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Values and Correlations between C-Reactive Protein and Apolipoprotein B after Treatment with Methotrexate at Patients with Rheumatoid Arthritis

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Keywords: Rheumatoid arthritis (RA); Methotrexate (MTX); C-reactive protein (CRP); Apolipoprotein B (Apo B)

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Abstract

BACKGROUND: Patients with rheumatoid arthritis (RA) are at increased risk of cardiovascular disease (CVD). Lipid changes related to inflammation have been described in RA. Methotrexate (MTX) treatment is effective in controlling inflammation and decreasing the CRP (C-reactive protein) values.

AIM: To examine the disease activity, CRP and Apo B values in the detection of new patients with active and untreated RA, and impact of MTX therapy on their levels after 6 months and one year of treatment, and the correlation between their values in this period.

METHODS: 80 patients with active and newly discovered RA patients who meet the American Rheumatology Association (ARA) 1987 revised criteria were treated with disease-modifying anti-inflammatory drugs (DMARDs) according to the protocol for treatment.

RESULTS: After a year of therapy RA patients achieved significant decrease in the DAS28 (disease activity score) ($p < 0.01$ and $p < 0.001$), and CRP values ($p < 0.001$). Levels of Apo B values at the 12 months were nonsignificantly higher compared to the results obtained at the beginning of the study ($p < 0.001$). After 6 and 12 months there was a weak nonsignificant negative correlation about the values of CRP and Apo B at baseline and after 12 months ($r = –0.15$ and $r = -0.12$ $p > 0.05$).

CONCLUSION: Use of MTX therapy at RA patients had a reduced effect on disease activity and inflammation, but the nonsignificance effect on the values of Apo B lipoproteins.

Introduction

Rheumatoid arthritis (RA), a chronic inflammatory joint disease of unknown aetiology, affects approximately one per cent of the general population. Estimated standardised mortality ratio's associated with RA range from 1.3 to 3.0. This increased mortality is largely attributable to CVD, particularly coronary atherosclerosis. The cardiovascular morbidity found in RA patients appears to be increased by twofold or more compared to the general population (age and sex-matched) [1], [2], [3], [4], [5].

Autoimmunity and inflammation play a major role in the development of atherosclerotic plaque formation in many rheumatological conditions including RA. The mechanisms underlying these changes include the interplay of inflammation and autoantibody formation. Thus treatment options to reduce CVD risk amongst these conditions share a common theme, with the use of DMARDs paramount to all [3], [5], [6].

Atherosclerosis is an inflammatory condition, with high inflammatory level implicated for developing CVD. Inflammatory markers such as IL-6, CRP and fibrinogen are associated with a high frequency of cardiovascular events. In particular, CRP has received

large attention due to its ability to independently predict cardiovascular events in the general population, which may in part, be due to its ability to directly contribute to the onset of CVD [7], [8], [9].

In RA patients, inflammatory markers such as the CRP and erythrocyte sedimentation rate are elevated and remain greater even in periods of low disease activity when compared to the general population. In patients with inflammatory arthritis who were followed up for 10 years, CRP levels independently predicted CVD mortality. The similarities between the inflammatory process of RA and atherosclerosis are remarkable. In both diseases, concentrations of IL-6, CRP and TNF-α are elevated, and both have similar patterns of activation for T-cells and macrophages [8], 10], [11].

Apolipoproteins are found on the surface of lipoproteins and regulate lipid metabolism. The apolipoproteins that are of clinical interest are apo B and apolipoprotein A1 (Apo A1). Apo B is found on LDL particles and is responsible for the clearance of LDL cholesterol through the LDL receptor pathway [12].

Apolipoprotein-related Mortality Risk (AMORIS) study investigated the use of apo B, Apo A1, and the apo B: apo A1 ratio at predicting fatal myocardial infarction (MI). The study followed 75 553 Swedish men and women from 1985 to 1996. The authors found that apo B and the apo B: apo A1 ratio were both strongly predictive of increased risk of fatal MI in both men and women. Furthermore, they found that apo B was a stronger predictor of the risk of fatal MI than LDL cholesterol. However, apo B, although a strong predictor of coronary heart disease, is not currently recommended as the primary target of therapy and there is not enough evidence to justify apo B replacing LDL cholesterol as the preferred target of therapy by National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Cholesterol in Adults (NCEP/ATP III) guidelines [1], [13], [14], [15].

Traditional synthetic DMARDs, such as MTX, Sulfasalazine and Hydroxychloroquine, have a protective role against CV risk. The mechanisms by which DMARD use influences CV risk are poorly understood, but lend support to the hypothesis that reducing inflammation is important in reducing CV risk. Of the traditional DMARDs, MTX is the most widely used and is known as the anchor drug in RA, yet the mechanisms underlying its anti-inflammatory properties are not fully understood [17].

Given the high level of systemic inflammatory burden that characterises RA, which is regarded as a key CV risk factor, alongside an increased prevalence of traditional risk factors, EULAR recommendations highlight the importance of adequate disease control to lower CV risk. The vulnerability of the carotid plaque is influenced by RA disease activity, and remission may alleviate this threat. Therefore, effective CV risk management will likely comprise not only adequate treatment of conventional risk factors but also tight and sustained disease activity control [6], [7], [18].

The purpose of this study is to examine the disease activity, CRP and Apo B values in the detection of new patients with active and untreated RA, and impact of MTX therapy on their levels at the same patients after 6 months and one year of treatment, and correlation between their values in this period.

Material and Methods

Inclusion criteria for patients

Eighty consecutive, unselected patients who were referred to the outpatient rheumatology clinic at the Clinical Center in Skopje were investigated. All patients fulfilled the American College of Rheumatology (ACR) 1987 criteria for RA, had an early disease with disease duration of less than one year without prior use of DMARDs and or systemic steroids [24].

Exclusion criteria for patients

Smokers or patients suffering from conditions that affect the lipid profile, such as diabetes mellitus, hypothyroidism, liver or kidney disease, Cushing's syndrome, Carcinoma, obesity (body mass index > 30) and a history of familial dyslipidemia, were excluded. Also, patients receiving medications affecting lipid metabolisms, such as lipid-lowering drugs, beta-blockers, oral contraceptives, estrogen, progestin, thyroxin and vitamin E, were excluded from the study [9].

Thirty healthy, non-smoking volunteers also participated in the study and were used as a control group and fulfilled the same exclusion criteria reported for the patient group. None of the subjects participating in the control group had a history of CVD. The control group was proportionally matched for age and sex to the patient group. All controls reported no significant changes in their body weight for at least three months before entry to the study. All patients and controls gave informed consent, and the study protocol was approved by the Institutional Ethics Committee [21].

Study design

Patients were treated with methotrexate (MTX; 0.2-0.6 mg/kg/week; mean ± standard deviation 15.5 ± 1.3). Disease activity was assessed by measuring the disease activity for 28 joint indices

score (DAS-28), while the clinical response was evaluated according to the ACR 50% response criteria. All patients were followed up every month for the first three months, and every three months after that. During the follow-up period, a questionnaire concerning changes in dietary habits was carefully fulfilled by all patients. The body weight was also measured appropriately in each visit.

Blood sampling and laboratory monitoring

Overnight fasting blood samples were obtained at baseline, 6 and after 12 months follow-up from both untreated RA patients and the control group. Serum apolipoprotein B was measured by immune-nephelometry with the aid of a Behring Nephelometer BN100 and reagents (antibodies and calibrators) from Behring Diagnostics GmbH (Liederbach, Germany). C-reactive protein (CRP) was measured by nephelometry.

Statistical analysis

Statistical analysis was performed using Statistica software, ver 7.1. Due to the distribution which was not normal (according to Kolmogorov-Smirnov test), the variable differences were tested using non-parametric tests (Wilcoxon Matched Pair Test or Friedman ANOVA test – Chi-Square). The correlation between parameters was analysed using the Pearson correlation coefficient. Significance was set up at $p < 0.05$.

Results

Patients and control groups who participated in our study were allocated several parameters such as: age, sex BMI (Body mass index), duration of illness, MHAQ, morning stiffness, the affected joints, swollen joints, VAS index, global doctor assessment, sedimentation rate of erythrocytes, CRP, and rheumatoid factor (RF). These parameters show disease activity in early studies (Table 1).

Table 1: Patients and controls characteristics

	RA (n = 80)	Controls (n = 30)
Age (year)	45.7 ± 9.8	45.2 ± 9.8
Sex: M/F	80 F	6/24
BMI (kg/m²)	22.3 ± 2.6	21.8 ± 2.2
Duration of disease (month)	6.2 ± 16.6	
MHAQ (1-4)	1.5 ± 0.5	
Morning stiffness	111.4 ± 133.2	
Affected Joints	7.8 ± 7.1	
Swollen joints	5.2 ± 3.7	
VAS (0-10)	7.0 ± 2.1	
Global doctors' assessment	4.5 ± 2.3	
Sedimentation rate(mm/h)	45.5 ± 30.3	
CRP (mg/1)	21.69 ± 29.4	
RF (positive/negative)	64/16	

BMI: Body Mass Index; MHAQ: Question modified to improve health VAS: visual analog (pain) score; CRP: C-reactive protein; RF: Rheumatoid factor.

During the study, 80 patients with newly discovered active and untreated RA were treated with Methotrexate. These 80 patients were selected according to those who have responded to the therapy. The patients who did not respond to the therapy (7 in number) were excluded from the study.

Figure 1 shows the DAS28 (Disease Activity Score in 28 joints) index at the beginning, after 6 and 12 months of therapy.

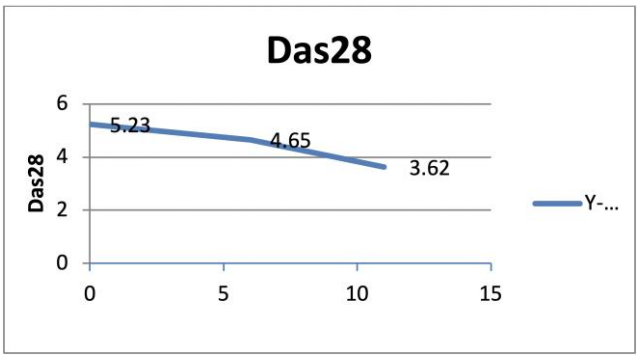

Figure 1: Disease activity score 28 (DAS28) at baseline, at 6, and 12 months during the treatment

At DAS28 score after 6 months for $p < 0.01$ there are significant differences in relation beginning, 6 and 12 months, the difference is significant ($p < 0.001$), and also in the relation beginning/12 month there is also a significant difference.

Table 2: Descriptive statistics / RA patients

	Valid N	Mean	Confidence -95,00%	Confidence +95,00%	Minimum	Maximum	Std.Dev.
CRP 0 m.	80	21.69	17.93	25.44	1.80	63.00	15.98
CRP 6 m.	80	20.51	12.00	29.01	1.00	307.00	36.19
CRP 12 m.	80	12.31	9.50	15.11	0.00	62.00	11.95
Apo B 0m.	80	1.79	1.67	1.92	0.70	3.30	0.53
Apo B 6 m.	80	1.79	1.67	1.92	0.60	3.50	0.54
Apo B 12 m.	80	1.83	1.71	1.95	0.70	3.50	0.52

CRP levels at baseline, at 6 months, and 12 months.

As for CRP, there was a significant consecutive decrease from baseline, both at 6 and at 12 months (for both variables, between each of time-points; Friedman ANOVA; $p < 0.001$) (Table 3).

Table 3: CRP levels at baseline, at 6 months, and 12 month

	Average Rank	Sum of Ranks	Mean	Std.Dev.
CRP 0 m.	2.44	175.50	21.69	15.98
CRP 6 m.	2.08	150.00	20.51	36.19
CRP 12 m.	1.48	106.50	12.31	11.95

Friedman ANOVA; Chi Sqr. (N = 80, df = 2) = 36.07, p = 0.000

For $Z = 5.16$ and $p < 0.001$ ($p = 0.000$) average values of CRP after 12 months ($x = 12.31$ mg/l) of therapy are significantly lower according to the values of CRP at the beginning ($x = 21.69$ mg//l) (Table 4).

Table 4: CRP / CRP beginning & CRP 12 m

Wilcoxon Matched Pairs Test				
	Valid	T	Z	p-level
CRP 0m. & CRP 12 m	80	361.50	5.16	0.000

Apolipoprotein B (Apo B) levels at baseline, at 6 months, and at 12 months.

As for Apo B, there was no significant consecutive difference from baseline, both at 6 and at 12 months (for both variables, between each of time-points; Friedman ANOVA; $p < 0.001$) (Table 5).

Table 5: Apo B levels at baseline, at 6 months, and 12 months

	Average Rank	Sum of Ranks	Mean	Std.Dev.
Apo B 0 m.	1.90	136.50	1.79	0.53
Apo B 6 m.	1.97	141.50	1.79	0.54
Apo B 12 m.	2.14	154.00	1.83	0.52

Friedman ANOVA; Chi Sqr. (N = 80, df = 2) = 2.80, p = 0.25.

For $Z = 0.94$ and $p > 0.05$ ($p = 0.35$) average values of Apo B after 12 months ($x = 1.83$ g/l) of therapy were nonsignificantly higher according to the values of Apo B at the beginning ($x = 1.79$ g/l) (Table 6).

Table 6: Apo B / Apo B beginning & Apo B 12 m.

Wilcoxon Matched Pairs Test				
	Valid	T	Z	p-level
Apo B 0 m. & Apo B 12 m.	80	871.00	0.94	0.35

Correlation in relation to CRP/Apo B.

Comparing the results of CRP and Apo B at baseline, after 6 and 12 months we found a weak nonsignificant negative correlation about the values of CRP and Apo B at baseline and after 12 months ($r = -0.15$ and $r = -0.12$, $p > 0.05$). In other words, the elevation of CRP by 1 mg/l was accompanied by a decrease of Apo B values by 0.005 g/l (Figure 2).

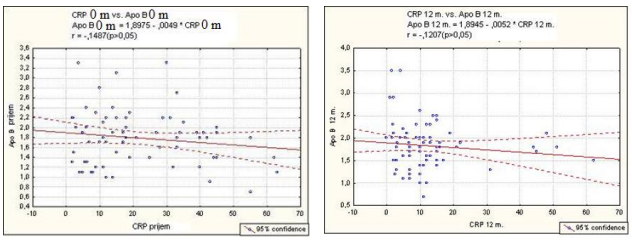

Figure 2: Correlation of CRP and Apo B levels at baseline (left); Correlation of CRP and Apo B levels at 12 months (right)

As for the relationship at 6 months, we found a moderately poor and weak insignificant correlation ($p > 0.05$).

Discussion

Our findings support the view that present chronic inflammation at RA patients affects the endothelium, and that, in association with atherosclerosis, it may be the mechanism that at least partly explains the increased mortality and morbidity occurring in patients with RA. Our goal was to determine the disease activity, values of CRP and Apo B lipoproteins in patients with active RA and DMARD-naïve RA patients before treatment and after 6 and 12 months of treatment with DMARDs, respectively with MTX. The patients with active RA had nonsignificantly increased levels of Apo B after 6 and 12 months of treatment with MTX. On the other hand, the values of acute phase reactant-CRP were lower after 6 months and one year of treatment. This suggests that moderate increasing levels of Apo B lipoproteins were accompanied by a decrease of inflammation at the end of the study.

Several studies have suggested that CRP has direct effects on the vessel wall promoting atherosclerosis. An association between high-grade, chronic CRP elevation and subclinical atherosclerosis in patients with RA has been reported. Additionally, a higher risk of CV events in patients with RA with chronic inflammation expressed by persistently increased CRP serum levels has been found, although high-sensitive C-reactive protein is shown to have a strong relationship with recurrent events of CVD in several randomised clinical trials [21], [22], [23].

The clinical importance of dyslipidemia concerning CV events or death in RA is unclear. Even though there is observational data that suggests that there is no significant difference between RA and non-RA subjects in the risk imparted by hyperlipidemia [21], it could be possible that non-traditional CVD risk factors, or other lipid parameters besides those found in cholesterol profiles, explain a greater proportion of CVD risk than in non-RA patients [24]. It has been proposed that the non-fasting apoB/apoA1 ratio was superior to any of the cholesterol ratios for estimation of the risk of acute myocardial infarction [25]. Some have suggested that the elevation in lipids after RA therapy might be offset by a reduction of more atherogenic molecules [26] such as apo B and apoA-I or total cholesterol.

Importance of apo B is because of apo B presence in very low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), large buoyant LDL and small dense LDL (sd-LDL), with one molecule of Apo B in each of these atherogenic particles. Therefore, total apo B reflects the total number of potentially atherogenic particles and in the AMORIS study was find that apo B has a stronger relationship with risk of fatal MI and other CV events than does non-HDL C [12], [15], [16]. Also, the report of the Uppsala Longitudinal Study of Adult Men (ULSAM), about these risk values correspond well with those found in the AMORIS study [27]. Same conclusions have been confirmed by many other studies (The EPIC-Norfolk study, Nurses' Health study, THROMBO study, GRIPS and Caerphilly studies, etc.) [12].

Katherine P. Liao report for a nonsignificant increase of apo B values and no significant correlation between change in CRP and apo B levels ($r = 0.14$, $P = 0.20$) and the atherogenic indices after treatment of RA patients [28]. At Sana P. study both Apo A1 and

Apo B are significantly lower in cases than in controls. Elevated Apo B levels indicate an increased risk of cardiovascular disease, but in their study, Apo B was 23% decreased in cases when compared to controls [29]. In a similar study, Magarò M et al. have also shown Apo A1 and Apo B to be significantly lower in RA patients. They have also shown reduced levels of albumin in these patients which perhaps indicate a reduced rate of synthesis of proteins by the liver reflected in the decreased levels of the apoproteins [30]. A study by Eva Hurt Camejo et al., showed an Apo B decrease by 7 %, while other lipoproteins were in the normal range in the RA patients and similar to those in the controls [31].

According to the use of antirheumatic drugs in RA, tumour necrosis factor inhibitors and MTX are associated with a decreased risk of all CVEs while corticosteroids and NSAIDs are associated with an increased risk. Targeting inflammation with tumour necrosis factor inhibitors or methotrexate may have positive cardiovascular effects in RA [32]. In about 10 comparative trials, a combination of MTX and a TNF-alpha antagonist was more effective than MTX monotherapy on functional status and symptoms, especially in initially severe RA. In practice, MTX is the first-line antirheumatic drug and [33] MTX does not have any effect on the lipid profile of RA and Westlake et al., suggested that MTX use is associated with a reduced risk of CVD events in patients with RA. This may be important early in the disease course. The mechanism for this possible benefit cannot be fully determined from the current literature but, is likely to be multi-factorial. As disease control continues to improve in RA, future studies need to address the impact of MTX and other synthetic and biologics DMARDs on CVD, which remains the leading cause of death and a significant comorbidity in these patients [34] As we have presented in our study MTX was the initial treatment as a monotherapy but also chosen by most rheumatologists, which is in accordance with the EULAR and ACR guidelines [35].

Therefore, the expert opinion is: identifying the RA phenotype at greatest risk of CVD, understanding the interplay of increased traditional risk factors, common inflammatory processes and RA-specific factors, and personalised use of DMARDs according to disease phenotype and comorbidity to reduce this risk are key areas for future research [32].

Limitations of Study: The sample size was small to allow for a generalisation of the results. The long-term effects of the treatment on lipids and disease activity can be deciphered only through further follow up.

In conclusion, we examined the impact of Methotrexate on disease activity, values of C-reactive protein and the Apolipoprotein B at patients with Rheumatoid Arthritis. Eighty patients with active and newly discovered RA after a year of therapy achieved a significant decrease in the DAS28 (disease activity score) and CRP values. Changes in Apo B levels between the start and the end of the study were with nonsignificant differences. Levels of Apo B at the 12 months were nonsignificantly higher compared to the results obtained at the beginning of the study. Use of MTX therapy at RA patients had a reduced effect on disease activity and inflammation, but nonsignificance effect on the values of Apo B lipoproteins.

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