accidents, heart failure, and peripheral arteriopathy [46]. In another study, López-Mejías et al. identified an association between cardiovascular disease and the NFKB1-94ATTG ins/del (rs28362491) gene polymorphism [47].

Limitations of the present study include some differences at baseline that may influence the response observed in HDL-C, including age differences and a trend toward longer disease duration in the group receiving ETA. Because the present study is a cohort, there was no randomized selection of patients being included in one or the other treatment arm, increasing the possibility of variables that may confound the outcomes. Therefore, we cannot totally exclude other potential confounding factors that may exert an influence on the increase in HDL-C levels obtained with ETA + MTX treatment. However, we restricted the inclusion of relevant confounders associated with changes in lipid levels, such as administration of antimalarials, prednisone, or a multiplicity of NSAID drugs during the study period. However, for ethical reasons, we advised all patients to stop smoking and to increase exercise, which may have contributed to the observed effects on lipids levels (although it is relevant to consider that although both groups received this advice, only the ETA + MTX group improved significantly in HDL-C measurements).

In summary, we observed that combined treatment with ETA + MTX increased HDL-C levels of patients with RA, without significantly affecting other lipids. These findings were independent of changes in TNF-α levels and may represent new information with respect to a protective effect of ETA + MTX combination against the development of atherosclerotic complications in RA. Further studies should evaluate whether this effect has clinical relevance for the decrease of atherosclerotic consequences such as stroke or myocardial infarction in patients with RA.

Ethical Approval

This project was approved by the Research and Ethics Board of the Mexican Institute for Social Security (IMSS) with Approval no. R-2006-1301-40.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

Norma Alejandra Rodriguez-Jimenez and Carlos E. Garcia-Gonzalez contributed equally to this work.

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Review Article

Cardiovascular Disease Risk amongst African Black Patients with Rheumatoid Arthritis: The Need for Population Specific Stratification

Ahmed Solomon,[1] Linda Tsang,[2] Angela J. Woodiwiss,[2] Aletta M. E. Millen,[2] Gavin R. Norton,[2] and Patrick H. Dessein[2]

[1] *Department of Rheumatology, Charlotte Maxeke Johannesburg Academic Hospital, Faculty of Health Sciences, University of the Witwatersrand, Parktown 2193, Johannesburg, South Africa*
[2] *Cardiovascular Pathophysiology and Genomics Research Unit, School of Physiology, Faculty of Health Sciences, University of the Witwatersrand, P.O. Box 1012, Melville 2109, Johannesburg, South Africa*

Correspondence should be addressed to Patrick H. Dessein; dessein@telkomsa.net

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Rheumatoid arthritis (RA) enhances the risk of cardiovascular disease to a similar extent as diabetes. Whereas atherogenesis remains poorly elucidated in RA, traditional and nontraditional risk factors associate similarly and additively with CVD in RA. Current recommendations on CVD risk stratification reportedly have important limitations. Further, reported data on CVD and its risk factors derive mostly from data obtained in the developed world. An earlier epidemiological health transition is intrinsic to persons living in rural areas and those undergoing urbanization. It is therefore conceivable that optimal CVD risk stratification differs amongst patients with RA from developing populations compared to those from developed populations. Herein, we briefly describe current CVD and its risk factor profiles in the African black population at large. Against this background, we review reported data on CVD risk and its potential stratification amongst African black compared to white patients with RA. Routinely assessed traditional and nontraditional CVD risk factors were consistently and independently related to atherosclerosis in African white but not black patients with RA. Circulating concentrations of novel CVD risk biomarkers including interleukin-6 and interleukin-5 adipokines were mostly similarly associated with both endothelial activation and atherosclerosis amongst African black and white RA patients.

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory and destructive joint disease that augments the risk of atherosclerotic cardiovascular disease (CVD) to a similar extent as diabetes [1–4]. Recent meta-analyses have documented a 2-fold increased risk of CVD events and a standardized cardiovascular mortality rate of 50% in RA [5, 6]. Patients with RA were also shown to experience a markedly enhanced cumulative incidence of silent myocardial infarction (MI) and sudden death as well as heart failure; the latter is strikingly often with preserved ejection fraction [1]. Thus, the presenting CVD features in RA differ from those in the general population. Further, death after an acute coronary syndrome is increased in RA [7]. What drives the enhanced risk for CVD in patients with RA?

Atherogenesis in RA remains poorly understood. Traditional and nontraditional risk factors associate similarly and additively with atherosclerosis and CVD events in RA patients [8–11]. Genetic factors contribute to the enhanced CVD risk in RA [12, 13]. However, amongst nonconventional risk factors, it is high-grade inflammation that is mostly implicated in increased atherogenesis in RA [14, 15]. Indeed, patients with RA experience high-grade inflammation driven by augmented cytokine production, which associates with metabolic risk including insulin resistance and reduced HDL

cholesterol concentrations [16–18]. A recent meta-analysis confirmed the impact of RA on metabolic risk [19]. Indeed, HDL concentrations were found to be reduced and the prevalence of diabetes increased in RA. Further, inflammatory molecules can also directly impair endothelial function [11, 20, 21].

Over the recent past, an impressively increasing number of investigators have reported on potential determinants of increased CVD in RA. However, over the past decades, in contrast to the substantial improvements in life expectancy in the non-RA population, which are further largely driven by reductions in CVD events in the developed world, the mortality of RA has remained remarkably constant thereby translating into a widening mortality gap between RA patients and the general population [3]. Congruent with this observation, currently recommended strategies on cardiovascular risk stratification in patients with RA were shown to have important limitations [22, 23]. A multicenter undertaken by "a transatlantic cardiovascular risk calculator for rheumatoid arthritis" (ATACC-RA) consortium recently successfully produced an RA specific cardiovascular risk calculator [24].

However, a further concern in the present context is that most information on CVD in both non-RA and RA subjects originates in developed countries that are largely inhabited by white populations whereas 80% of the CVD risk burden now arises in middle income and low income countries [25]. In this regard, at least in part due to previous colonialism and the subsequent related apartheid system that was only officially terminated in 1994, African black persons currently represent a mostly developing population. The increase in incident CVD in poorer populations is attributable to the epidemiological health transition [26]; the stages and characteristics of which are presented in Table 1. Presently, most sub-Saharan black South Africans are reportedly in stages 1 and 2 of this transition [27]. Being in epidemiological transition translates into sustaining different cardiovascular risk factor profiles and, consequently, altered CVD presentations [26]. It is therefore conceivable that data on atherosclerotic CVD and its stratification obtained in patients with RA from developed populations cannot be directly extrapolated to those that belong to developing populations.

Herein, we briefly describe current CVD and its risk factor profiles in the African black population at large. Against this background, we then review reported data on CVD risk and its potential stratification amongst African black compared to white patients with RA. Finally, we suggest future research perspectives in the present context.

2. Cardiovascular Disease and Its Risk Factor Profiles amongst the African Black Population at Large

2.1. Cardiovascular Disease Burden. There is an overall paucity of large scale epidemiological data on CVD and its risk factors in African black people. In the 2010 South African Medical Research Council report on causes of death, cerebrovascular disease was listed as the 5th and coronary artery disease as the 8th most common causes of death [28]. Moreover, peripheral arterial disease was identified in 29% of outpatients in a rural community in South Africa [29].

Strong evidence towards an early epidemiological transition stage currently experienced by African black persons comes from studies on CVD event types in this population. Although coronary artery disease (CAD) is reportedly distinctly uncommon, it was recently identified in 10% of black patients presenting to hospital with heart disease in a study that originated in Johannesburg, South Africa [30]. Also, whereas stroke incidence was found to remain lower, stroke occurs at a younger age and results in high and possibly larger mortality than in high-income regions [31–33]. There is further an emerging risk of ischemic as opposed to hemorrhagic stroke that relates to older age and the presence of diabetes [31, 34]. In a recent hospital-based study, that included 207 African black and 47 white stroke patients, the frequency of ischemic stroke and cerebral hemorrhage was 68% versus 77% and 27% versus 15%, respectively [31]. These differences were not significant. Heart failure mostly attributed to hypertension and idiopathic dilated cardiomyopathy is the most frequently made diagnosis amongst African black patients presenting with heart disease [30].

2.2. Cardiovascular Risk Factors. With regard to CVD risk factors, the low incidence of CAD has generally been attributed to low total cholesterol and high HDL cholesterol concentrations in African black persons [35]. However, recent studies reported reduced HDL cholesterol concentrations in this population, and low total cholesterol levels could be attributed to concurrent low HDL cholesterol levels [36]. Indeed, an alternative and more conceivable explanation is a more limited lifetime exposure to CVD risk factors, which is in line with the current rapid urbanization in this population [37]. In this regard, the prevalence of all major traditional CVD risk factors, except from low tobacco consumption, was found to be high and rising further in recent African black population studies [38–40]. In addition, particularly South African black women generally sustain much larger obesity rates than other groups living in the same region [41]. With regard to psychosocial stress as a potential CVD risk factor, the recent World Health Organization Mental Health Survey revealed that within the historical context of early after apartheid, anxiety and other mood disorders were relatively more prevalent and severe in South Africa than in other participating countries [42].

2.3. Impact of Cardiovascular Risk Factors on Cardiovascular Disease. In the INTERHEART Africa study and the associations of modifiable CVD risk factors with acute MI were similar to those in the overall INTERHEART study, with smoking, diabetes, hypertension, abdominal obesity, and dyslipidemia providing a population attributable risk of 89.2% for acute MI [25]. However, a history of hypertension revealed a higher MI risk in the African black group. In relatively large stroke studies amongst African black patients, hypertension was the most frequently implicated cause [31, 32].

Table 1: The epidemiological health transition stages and their characteristics.

Stage	Circumstance	Environmental factors and related CVD risk factors	CVD events
1	Living in rural area	Infections and nutritional deficiencies	Rheumatic heart disease and cardiomyopathy
2	Early urbanization	Reduced infection and improved nutrition, psychosocial stress, and hypertension	Heart failure and hemorrhagic stroke
3	More advanced urbanization	Lifestyle changes: increased fat intake, cigarette smoking, and inactivity	Atherosclerotic CVD and ischemic stroke at young age
4	Established urbanization	Improved health care and CVD prevention	CVD and stroke in the elderly

CVD: cardiovascular disease.

Both systolic and diastolic blood pressures are further important determinants of diastolic function in this population [43]. Importantly, the potential influence of excess adiposity on stroke risk was not reported and the cause remained unidentified in 43% of cases. Excess adiposity is associated with hypertension as well as diastolic left ventricular function and systemic inflammation in this population [44, 45]. The risk of tobacco related CVD (as well as cancer) in urban African black persons is similar to that reported in developed populations [46]. Even mild current smoking was strongly associated with blood pressure in an African black population study [47]. Interestingly, psychosocial stress but not hypertension was associated with angiopoietin-2 and vascular endothelial growth factor-A concentrations, which are markers of angiogenesis that associate with vascular dysfunction in African black subjects [48]. Whether novel CVD risk biomarkers can improve CVD risk stratification beyond conventional CVD risk factors in this population remains however largely unknown.

3. The Impact of Rheumatoid Arthritis on Cardiovascular Risk Factors, Atherosclerosis, and Their Relations amongst Black Africans

The potential impact of RA on cardiovascular risk factor profiles including traditional risk factors and systemic inflammation, atherosclerosis, and their relationships was investigated in 274 African black patients of which 115 had established RA [49].

3.1. Cardiovascular Risk Factor Profiles. Amongst conventional risk factors, overall and abdominal adiposity as estimated by body mass index and waist-height ratio, respectively, were markedly reduced in RA. Dyslipidemia was less prevalent in RA, a finding that was explained by reduced adiposity and chloroquine use. RA patients were more often former smokers [(odds ratio (OR)) (95% confidence interval (CI)) = 2.48 (1.03–5.99)]. However, other conventional risk factors including fat distribution (waist-hip ratio), current smoking, diabetes, and hypertension prevalence as well as the number of major traditional risk factors did not differ by RA status.

With regard to nonconventional cardiovascular risk factors, circulating CRP concentrations were similar in both groups and those of IL-6 were actually reduced in RA, possibly as a result of reduced adiposity.

3.2. Atherosclerosis Burden. The mean ultrasound determined carotid artery intima-media thickness (cIMT) was 0.700 (0.085) and 0.701 (0.111) mm which was similar in RA and non-RA subjects in univariate and adjusted analysis.

3.3. Risk Factors Associated with Atherosclerosis. Clinical RA activity characteristics were consistently unrelated to systemic inflammatory markers, even in patients with moderate or high disease activity (Clinical Disease Activity Index > 10). By contrast, non-RA characteristics comprising adiposity indices, smoking and alcohol consumption status, and angiotensin converting enzyme inhibitor use were related to systemic inflammation and to a similar extent in persons with and without RA.

Amongst cardiovascular risk factors, only low density lipoprotein concentrations were weakly associated (partial $R = 0.153$ to 0.135; $P = 0.03$ to 0.06) depending on covariates included in mixed regression models with atherosclerosis in all participants and, again, RA did not impact this and all the other risk factor-atherosclerosis relationships.

Taken together, amongst black Africans from a developing population, RA can currently have an impact on individual conventional risk factors but is not associated with an increased overall increased traditional and nontraditional cardiovascular risk factor and atherosclerosis burden. The distinctly low prevalence of extra-articular manifestations in black Africans with RA points towards an inflammatory process that is mostly restricted to the joints [50]. Indeed, particularly our findings of similar CRP and lower IL-6 concentrations in RA compared to non-RA subjects as well as the consistent lack of relationships between clinical disease activity markers and the respective acute phase responses suggest that an absent IL-6 release by inflamed RA joints into the circulation can account for the unaltered risk. Is the atherosclerotic cardiovascular risk factor burden presently still more favorable in black compared to other Africans with established RA?

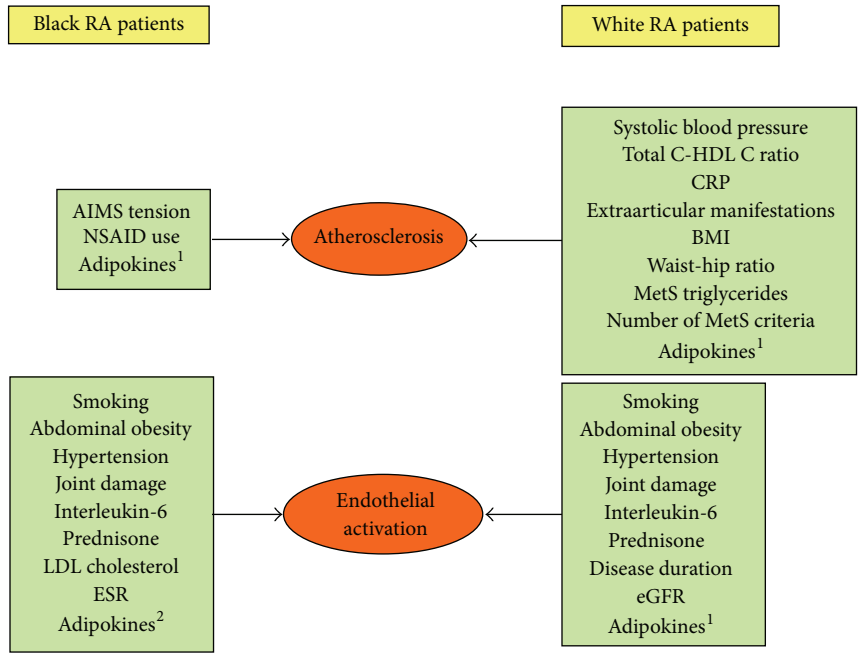

Figure 1: Cardiovascular risk factors that were associated with atherosclerosis and endothelial activation in African black and white patients with RA. [1]Adiponectin, leptin, resistin, retinol binding protein-1, and chemerin. [2]Leptin, resistin, retinol binding protein-1, and chemerin.

4. Cardiovascular Risk Factor Profiles amongst Black and Other Africans with RA

4.1. Major Conventional Risk Factors. Potential disparities in atherosclerotic CVD risk factor profiles between 291 black and 335 (229 whites, 64 Asian, and 42 mixed ancestry) other Africans with RA were determined [51]. Compared to other Africans, black Africans smoked less frequently but had more prevalent hypertension and diabetes together with concurrent lower total as well as HDL cholesterol concentrations that resulted in unaltered atherogenic indices. These results are congruent with those on cardiovascular risk factor profiles in non-RA black persons in sub-Saharan Africa as outlined previously. More importantly in the present context, these findings translated into global scores for major conventional risk factor-mediated future atherosclerotic CVD event rates that were not reduced in black compared to other African RA patients.

4.2. Metabolic Syndrome and Its Components. The metabolic syndrome (MetS) reportedly predicts incident diabetes and atherosclerotic CVD, and its presence calls for lifestyle intervention. In this study, the MetS blood pressure and HDL criteria were more prevalent whereas the respective triglyceride criterion was less frequent amongst African black compared to other African patients with RA. In developed populations, increased triglyceride and decreased HDL cholesterol production typically concur [36]. However, low triglyceride concentrations despite the presence of reduced HDL levels were also previously reported in African black non-RA subjects [36]. Importantly, in the present context also, the overall metabolic risk burden as estimated by MetS prevalence and the number of MetS criteria was similar in African black compared with other African patients with RA.

4.3. Nonconventional Risk Factors. Black ethnicity did not independently associate with nonconventional cardiovascular risk factors including rheumatoid factor status, markers of inflammation, and brachial pulse pressures. Mixed-ancestry Africans without RA reportedly still sustain a lower risk for ischemic heart disease than white and Asian Africans [25]. When we excluded Africans of mixed ancestry from our analysis, the findings were unaltered.

Taken together, overall conventional and nonconventional CVD risk burdens and arterial stiffness were similar in black compared to other African patients with RA. This indicates that CVD risk should be assessed and managed irrespective of ethnic origin and epidemiological transition stage in RA. However, amongst Africans, is the atherosclerosis burden and the impact of cardiovascular risk factors on atherosclerosis, as large in black compared to white patients with RA?

5. The Atherosclerosis Burden and Its Associations with Conventional Risk Factors and Inflammation in Black and White Africans with RA

The carotid atherosclerosis burden and its relationship with major conventional and nonconventional cardiovascular risk factors between Africans with RA were compared between 121 black and 122 white Africans with RA [52]. The risk factors that were associated with atherosclerosis in African black and white patients with RA are shown in Figure 1.

5.1. Atherosclerosis Burden. The mean ± SD cIMT was 0.694 ± 0.097 mm in black and 0.712 ± 0.136 mm in white patients with RA; forty-three (35.5%) of the black and 54 (44.3%) of Caucasian patients had plaque. Plaque prevalence and carotid intima-media thickness (cIMT) did not differ between black and white patients in univariate and adjusted analysis.

5.2. Major Conventional Risk Factors and RA Characteristics Associated with Atherosclerosis. Upon using interaction terms, population grouping consistently influenced the relations of cardiovascular risk factors with cIMT and plaque. Therefore, cardiovascular risk factor atherosclerosis was determined in stratified analysis, that is, in black and white patients separately. This revealed that systolic blood pressure, the cholesterol-HDL cholesterol ratio, CRP concentrations, and the presence of extra-articular manifestations are independently related to cIMT or/and plaque in white but not black patients with RA. In sharp contrast, the Arthritis Impact Measurement Scales tension score and the use of nonsteroidal anti-inflammatory agents were associated with atherosclerosis in black but not white participants. The Framingham score was significantly associated with atherosclerosis in white but not black patients.

These findings indicate that the atherosclerosis burden is currently as large in black Africans with RA from a developing population as it is in whites from a developed population and further reinforce the notion that adequate cardiovascular risk assessment and management are required in Africans with RA irrespective of ethnicity. Equally important, the findings in this study suggest that major conventional risk factor and systemic inflammation markers are unreliable in cardiovascular risk stratification amongst black Africans with RA. We therefore believe that the systematic use of alternative risk evaluation tools such as vascular imaging by carotid ultrasound [22] may be particularly warranted in this context.

5.3. The Relation of Adiposity with Atherosclerosis in African Black Compared to White Women with RA. As obesity is particularly prevalent amongst African Black women, and the potential impact of adiposity on atherosclerosis was examined. Included patients with RA comprised 108 black and 95 white women [53].

BMI and waist-to-height ratio were substantially larger in African black compared to white women with RA (29.9 (6.6) versus 25.3 (4.9) kg/m ($P = 0.002$) and 0.59 (0.09) versus 0.53 (0.08) ($P = 0.01$), resp.).

Anthropometric measures independently associated with the metabolic risk factors of blood pressure, lipid variables, and glucose; population grouping did not impact these relationships. However, in white women, body mass index (BMI) was related to cIMT and adverse fat distribution as estimated by waist-hip ratio associated with plaque; by contrast, none of the anthropometric measures were related to atherosclerosis in African black women with RA. The adiposity-atherosclerosis relations were explained by metabolic risk factors amongst white women with RA.

These findings indicate that obesity as estimated by anthropometric measures in women with RA from developing groups of black African descent does not yet translate into atheroma and hence does not currently represent enhanced atherosclerosis risk, whereas body mass index and waist-to-hip ratio should be considered in cardiovascular risk assessment amongst white women with RA. This supports the notion that optimal CVD risk stratification is likely to differ amongst black and white African women with RA.

5.4. The Association of MetS and Its Components with Atherosclerosis in African Black Compared to White Women with RA. The associations between MetS and its components and atherosclerosis were investigated in 104 African black and 93 white women [54].

The MetS and MetS HDL-cholesterol component prevalence were markedly larger in black compared to white female participants (30.8% versus 9.7%; OR (95% CI) = 10.11 (1.76–58.03) ($P = 0.009$) and 21.2% versus 15.1%; OR (95% CI) = 6.14 (1.11–33.92) ($P = 0.036$)), MetS triglycerides and the number of MetS criteria associated independently with plaque in white but not black women with RA. These findings indicate that the current markedly adverse metabolic risk factor profiles in black African patients with RA do not yet represent an enhanced atherosclerosis burden.

6. The Potential Impact of Cardiovascular Risk Factors on Early Endothelial Activation in African Black and White RA Patients

In an attempt to further elucidate disparities in CVD risk and its potential effective stratification amongst African black and white RA patients, independent relations of major conventional risk factors and systemic inflammation with surrogate markers of early atherogenesis were examined. The risk factors that were associated with endothelial activation in African black and white patients with RA are also shown in Figure 1. Participants included 112 African black and 105 white patients with RA [55]. Evaluated endothelial activation molecule concentrations included those of E-selectin, vascular adhesion molecule-1, intercellular adhesion molecule-1, and monocyte chemoattractant protein-1. These molecules mediate the initial stages of atherosclerosis and their circulating concentrations associate with prevalent and incident atherosclerosis in RA [20, 21, 56].

In all patients, 3 conventional (smoking, abdominal obesity, and hypertension) and 3 nonconventional cardiovascular risk factors (joint damage, IL-6 concentrations, and prednisone use) were associated with endothelial activation. Interleukin-6 was the only risk factor that was related to each endothelial activation molecule and independently contributed by 18% and significantly more than other risk factors to the variation in overall endothelial activation as estimated by an SD (z) score of endothelial activation molecule concentrations. The independent interleukin-6-overall endothelial activation relationships were reproduced in various subgroups. In addition, LDL cholesterol concentrations and the erythrocyte concentrations were associated with endothelial activation in African black but not white patients. Also, disease duration and glomerular filtration rate related to

surrogate markers of early atherogenesis in African white but not black participants.

Upon using cardiovascular risk biomarkers, and in contrast to the previously discussed investigations, this study revealed the similarities in CVD risk factor-endothelial activation relations in African black compared to white RA patients mostly. Nevertheless, this investigation again documented that disparities in the potential role of CVD risk factors with possible if not likely implications in cardiovascular risk stratification, exist amongst African black and white patients with RA. Overall, interleukin-6 concentrations are related consistently, markedly, and to a larger extent than other cardiovascular risk factors to endothelial activation in RA. In fact, IL-6 concentrations were numerically more strongly associated with endothelial activation in African black compared to white RA patients partial ($R = 0.416$ versus 0.378). Notably in the present context, IL-6 concentrations were also shown to be associated with coronary artery calcification scores that represent atherosclerosis, in RA [57]. Taken together, the findings support observations alluded to the above, which indicate that there is a need for alternative cardiovascular stratification tools in this case comprising the use of biomarkers, in African black Africans with RA.

7. The Relation of Circulating Adipokine Concentrations with Endothelial Activation and Atherosclerosis in Africans with RA

Whereas anthropometric measures, which represent indicators of fat mass, did not relate to atherosclerosis in African black patients with RA, it is now well established that adipose tissue constitutes a highly active endocrine and metabolic organ. Indeed, adipocytes produce a large range of molecules that are referred to as adipocytokines, which mediate the impact of adipose tissue on the risk for CVD and diabetes as well as different bodily functions including immunity, appetite, and energy expenditure [58–64]. Examples of adipokine effects comprise the modulating influence of adiponectin, visfatin, nesfatin, vaspin, and chemerin on obesity-related vascular complications [58, 59] as well as those of adiponectin, leptin, resistin, visfatin, and chemerin on inflammatory and destructive processes [60–63] and cardiovascular risk [64] in RA.

Importantly, in the present context, the production and effects of adipokines can be altered by the presence of autoimmunity [64] and depend on pathophysiological context both in non-RA [59] and RA subjects [64]. Adipokines participate in the pathophysiology of RA and circulating concentrations of leptin [65] and adiponectin [66] relate to metabolic risk whereas those of resistin are associated with systemic inflammation in this disease [67]. Interestingly, visfatin is not associated with inflammation or metabolic syndrome in patients with severe RA [68]. Indeed, the role of adipokines in cardiovascular risk amongst patients with RA remains uncertain. As excess adiposity is highly prevalent in African black patients with RA and adipokines reflect not only fat mass but also adipocyte bioactivity, could the evaluation of adipokine concentrations assist in the exploration of CVD risk and its stratification in this context?

In this regard, several investigations on the relations of adipokines with CVD risk amongst approximately 120 African black and 120 white patients with RA were recently reported. Indeed, adiponectin [69, 70], leptin [71], chemerin [72], and retinol binding protein-4 [73] were associated with metabolic risk factors. More importantly, adiponectin [70, 74], leptin [71, 75], chemerin [72], retinol binding protein 4 [73], and resistin [76, 77] were each independently related to surrogate markers of endothelial activation and atherosclerosis in RA (Figure 1). A detailed account of the different findings is beyond the scope of this review. Pertinently however, the independent relations of each of the 5 studied adipokines with endothelial activation and atherosclerosis were mostly documented in groups stratified on the basis of the presence or absence of different conventional or nonconventional risk factors [70–77]. These findings amply document that pathophysiological context impacts adipokine-CVD risk relations and indeed suggest that adipokine concentrations can contribute to improved CVD stratification in RA.

With regard to population origin, whereas adiponectin and leptin production is increased or unaltered in RA patients from developed populations, circulating concentrations of both adipokines were reduced in black African RA compared to non-RA subjects [69]. However, black population origin did not impact adipokine-endothelial activation [70] and atherosclerosis [74] with a single exception. The latter comprised a paradoxically direct association between adiponectin concentrations and endothelial activation amongst white but not black Africans with RA [70]. In contrast to the other investigated adipokines, adiponectin reduces atherosclerosis risk in non-RA subjects. Paradoxical adipokine-endothelial activation relations in RA likely represent compensatory changes in adipokine production in the presence of increased cardiovascular risk and in an attempt to reduce this risk [70]. Indeed, the paradoxical adiponectin-endothelial activation relation concurred with a borderline significant inverse association of adiponectin with carotid plaque, an indicator of severe, advanced, and high risk atherosclerosis in white RA patients [74].

Adiponectin is further a potential therapeutic target in RA [69]. If our findings are confirmed in future longitudinal and mechanistic studies, then adiponectin inhibition would be expected to potentially enhance CVD risk particularly in white patients with RA.

Overall, these studies indicate that, in contrast to conventional and previously investigated nonconventional cardiovascular risk factors, adipokine concentrations may represent promising tools in CVD risk stratification in black Africans with RA.

8. Limitations and Future Perspectives

The most important limitation of currently available data on CVD and its risk factors in African black patients with RA is that they consistently derive from cross-sectionally

designed investigations. Longitudinal studies with the additional inclusion of CVD events as an outcome measure in this patient population are underway. Also, formal evaluation of aortic and left ventricular function is needed, particularly considering the high prevalence of hypertension in African black persons including those with RA and heart failure in the African black population at large. Investigations addressing this limitation of previous reports have also been initiated.

Antirheumatic drugs comprising nonsteroidal anti-inflammatory agents (NSAID), corticosteroids, and synthetic and biologic disease modifying agents for rheumatic disease (DMARD) can influence CVD risk in RA [2, 17, 18, 21]. In this regard, investigations performed in the USA documented that markers of sociodemographic disadvantage including black ethnicity associate with less frequent use and later initiation of synthetic and biologic DMARD as well as more regular NSAID use [78–80]. However, with the exception of absent versus infrequent use of biologic DMARD in African black compared to white RA patients, both groups employed similar antirheumatic drug regimens in our settings [51, 53].

9. Conclusion

The present review argues not only against the extrapolation of findings on atherogenesis and recommendations on CVD risk stratification derived in non-RA to RA populations but also against that of data originating in patients with RA that belong to developed populations to those from developing populations. In this regard, we found that routinely assessed traditional and nontraditional CVD risk factors were consistently and independently related to atherosclerosis in African white but not black patients with RA. By contrast, circulating concentrations of novel CVD risk biomarkers including interleukin-6 and interleukin-5 adipokines were mostly similarly associated with both endothelial activation and atherosclerosis amongst African black and white RA patients. Reliable CVD risk stratification in African black RA patients may prove to require systematic vascular imaging such as carotid ultrasonography and possibly the use of novel CVD risk markers.

Abbreviations

RA: Rheumatoid arthritis
AIMS: Arthritis impact measurement scales
NSAID: Nonsteroidal anti-inflammatory agents
LDL: Low density lipoprotein
ESR: Erythrocyte sedimentation rate
C: Cholesterol
HDL: High density lipoprotein
CRP: C-reactive protein
BMI: Body mass index
MetS: Metabolic syndrome
eGFR: Estimated glomerular filtration rate.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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