Association of apolipoprotein B/apolipoprotein A1 ratio and cardiovascular events in rheumatoid arthritis: results of the CARMA study

S. Zegarra-Mondragón[1], R. López-González[2], M.A. Martín-Martínez[3], C. García-Gómez[4], F. Sánchez-Alonso[3], C. González-Juanatey[5], S. Manrique Arija[6], G. Bonilla Hernán[7], S. Martínez Pardo[8], A. Ruibal Escribano[9], E. Pagán García[10], E. Delgado Frías[11], J. Rivera Redondo[12], M. Delgado Sánchez[13], A.B. Rodríguez Cambrón[14], M.J. Moreno Ramos[15], S.A. Rodríguez Montero[16], M.T. Navío Marco[17], M. Morcillo Valle[18], J. García González[19], J. Bachiller Corral[20], J. Llorca[21], S. Castañeda[22], M.A. González-Gay[23-25], on behalf of the CARMA Project Collaborative Group.

[1]Division of Rheumatology, Hospital de Manises, Valencia; [2]Division of Rheumatology, Hospital Universitario Hospital General Virgen de la Concha, Zamora; [3]Research Unit of Spanish Society of Rheumatology, Madrid; [4]Division of Rheumatology, Consorci Sanitari de Terrassa, Terrassa, Barcelona; [5]Division of Cardiology, Hospital Lucus Augusti, Lugo; [6]Division of Rheumatology, Hospital Regional Universitario de Málaga, Málaga; [7]Division of Rheumatology, Hospital Universitario La Paz, Madrid; [8]Division of Rheumatology, Hospital Universitari Mútua Terrassa, Barcelona; [9]Division of Rheumatology, Hospital Universitario de Araba, Vitoria-Gasteiz; [10]Division of Rheumatology, Hospital Universitario Los Arcos del Mar Menor, Murcia; [11]Division of Rheumatology, Hospital Universitario de Canarias, Tenerife; [12]Division of Rheumatology, Instituto Provincial de Rehabilitación, Madrid; [13]Division of Rheumatology, Hospital Universitario Nuestra Señora de Candelaria, Tenerife; [14]Division of Rheumatology, Hospital Universitario Severo Ochoa, Madrid; [15]Division of Rheumatology, Hospital Universitario Virgen de la Arrixaca, Murcia; [16]Division of Rheumatology, Hospital Universitario Virgen de Valme, Sevilla; [17]Division of Rheumatology, Hospital Universitario Infanta Leonor, Madrid; [18]Division of Rheumatology, Hospital El Escorial, Madrid; [19]Division of Rheumatology, Hospital Universitario 12 de Octubre, Madrid; [20]Division of Rheumatology, Hospital Universitario Ramón y Cajal, Madrid; [21]University of Cantabria and CIBER Epidemiología y Salud Pública (CIBERESP), Santander; [22]Division of Rheumatology, Hospital Universitario de La Princesa, IIS-Princesa, Cátedra UAM-ROCHE, EPID-Future, Universidad Autónoma (UAM), Madrid; [23]University of Cantabria, Division of Rheumatology, Hospital Universitario Marqués de Valdecilla, Santander; [24]Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, IDIVAL, Santander, Spain; [25]University of the Witwatersrand, Cardiovascular Pathophysiology and Genomics Research Unit, School of Physiology, Faculty of Health Sciences, South Africa.

Abstract

Objective

To assess the plasma apolipoprotein B/apolipoprotein A1 ratio and its potential association with cardiovascular events (CVE) in patients with rheumatoid arthritis (RA).

Methods

A baseline analysis was made of the CARdiovascular in rheuMAtology Project (CARMA), a 10-year prospective study evaluating the presence of at least one CVE in 775 Spanish patients with RA. Of them, 29 had already experienced CVE prior to the inclusion in the study. We assessed the association between the elevation of the apoB/apoA1 ratio with the presence of CVE according to a logistic regression model for possible confounding factors. We also analysed the main parameters of activity of RA and parameters related to lipid metabolism. RA patients were classified according to treatment: patients treated with disease-modifying anti-rheumatic drugs without biologics and those undergoing biologic therapy (anti-TNF-α, anti-IL-6 receptor, and other biologic agents).

Results

The apoB/apoA1 ratio of patients who had experienced CVE was higher than that of patients without previous CVE (0.65 vs. 0.60). However, the difference between both subgroups did not reach statistical significance (p=0.197). It was also the case after the multivariate analysis [OR: 1.48 (95% CI: 0.15–14.4); p=0.735]. RA patients from the group with CVE were more commonly receiving lipid-lowering treatment with statins than those without CVE history (41.4% vs. 20%, p=0.005). High HAQ and high atherogenic index were significantly associated with the presence of CVE. There was no statistical association between the type of biologic therapy used in RA and the presence of CVE.

Conclusion

No association between ApoB/apoA1 ratio and CVE was found at the baseline visit of patients with RA from the CARMA study.

Key words

cardiovascular disease, rheumatoid arthritis, lipids, apolipoprotein A1, apolipoprotein B

*Sixto Zegarra-Mondragón, MD**
*Ruth López-González, MD, PhD**
María A. Martín-Martínez, MD
Carmen García-Gómez, MD, PhD
Fernando Sánchez-Alonso, MD
Carlos González-Juanatey, MD, PhD
Sara Manrique Arija, MD, PhD
Gema Bonilla Hernán, MD
Silvia Martínez Pardo, MD
Ana Ruibal Escribano, MD
Encarnación Pagán García, MD
Esmeralda Delgado Frías, MD, PhD
Javier Rivera Redondo, MD, PhD
Mónica Delgado Sánchez, MD
Ana Belén Rodríguez Cambrón, MD
Manuel José Moreno Ramos, MD, PhD
Sergio Antonio Rodriguez Montero, MD
Maria Teresa Navío Marco, MD, PhD
Mercedes Morcillo Valle, MD
Javier García Gonzalez, MD
Javier Bachiller Corral, MD, PhD
Javier Llorca, MD, PhD
Santos Castañeda, MD, PhD
Miguel A. González-Gay, MD, PhD

** These authors share first authorship of this work.*

The members of the CARMA Project Collaborative Group are listed on page 668.

Please address correspondence to:
Miguel A. González-Gay,
Hospital Universitario Marqués de Valdecilla, IDIVAL
Avenida de Valdecilla, s/n,
39008 Santander, Spain.
E-mail: miguelaggay@hotmail.com

Received on April 12, 2019; accepted in revised form on September 2, 2019.

Funding: this project has been supported by an unrestricted grant from Abbvie, Spain. However, the design, analysis, interpretation of results and preparation of the manuscript has been made independently of Abbvie. Dr González-Gay's studies have been supported by grants from Fondo de Investigaciones Sanitarias PI06/0024, PS09/00748 and PI12/00060, PI15/00525, PI18/00043, and RD12/0009/0013 and RD16/0012 (RIER) from Instituto de Salud Carlos III (ISCIII) (Spain), co-funded by FEDER funds.

Competing interests: none declared.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease associated with increased risk of cardiovascular (CV) disease (1, 2). This is the result of a process of accelerated atherosclerosis (3). Apart from the role of traditional CV risk factors (CVRFs) (4), the excess of CV disease observed in patients with RA is also attributed to the presence of chronic inflammation (5) and the concurrence of a genetic component (6). Recently, the role of adipokines has been suggested as a striking link between adiposity, inflammation, and cardiometabolic diseases in these patients, mainly related with endothelial dysfunction and insulin resistance (7). Regarding CVRFs, alterations in lipid metabolism play a special role, given that lipids undergo important pro-atherogenic molecular transformations that are usually linked to chronic inflammation (8, 9).

Apolipoproteins are proteins that bind lipids to form the lipoproteins that transport the lipids through the lymphatic and circulatory systems. Apolipoprotein B (apo B) is the primary apolipoprotein in low-density lipoprotein (LDL), which is responsible for transporting cholesterol to the tissues. In contrast, apolipoprotein A1 (apo A1), the major protein component in high-density lipoprotein (HDL), expresses its anti-atherogenic properties by transporting cholesterol from tissues to the liver (10). Interestingly, the ratio between these two apolipoproteins has been associated with CV risk (11). In fact, an increased apoB/apoA1 ratio is one of the strongest predictive risk factors for suffering future CV events (CVE) in the general population (12, 13). However, the impact of this association has not been well elucidated in patients with chronic inflammatory rheumatic diseases (CIRD). In this context, in an attempt to find new predictors of CVD in RA, we assessed the association of this ratio with CVE (14), because the evaluation of CV risk through traditional CVRFs underestimates the risk of suffering a CVE in patients with RA. Taking all these considerations into account, the purpose of the present study was to evaluate the plasma apoB/apoA1 ratio and its association with CVE in Spanish patients with RA enrolled in the "CARdiovascular in rheuMAtology" (CARMA) project, a real-world prospective study designed to determine the CV morbidity and mortality risk in patients with CIRD.

Material and methods

Study design

Cross-sectional analysis from the baseline visit of the CARMA study, a 10-year prospective study aimed to identify the CVD risk profile in Spanish patients with RA, ankylosing spondylitis and psoriatic arthritis followed at 67 Outpatients Rheumatology Units after 10 years of follow-up.

Patient recruitment

For this study, a total of 775 patients diagnosed with RA were included. The 67 participants Rheumatology Units were randomly selected from Spanish National Health System hospitals after a probabilistic cluster sampling from the database of the Spanish Society of Rheumatology (SER).

The inclusion criteria for the recruitment period (July 2010-January 2012) were patients older than 18 years with a diagnosis of RA according to the 1987 American College of Rheumatology (ACR) classification criteria (15). Information on the sample size of the project and baseline characteristics of the population was previously described by Castañeda *et al* (16).

The study was performed following the principles outlined in the Helsinki Declaration (17), and the study protocol was approved by the Ethics Committee for Clinical Research of Lugo, Galicia, Spain (approval protocol number: 2009/077) and later in all participants centres. All patients signed a written informed consent to participate in the study and to publish the data obtained.

Variables and operative definitions

The dependent variable was the presence of at least one CVE in patients with RA, defined by the following conditions: i) ischaemic heart disease (IHD) defined by a personal history of acute myocardial infarction (AMI) or non-silent angina; ii) cerebrovascular accident (CVA): any vascular episode documented, transient or established, haem-

orrhagic or ischaemic, in the brain; iii) congestive heart failure (CHD) including all cases of heart failure according to the Framingham criteria (18) (episodes of non-cardiac dyspnea were excluded); iv) peripheral arterial disease (PAD) defined as a chronic or acute occlusive disease of the lower extremities caused by atherosclerotic arterial.

Traditional CVRF

Traditional CVRFs analysed were: 1) Obesity: based in the body mass index (BMI), kg/m^2, using the WHO criteria (lower weight BMI <18.5, normal weight BMI between 18.5–24.9, overweight BMI between 25–29.9 and obesity BMI ≥30 kg/m^2); 2) Physical activity level (low, medium or intense) according to daily activity (low activity: sitting most of the time; moderate activity: standing most of the time and with little movement or effort; intense activity: walking most of the time or performing tasks that require high physical activity); 3) Hypertension: Patients were considered to have hypertension if before baseline recruitment they had been diagnosed as having hypertension by their family physicians or if systolic blood pressure (BP) was ≥140 mmHg and/or diastolic BP ≥90 mmHg; 4) Dyslipidaemia: if before baseline recruitment they were taking lipid-lowering drugs because a diagnosis of dyslipidaemia or at the time of recruitment they had an abnormal amount of lipids [triglycerides (TG) and/or total cholesterol (TC)] in the blood. Hypercholesterolaemia was defined when serum TC was ≥240 mg/dL (6.5 nmol/L) in two different times or if the patient was under treatment for hypercholesterolaemia. Hypertriglyceridaemia was defined when blood TG levels were ≥150 mg/dL in two different consecutive occasions or if the patient was under therapy for hypertriglyceridaemia; 5) Smoking was stratified in 3 categories: current smokers (<10, 10–20, >20 cigarettes/day), ex-smokers (time past >1 year) and never smokers; 6) Diabetes mellitus (DM), if before baseline recruitment patients had been diagnosed as having diabetes mellitus or at the time of recruitment the serum levels of glucose ≥126 mg/dL (7.0 mmol/L) after nocturnal fasting; 7) Family history of IHD (current or not).

Parameters related with lipid metabolism

The serum apoB/apoA1 ratio was considered a primary criterion of evaluation, expressed as a continuous variable. Regarding lipid metabolism, the main parameters analysed were: TC, TG, LDL-cholesterol (LDL-c), HDL-cholesterol (HDL-c), apolipoprotein A1 (apo-A1), apolipoprotein B (apo-B), TC/HDL-c ratio (atherogenic index), and also LDL-c/HDL-c. All the variables were measured in mg/dL.

Parameters associated with disease activity and therapy

We analysed the main parameters of inflammation and RA activity, including the number of tender and swollen joints (TJ and SJ), C-reactive protein (CRP) in mg/L, erythrocyte sedimentation rate (ESR) in mm/h (Westergren method); DAS28-ESR activity score, expressed a continuous variable; rheumatoid factor (RF) (positive or negative) and anti-cyclic citrullinated peptide antibodies (anti-CCP) (positive or negative).

RA treatment as an added variable was classified in 4 categories: a) only disease-modifying anti-rheumatic drugs (DMARDs): sulfasalazine, methotrexate and/or leflunomide; b) treatment with tumor necrosis factor antagonists (anti-TNFα agents); c) treatment with IL-6 receptor antagonists (tocilizumab); and d) other biologic therapies (rituximab or abatacept). Glucocorticoid treatment and non-steroidal anti-inflammatory drugs (NSAIDs) were not considered as a different category.

Statistical analysis

Variables were described according to their typology and distribution. Categorical variables were described using frequencies and percentages. Differences between groups were compared using chi-squared tests. Continuous variables that followed a Normal distribution were described using the mean and standard deviation (SD) and the differences between groups were assessed using analysis of variance tests.

Bivariate study was done for evaluating the demographic and clinical characteristics of the patients as well as the traditional CVRFs. The association between CVE and RA patients was completed by a logistic regression model for potential confounding factors. To reduce variability in the methods of measurement of apoB/apoA1 across the participating hospitals, mixed multivariate regression models were constructed with robust variance estimators using the hospital as a cluster for variable estimation. The selection of adjusted variables in the multivariate model was based on clinical judgment and those with a *p*-value ≤0.20 in the bivariate analysis. Multicollinearity among independent variables was also explored to build the model. Data management and statistical analysis were centralised at the Research Unit of the SER following a pre-established analysis plan. All the analyses were performed using the Stata 13.1 package (Copyright 1985-2013 StataCorp LP 4905. Lakeway Drive, College Station, Texas 77845, USA).

Results

Demographic and clinical characteristics of our study of patients with RA

From 775 RA patients included in the CARMA study, 29 had already experienced CVE before their inclusion in the study. Of all of them, only 591 and 603 patients had data on the plasma apoA1 and apoB levels, respectively, at the baseline visit, without loss of registry of apolipoprotein values in the 29 cases that had suffered a CVE.

Table I shows the clinical characteristics, comorbidities and laboratory data of the RA patients included in the present study. In total, 75% were women, with a mean age of 56.6±12.3 years. The patients who had experienced CVE had an older age with a higher frequency of hypertension and hypercholesterolaemia with statistical significance with respect to the group without CVE history.

Regarding clinical features, the group of patients who had suffered a CVE has increased Health Assessment Questionnaire (HAQ) with respect to the group without history of CVE at the time of inclusion in the study.

Table I. Baseline sociodemographic, traditional cardiovascular risk factors and clinical characteristics of patients.

	Total (n=775)	No CVE (n=746)	CVE (n=29)	*p*-value
Sociodemographic features				
Age at inclusion, years, mean (SD)	56.6 (12.3)	56.1 (12.2)	68.4 (8.7)	**<0.001**
Age at the beginning of disease, years, mean (SD)	45.8 (13.4)	45.4 (13.1)	58.0 (14.1)	**<0.001**
Sex, female, n (%)	581 (75.0)	576 (76.0)	14 (48.3)	**0.001**
Educational level, n (%)				
- Elementary	467 (60.9)	442 (59.9)	25 (86.2)	
- Secondary /University	300 (39.1)	296 (40.1)	4 (13.8)	**<0.001**
Traditional CVRF				
BMI, kg/m^2, mean (SD)	26.9 (4.8)	26.8 (4.8)	28.4 (4.8)	0.076
Hypertension, n (%)	236 (30.5)	215 (28.8)	21 (72.4)	**<0.001**
Hypercholesterolaemia, n (%)	238 (30.7)	224 (30.0)	154 (48.3)	**0.037**
Smoking status, n (%)				
- Current smokers	189 (24.4)	187 (24.1)	2 (6.9)	
- Past smokers	202 (26.1)	191 (24.6)	11 (37.9)	
- Never smoking	384 (49.6)	368 (47.5)	16 (55.2)	0.061
Family history of IHD, n (%)	96 (12.4)	90 (11.6)	6 (20.7)	0.170
Diabetes, n (%)				**<0.001**
Non-insulin dependent	46 (5.9)	40 (5.5)	6 (20.7)	**<0.001**
Without organic damage	10 (1.3)	10 (1.3)	0 (0.0)	0.573
With organic damage	3 (0.4)	2 (0.3)	1 (3.5)	**0.003**
Clinical characteristics				
Disease duration, mean (SD)	10.2 (8.9)	10.2 (8.9)	9.8 (10.3)	0.806
Tender joint count (out of 28), median [p25–p75]	1 [0-3]	1 [0-3]	2 [0-4]	0.322
Swollen joint count (out of 28), median [p25–p75]	0 [0-2]	0 [0-2]	0 [0-1]	0.267
CRP, mg/L, median [p25–p75]	1.4 [0.4-4.5]	1.4 [0.4-4.4]	1.2 [0.2-7.4]	0.244
ESR, mm/first hour, median [p25–p75]	17.0 [9.0–29.0]	17.0 [9.0-29.0]	17.0 [10.0-25.0]	0.873
DAS28-ESR, mean (SD)	3.2 (1.3)	3.2 (1.2)	3.4 (1.3)	0.447
RF positive, n (%)	594 (76.7)	571 (76.5)	23 (79.3)	0.730
Anti-CCP positive, n (%)	463 (59.7)	442 (59.3)	21 (72.4)	0.156
HAQ (0–3), median [p25-p75]	0.5 [0.1 -1.1]	0.5 [0.1 -1.1]	1.0 [0.5-1.6]	**0.001**

Anti-CCP: anti-cyclic citrullinated peptide antibodies; BMI: body mass index; CRP: C-reactive protein; CVE: cardiovascular events; DAS28-ESR: Disease Activity Score using 28 swollen or tender joint count and ESR; DMARD: disease-modifying anti-rheumatic drugs; ESR: erythrocyte sedimentation rate; HAQ (0–3): Health Assessment Questionnaire; IHD: ischaemic heart disease; RF: rheumatoid factor; SD: standard deviation; TNF: tumour necrosis factor. **In bold**, all significant values ($p<0.05$).

Table II. Lipid profiles of patients with rheumatoid arthritis stratified by cardiovascular disease.

	Total (n=775)	No CVE (n=746)	CVE (n=29)	*p*-value
ApoB/ApoA1 ratio, mean (SD)	0.60 (0.01)	0.60 (0.01)	0.65 (0.06)	0.197
Triglycerides (mg/dL), mean (SD)	95.3 (2.2)	94.8 (2.3)	107.6 (12.2)	0.275
Total cholesterol (mg/dL), mean (SD)	204.2 (35.6)	204.4 (35.8)	197 (29.5)	0.267
HDL-c (mg/dL), mean (SD)	55.2 (0.9)	55.6 (0.9)	47.1 (4.1)	0.068
LDL-c (mg/dL), mean (SD)	110.2 (1.8)	110.4 (1.8)	103 (1.8)	0.477
Lipoprotein (a) (mg/dL), mean (SD)	26.6 (1.6)	26.9 (1.7)	16.4 (7.59)	0.227
Apo A1 (mg/dL),mean (SD)	163.0 (1.3)	163.3 (1.3)	156.4 (7.1)	0.295
Apo B (mg/dL), mean (SD)	94.4 (1.0)	94.4 (1.0)	94.2 (4.3)	0.965
LDL-c/HDL-c, mean (SD)	2.19 (1.01)	2.18 (0.98)	2.43 (1.66)	0.462
Atherogenic index, mean (SD) (Total cholesterol/HDL-c)	3.6 (1.3)	3.6 (1.3)	4.1 (2.3)	**0.047**

Apo: apolipoprotein; Atherogenic index: total cholesterol/HDL-c; CVE: cardiovascular events; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol. **In bold**, all significant values ($p<0.05$).

Lipid metabolism alterations

The lipid panel included in the study and the lipid levels analysed are shown in Table II.

In the bivariate analysis, no statistically significant differences were found in the lipid profile between patients with or without a history of CVE, except for the atherogenic index (TC/HDL-c ratio), which was higher in the group with a CVE history compared to the other group ($p=0.047$).

With respect to the main variable of the study, although apoB/apoA1 ratio was slightly higher in patients with CVE history compared to those without CVE (0.65 *vs*. 0.60), this difference was not statistically significant ($p=0.197$).

Statins were more commonly prescribed in patients from the group with CVE than in those without CVE

Table III. Baseline therapies of the population included in the study.

	Total (n=775)	No CVE (n=746)	CVE (n=29)	*p*-value
Statins, n (%) *	161 (20.8)	149 (20.0)	12 (41.4)	**0.005**
Glucocorticoids, n (% ever treated)	357 (46.1)	340 (45.6)	17 (58.6)	0.167
Synthetic DMARDs, n (%)	653 (84.3)	671 (84.1)	26 (89.7)	0.416
Anti-TNF drugs, n (%)	226 (29.2)	216 (29.0)	10 (34.5)	0.52
Tocilizumab, n (%)	30 (3.9)	30 (4.0)	0 (0.0)	0.271
Other biologic DMARDs, n (%)	47 (6.1)	46 (6.2)	1 (3.5)	0.547
Methotrexate, n (%)	541 (69.81)	23 (79.31)	518 (69.44)	0.256
Leflunomide, n (%)	172 (22.19)	4 (13.79)	168 (22.52)	0.267
Infliximab, n (%)	48 (6.19)	2 (6.9)	46 (6.17)	0.873
Etanercept, n (%)	95 (12.26)	3 (10.34)	92 (12.33)	0.749
Adalimumab, n (%)	85 (10.97)	5 (17.24)	80 (10.72)	0.27
Golimumab, n (%)	8 (1.03)	0 (0)	8 (1.07)	0.575
Certolizumab, n (%)	5 (0.65)	0 (0)	5 (0.67)	0.658
Rituximab, n (%)	27 (3.48)	0 (0)	27 (3.62)	0.297
Abatacept, n (%)	20 (2.58)	1 (3.45)	19 (2.55)	0.764

CVE: cardiovascular events; DMARDs: disease-modifying anti-rheumatic drugs; TNF: tumour necrosis factor.
In bold, all significant values ($p<0.05$).

Table IV. Multivariate analysis to determine the association between ApoB/ApoA ratio and CVE in patients with RA.

Variables	Crude OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Age at the onset of the study	1.1 (1.06-1.15)	**<0.001**	1.09 (1.03-1.01)	**0.002**
Sex (ref. female)	0.29 (0.14-0.62)	**0.001**	0.57 (0.18-1.9)	0.35
ApoB/ApoA ratio	3.40 (0.53-21.77)	0.197	1.48 (0.15-14.4)	0.735
Smoking (ref. current smokers)				
- Never smoking	4.07 (0.92-17.84)	0.06	2.66 (0.49-14.43)	0.26
- Past smokers	5.39 (1.18-24.62)	0.30	2.13 (0.34-13.29)	0.42
Family history of IHD (ref. no)	1.89 (0.75-4.78)	0.18	2.51 (0.77-8.24)	0.13
Diabetes (ref. no)				
- Non-insulin dependent	4.75 (1.82-12.32)	**0.001**	5.42 (1.69-17.4)	**0.004**
- Without organic damage	--	--	--	--
- With organic damage	15.77 (1.38-180.54)	**0.003**	9.28 (0.51-169.65)	0.13
Hypertension (ref. no)	6.48 (2.83-14.86)	**<0.001**	2.29 (0.82-6.36)	0.11
Hypercholesterolaemia (ref. no)	2.18 (1.03-4.58)	**0.04**	0.88 (0.32-2.42)	0.80
HDL-c	0.99 (0.97-1.00)	**0.07**	0.99 (0.97-1.01)	0.32
Anti-CCP positive (ref. no)	1.81 (0.79-4.13)	0.16	1.33 (0.47-3.78)	0.59
Biologic DMARDs	0.97 (0.45-2.08)	0.93	1.34 (0.49-3.65)	0.57

All variables were recorded at the time of inclusion in the study. Anti-CCP: anti-cyclic citrullinated peptide antibodies; Apo: apolipoproteins; CVE: cardiovascular events; DMARDs: disease-modifying anti-rheumatic drugs; HDL-c: high-density lipoprotein cholesterol; IHD: ischaemic heart disease; ESR: erythrocyte sedimentation rate; OR: odds ratio; adjusted OR for all variables included in the multivariate model; RA: rheumatoid arthritis.
In bold, all significant values ($p<0.05$).

history (41.4% *vs*. 20% in spite of 20; $p=0.005$) (Table III).

Patients with CVE or without CVE history did not show differences in the anti-rheumatic treatment prescribed: biologic or synthetic DMARDs. It was also the case for the type of biologic agent administered: anti TNF-α, tocilizumab, rituximab or abatacept.

A multivariate analysis was performed to determine the association between ApoB/ApoA ratio and CVE in patients with RA. However, as shown in Table IV, apoB/apoA1 ratio did not reach statistically significant differences [OR: 1.48 (95% CI: 0.15–14.4); $p=0.735$] after adjustment for the main confounding factors. However, patients with non-insulin dependent type 2 DM had an increased risk of CVE (Table IV).

Discussion

In the present study, no association was found between the apoB/apoA1 ratio and CVE history in patients with RA included in the baseline visit of the CARMA project, although the ratio was slightly higher in patients with a CVE history.

Besides homocysteine, lipoprotein (a) and atherogenic index, ApoB/ApoA1 is a predictive lipid parameter associated with CVE in the general population (19). According to INTERHEART study, a case-control study where participants were recruited from 52 countries worldwide, the risk of developing a CVE correlated with a higher plasma apoB/apoA1 ratio in the general population, being this risk higher than smoking, hypertension, DM, and abdominal obesity. In fact, the proportion of apoB/apoA1 and smoking could explain up to 70% of the CV risk in this study, after the multivariate analysis and the evaluation of the

attributable risk of the population (20). The AMORIS study showed that patients with RA had a 1.6 higher incidence rate of myocardial infarction and stroke compared to the general population, although there was no statistical significance related to total cholesterol or triglycerides (21, 22). However, after multivariate analysis, the apoB/apoA1 ratio was the best factor associated with the risk of CVE. Also, a prospective Scandinavian study in RA patients showed that apoB/apoA1 ratio, TG levels, ESR and haptoglobin were associated with the presence of CVE (23). Moreover, in another prospective study, the authors highlighted that an increase in the apoB/apoA1 ratio during follow-up was significantly associated with an increase in the diameter of the carotid plaque after 5 years from the diagnosis of RA (24) and, consequently, increased the risk of CVD.

Although our study included a high number of patients, the absence of an association between the apoB/apoA1 ratio and the risk of CVE could be partially explained because RA patients with CVE history were more commonly undergoing treatment with statins than the other group. Therefore, they probably had more reliable control of systemic inflammation and atherogenesis, including the role of this kind of drugs in the immunomodulation of the T cell-mediated inflammatory endothelial response (25). Furthermore, it has been described that in context of chronic inflammation, as occurs in RA patients, HDL-c and apoA1 levels fall and they often increase following anti-rheumatic therapy (26). In keeping with that, an observational study revealed that the use of DMARDs in 80 patients with RA had a beneficial effect in increasing levels of apo A1, with a potential decrease in the risk of CVE (27).

Some studies have shown that the association between traditional lipid parameters (TC/HDL-c and LDL-c/HDL-c) and CVE would decrease after a period of treatment with statins, while the association between the apoB ratio/apoA1 and CVE would not be influenced following treatment with these agents (28, 29).

The atherogenic index was statistically associated with the CVE in our patients with RA, as reported in other studies that also described a relationship between this parameter and the CV risk (30, 31). Other factors such as age and non-insulin-dependent DM were also associated and they are among the classic risk factors for CVE (32, 33).

A high score of HAQ is related to a progressive and active disease that has also been described associated with CVE (34). Therefore, a reduction in the inflammatory burden may lead to a better quality of life and a reduction of the CV risk in patients with RA. On the other hand, an increased risk of CVE was found in our RA patients with non-insulin-dependent DM type 2.

The use of biologic therapy has been associated with better control of the disease and a reduction of CV risk in patients with RA. ApoA1 has been related to anti-inflammatory and anti-atherogenic properties. Its action is independent of HDL-c and it is also involved in the inhibition of the synthesis of TNF-α and IL-1β (35). Certainly, it has been described that this apolipoprotein behaves as a biomarker related to the response to treatment with infliximab in patients with RA (36). Ajeganova et al. showed that biologic therapies increased the level of apoA1 in patients with RA and consequently decreased the apoB/apoA1 ratio (37). However, in our study, we did not find statistically significant differences to associate the type of biological therapy received with the presence of CVE. Moreover, as previously mentioned, some adipokines play a potential role in the risk of CVE in patients with RA. With respect to this, the use of tocilizumab (TCZ), a biologic agent that inhibits IL-6, may have a potential cardioprotective effect modulating serum levels of adiponectin and chemerin in patients with RA (38) as well as decreasing the levels of the activator plasminogen inhibitor 1 (PAI-1), which preserves fibrinolysis and reduces the risk of thrombotic CVE in these subjects (39). Similarly, the intravenous administration of TCZ has proved to yield a rapid and statistically significant reduction on insulin resistance along with a significant increase of insulin sensitivity in non-diabetic RA patients (40). These findings support the potential beneficial effect of the IL-6 blockade on the mechanisms associated with the development of metabolic syndrome and cardiovascular disease in patients with RA (40). In addition, TCZ decreases the levels of lipoprotein (a), a lipoprotein with atherogenic and thrombogenic properties; although it does not seem to affect plasma values of apolipoproteins (41). Therefore, although this drug appears to reduce CV risk, it is not reflected in the estimated CV risk as assessed by the apoB/apoA1 ratio. Nevertheless, this protective effect against CVE may also be associated with the use of other biologic therapies. In this regard, a retrospective study that assessed the risk of acute CVE during a hospitalisation period in patients with RA did not show differences in medium-term risk of CVE between patients who received TCZ compared to those who were treated with etanercept (42).

Our study included an important national cohort of patients with RA, being the first study in our country that seeks to establish an association between the apoB/apoA1 ratio and the presence of CVE in patients with CIRD. However, it has some limitations such as the cross-sectional design used, which did not allow us to establish causality between data found and the results that we obtained. In addition, it is important to emphasise that our cohort included a series of patients periodically followed-up at the outpatient clinics. They were submitted to a tight control strategy and a high number of them were undergoing biologic therapy. This management may have had an influence decreasing the frequency of CVE in this population, what may have underestimated the actual relevance of the ApoB/apoA1 ratio in the risk of CVE.

In conclusion, apoB/apoA1 ratio has not been associated with the presence of CVE in patients with RA undergoing anti-rheumatic treatment at the baseline visit of our Spanish longitudinal cohort study on patients with RA. Prospective studies are needed to evaluate if this ratio may be a predictor factor of development of CVE in patients with RA or other chronic inflammatory rheumatic diseases.

Acknowledgements

This publication was aided by members of the Research Unit of the Spanish Society of Rheumatology (SER). The authors thank all of the health professionals and patients who generously participated in this study. Furthermore, the authors thank the approval of the study from all participating centres.

The CARMA Project Collaborative Group:

The members of the CARdiovascular in rheuMAtology Project Collaborative Group include: Eugenia Gonzalez de Rabago, Elena Alonso Blanco Morales, J. Carlos Fernández Lopez, Natividad Oreiro Villar, Antonio Atanes Sandoval, Francisco J. Blanco García (Complejo Hospitalario A Coruña, Xubias de Arriba, A Coruña); Cayetano Alegre De Miquel, Marıa J. González Fernández, Ramón Huguet Codina, Beatriz Yoldi, Mercedes Ramentol (Instituto Dexeus, Barcelona); Gabriela Ávila, Sara Marsal Barril, Estefania Quesada (Hospital Universitari Vall d'Hebron, Barcelona); Martina Steiner, Santiago Muñoz, Tatiana Cobo (Hospital Infanta Sofía, Madrid); Fernando Gamero, José García Torón, (Hospital S. Pedro de Alcántara, Cáceres); Pilar Espino, Inmaculada Ros, Mónica Ibáñez, and Claudia Murillo (Hospital Son Llatzer, Palma de Mallorca); Jesús Tornero Molina (Hospital Univ. de Guadalajara); Raimon Sanmartí, Horacio Berman, Sonia Cabrera, and Virginia Ruiz (Hospital Clinic i Provincial, Barcelona); Oscar Fontseré Patón, Benjamín Fernández Gutierrez, and Lydia Abasolo (Hospital Clínico Univ. San Carlos, Madrid); Jose M. Pina, Dolores Fábregas Canals (Hospital de Barbastro, Huesca); Joan M. Nolla (Hospital Univ. de Bellvitge, Barcelona); Miriam García Arias, Mirem Uriarte, Jesús A. García Vadillo, and Rosario García de Vicuña (Hospital Univ. de La Princesa, Madrid); Antonio Fernández Nebro, Maria Angeles Belmonte López, Inmaculada Ureña, María V. Irigoyen, Virginia Coret Cagigal (Hospital Regional Univ. Carlos Haya, Málaga); Daniel Pielfort Garrido, Angel M. García Aparicio, Rebeca Belmonte Gómez, Pastora Granados Bautista, Azucena Hernandez Sanz (Hospital Virgen de la Salud, Toledo); Francisco J. Manero, Fernando Jimenez Zorzo, Eugenio Giménez Ubeda, Jesús Marzo Gracía, Chesús Beltrán Audera, Marta Medrano, Ángela Pecondón (Hospital Univ. Miguel Servet, Zaragoza); Celia Erausquin, Soledad Ojeda, Juan C. Quevedo, Félix Francisco, Carlos Rodríguez Lozano (Hospital Dr. Negrín, Las Palmas de Gran Canaria); Francisco J. López Longo, Delia Gerona, Carlos González Fernández, Indalecio Monteagudo (Hospital Gregorio Marañón, Madrid); Javier del Pino, María Dolores Sánchez González (Hospital Univ. de Salamanca); Alfonso Corrales, María E. Peiró (Hospital Univ. Marqués de Valdecilla, Santander); José M. Senabre, José C. Rosas (Hospital Marina Baixa, Alicante); Isabel Rotés, Estefanía Moreno, Alba Erra, Dolors Grado (Hospital San Rafael, Barcelona); Javier Calvo, Amalia Rueda (Hospital General Universitario, Valencia); Ingrid Möller, Isabel Rodríguez (Instituto Poal, Barcelona); Carmen Barbadillo (Hospital Univ. Puerta de Hierro, Madrid); Enrique Raya, Pilar Morales, Ana Nieto, Inmaculada Jiménez, Cesar Magro (Hospital Clínico Univ. San Cecilio, Granada); Sergio Ros Expósito (Hospital de Viladecans, Barcelona); Ginés Sánchez Nievas, Enrique Júdez Navarro, Manuela Sianes Fernández, María A. García Morales, Isabel Labiano Bastero, Gloria García Consuegra and Natalia Palmou (Hospital General de Albacete); Manel Pujol, Elena Riera Alonso, Georgina Salvador (Hospital Mutua Terrassa, Terrassa); Beatriz González Alvarez, Alberto Cantabrana (Hospital Ntra. Sra. de Candelaria, Santa Cruz de Tenerife); Sagrario Bustabad (Hospital Univ. de Canarias, La Laguna, Tenerife); Alejandro Muñoz, Luis María Jimenez (Hospital Univ. de Valme, Sevilla); Teresa Gonzalez Hernandez (Instituto Provincial de Rehabilitación, Madrid); Francisco J. González Polo (Hospital de Cantoblanco, Madrid); Raul Menor Almagro (Hospital de Jerez de la Frontera, Jerez de la Frontera, Cádiz); José M. Moreno, Emilio Giner Serret, Carla Lannuzzelli Barroso (Hospital Obispo Polanco, Teruel); Laura Cebrián Méndez (Hospital Infanta Leonor, Madrid); Cristina Fernández Carballido (Hospital General de Elda, Alicante); Pablo Mesa del Castillo (Hospital Los Arcos, Murcia); Esperanza Naredo, Ana Cruz Valenciano, Cristina Macías Villa (Hospital Severo Ochoa, Madrid); Ana Turrión (Hospital Príncipe de Asturias, Madrid); Julio Sánchez, María Galindo (Hospital Univ. 12 de Octubre, Madrid); Eduardo Collantes, Desiree Ruiz, Pilar Font (Hospital Univ. Reina Sofía, Córdoba); Gema Bonilla (Hospital Univ. La Paz, Madrid); Antonio López Meseguer (Hospital Gutiérrez Ortega, Valdepeñas, Ciudad Real); María J. Moreno Martínez; María D. Beteta Fernández, Luis F. Linares (Hospital Virgen de la Arrixaca, Murcia); María L. González Gómez (Hospital del Escorial, Madrid); Natalia A. Rivera, Olaia Fernández Berrizbeitia, María L. García Vivar (Hospital de Basurto, Bilbao); Manel Riera, Yolanda María León (Hospital Dos de Maig, Barcelona); Joan Maymó, Miriam Amirall, Silvia Iniesta Escolano, Silvia Sánchez Serrano, María P. Lis Bona (Hospital del Mar, Barcelona); Jordi Fiter, Julia Fernández Melón, Luis Espadaler (Hospital Univ. Son Espases, Palma de Mallorca); Olga Maiz, Joaquín Belzunegui (Hospital de Donostia, Donostia); César Díaz (Hospital Santa Creu i Sant Pau, Barcelona); Ramón Valls (Hospital de Palamós, Gerona); Iván Castellví, María Bonet, Estefania Moreno Ruzafa (Hospital Comarcal de L'Alt Penedés, Vilafranca del Penedés, Barcelona); Jaime Calvo Alen (Hospital Sierrallana, Torrelavega); Trinidad Pérez Sandoval (Complejo Asistencial de León); Eva Revuelta Evrard (Hospital General de Ciudad Real); Javier R. Godo, Cruz Fernández Espartero (Hospital General de Móstoles, Madrid); Francisco J. Navarro Blasco, J. Antonio González (Hospital General Univ. de Elche, Alicante); José A. Miranda-Filloy (Hospital Xeral Calde, Lugo).

References

1. AVINA-ZUBIETA JA, THOMAS J, SADATSAFAVI M, LEHMAN AJ, LACAILLE D: Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies. *Ann Rheum Dis* 2012; 71: 1524-29.
2. CASTAÑEDA S, NURMOHAMED MT, GONZALEZ-GAY MA: Cardiovascular disease in inflammatory rheumatic diseases. *Best Pract Res Clin Rheumatol* 2016; 30: 851-69.
3. GONZALEZ-GAY MA, GONZALEZ-JUANATEY C, VAZQUEZ-RODRIGUEZ TR, MARTIN J, LLORCA J: Endothelial dysfunction, carotid intima-media thickness, and accelerated atherosclerosis in rheumatoid arthritis. *Semin Arthritis Rheum* 2008; 38:67-70.
4. CROWSON CS, ROLLEFSTAD S, IKDAHL E *et al*.: Impact of risk factors associated with cardiovascular outcomes in patients with rheumatoid arthritis. *Ann Rheum Dis* 2018; 77: 48-54.
5. GONZALEZ-GAY MA, GONZALEZ-JUANATEY C, LÓPEZ-DIAZ MJ *et al*.: HLA-DRB1 and persistent chronic inflammation contribute to cardiovascular events and cardiovascular mortality in patients with rheumatoid arthritis. *Arthritis Rheum* 2007; 15: 125-32.
6. LOPEZ-MEJIAS R, CASTAÑEDA S, GONZALEZ-JUANATEY C *et al*.: Cardiovascular risk assessment in patients with rheumatoid arthritis: The relevance of clinical, genetic and serological markers. *Autoimmun Rev* 2016; 15: 1013-30.

7. RUSCITTI P, DI BENEDETTO P, BERARDICURTI O *et al*.: Adipocytokines in rheumatoid arthritis: the hidden link between inflammation and cardiometabolic comorbidities. *J Immunol Res* 2018; 1: 1-10.
8. GONZALEZ-GAY MA, GONZALEZ-JUANATEY C: Inflammation and lipid profile in rheumatoid arthritis: bridging an apparent paradox. *Ann Rheum Dis* 2014; 73: 1281-3.
9. MCGRATH CM, YOUNG SP: Lipid and metabolic changes in rheumatoid arthritis. *Curr Rheumatol Rep* 2015; 17: 57.
10. ZANNIS VI, CHRONI A, KRIEGER M: Role of apoA-I, ABCA1, LCAT, and SR-BI in the biogenesis of HDL. J *Mol Med* 2006; 84: 276-94.
11. WALLDIUS G, JUNGNER I: The apoB/apoA-I ratio: a strong, new risk factor for cardiovascular disease and a target for lipid-lowering therapy--a review of the evidence. *J Intern Med* 2006; 5: 493-519.
12. PERK J, DE BACKER G, GOHLKE H *et al*.: European Guidelines on cardiovascular disease prevention in clinical practice: The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Atherosclerosis* 2012; 223: 1-68.
13. INGELSSON E, SCHAEFER EJ, CONTOIS JH *et al*.: Clinical utility of different lipid measures for prediction of coronary heart disease in men and women. *J Am Med Assoc* 2007; 298: 776-85.
14. KNOWLTON N, WAGES JA, CENTOLA MB *et al*.: Apolipoprotein B-containing lipoprotein subclasses as risk factors for cardiovascular disease in patients with rheumatoid arthritis. *Arthritis Care Res* 2012; 64: 993-1000.
15. ARNETT FC, EDWORTHY SM, BLOCH DA *et al*.: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-24.
16. CASTANEDA S, MARTIN-MARTINEZ MA, GONZALEZ-JUANATEY C *et al*.: CARMA Project Collaborative. Cardiovascular morbidity and associated risk factors in Spanish patients with chronic inflammatory rheumatic diseases attending rheumatology clinics: baseline data of the CARMA Project. *Semin Arthritis Rheum* 2015; 44: 618-26.
17. WORLD MEDICAL ASSOCIATION (WMA): The Declaration of Helsinki (DoH) of the World Medical Association - Ethical principles for medical research in humans. 64th General Assembly; 2013. Fortaleza, Brazil: AMM; 2013.
18. LEVY D, LARSON MG, VASAN RS, KANNEL WB, HO KK: The progression from hypertension to congestive heart failure. *JAMA* 1996; 275: 1557-62.
19. HOLME I, AASTVEIT AH, HAMMAR N, JUNGNER I, WALLDIUS G: Lipoprotein components and risk of congestive heart failure in 84 470 men and women in the Apolipoprotein MOrtality RISk study (AMORIS). *Eur J Heart Fail* 2009; 11: 1036-42.
20. YUSUF S, HAWKEN S, OUNPUU S *et al*.; INTERHEART STUDY INVESTIGATORS: Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control Study. *Lancet* 2004; 364: 937-52.
21. WALLDIUS G, JUNGNER I, HOLME I, AASTVEIT AH, KOLAR W, STEINER E: High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. *Lancet* 2001; 358: 2026-33.
22. HOLME I, AASTVEIT AH, HAMMAR N, JUNGNER I, WALLDIUS G: Relationships between lipoprotein components and risk of ischaemic and haemorrhagic stroke in the Apolipoprotein MOrtality RISk study (AMORIS). *J Intern Med* 2009; 265: 275-87.
23. ÖHMAN M, ÖHMAN ML, WÅLLBERG-JONSSON S: The apoB/apoA1 ratio predicts future cardiovascular events in patients with rheumatoid arthritis. Scand J Rheumatol 2014; 43: 259-64.
24. AJAGENOVA S, EHRNFELT C, ALIZADEH R *et al*.: Longitudinal levels of apolipoproteins and antibodies against phosphorylcholine are independently associated with carotid artery atherosclerosis 5 years after rheumatoid arthritis onset-a prospective cohort study. *Rheumatology* (Oxford) 2011; 50: 1785-93.
25. SMALDONE C, BRUGALETTA S, PAZZANO V, LIUZZO G: Immunomodulator activity of 3-hydroxy-3-methilglutaryl-CoA inhibitors. *Cardiovasc Hematol Agents Med Chem* 2009; 7: 279-94.
26. ROBERTSON J, PETERS MJ, MCINNES IB *et al*.: Changes in lipid levels with inflammation and therapy in RA: a maturing paradigm. *Nat Rev Rheumatol* 2013; 9: 513-23.
27. ISMAILI H, MULIĆ-BAČIĆ S, KAREMANI N, OROVČANEC N: Effect of disease-modifying antirheumatic drugs on the values of apolipoprotein A-1 and acute phase reactants in patients with active rheumatoid arthritis. *Reumatizam* 2016; 63: 9-14.
28. GOTTO AM, WHITNEY E, STEIN EA *et al*.: Relation between baseline and on-treatment lipid parameters and first acute major coronary events in the Airforce/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). *Circulation* 2000; 101: 477-84.
29. SIMES RJ, MARSCHNER IC, HUNT D *et al*.: Relationship between lipid levels and clinical outcomes in the long-term intervention with pravastatin in the ischemic disease (LIPID) trial. To what extent is the reduction in coronary events with pravastatin explained by on-study lipid levels? *Circulation* 2002; 105: 1162-69.
30. POPA CD, ARTS E, VAN RIEL PL: Atherogenic index and high-density lipoprotein cholesterol as cardiovascular risk determinants in rheumatoid arthritis: the impact of therapy with biologicals. *Mediators Inflamm* 2012; 2012: 785946.
31. BATUN-GARRIDO JA, OLAN F, HERNANDEZ-NUÑEZ E: Dyslipidemia and atherogenic risk in patients with rheumatoid arthritis. *Clin Investig Arterioscler* 2016; 28: 123-31.
32. VLACHOPOULOS C, AZNAOURIDIS K, STEFANADIS C: Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol* 2010; 55: 1318-27.
33. JIAO FF, FUNG CS, WONG CK *et al*.: Effects of the Multidisciplinary Risk Assessment and Management Program for Patients with Diabetes Mellitus (RAMP-DM) on biomedical outcomes, observed cardiovascular events and cardiovascular risks in primary care: a longitudinal comparative study. *Cardiovasc Diabetol* 2014; 13: 127.
34. SOLOMON DH, REED GW, KREMER JM *et al*.: Disease activity in rheumatoid arthritis and the risk of cardiovascular events. *Arthritis Rheumatol* 2015; 67: 1449-55.
35. KNOWLTON N, WAGES JA, CENTOLA MB, ALAUPOVIC P: Apolipoprotein-defined lipoprotein abnormalities in rheumatoid arthritis patients and their potential impact on cardiovascular disease. *Scand J Rheumatol* 2012; 41: 165-59.
36. TROCME C, MAROTTE H, BAILLET A *et al*.: Apolipoprotein A-I and platelet factor 4 are biomarkers for infliximab response in rheumatoid arthritis. *Ann Rheum Dis* 2009; 68: 1328-33.
37. AJAGENOVA S, FISKERUD R, DE FAIRE U, HAFSTRÖM I, FROSTEGÅRD J: Effect of biological therapy on levels of atheroprotective antibodies against phosphorylcholine and apolipoproteins in rheumatoid arthritis – a one-year study. *Clin Exp Rheumatol* 2011; 29: 942-50.
38. FIORAVANTI A, TENTI S, BACARELLI MR *et al*.: Tocilizumab modulates serum levels of adiponectin and chemerin in patients with rheumatoid arthritis: potential cardiovascular protective role of IL-6 inhibition. *Clin Exp Rheumatol* 2019; 37: 293-300.
39. MAKRILAKIS K, FRAGIADAKI K, SMITH J, SFIKAKIS PP, KITAS GD: Interrelated reduction of chemerin and plasminogen activator inhibitor-1 serum levels in rheumatoid arthritis after interleukin-6 receptor blockade. *Clin Rheumatol* 2015; 34: 419-27.
40. CASTAÑEDA S, REMUZGO-MARTÍNEZ S, LÓPEZ-MEJÍAS R *et al*.: Rapid beneficial effect of the IL-6 receptor blockade on insulin resistance and insulin sensitivity in non-diabetic patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2019; 37: 465-73.
41. GARCIA GOMEZ C, MARTIN-MARTINEZ MA, CASTAÑEDA S *et al*.: Lipoprotein(a) concentrations in rheumatoid arthritis on biologic therapy: Results from the CARdiovascular in rheuMAtology study project. *J Clin Lipidol* 2017; 11: 749-56.
42. GENERALI E, CARRARA G, SELMI C *et al*.: Comparison of the risks of hospitalisation for CVE in patients with rheumatoid arthritis treated with tocilizumab and etanercept. *Clin Exp Rheumatol* 2018; 36: 310-13.