Original scientific paper
616.72-002.77-085.277

EFFECT OF METHOTREXATE ON THE VALUES OF RHEUMATOID FACTOR AND LIPOPROTEIN (A) AND CORRELATIONS BETWEEN THEIR VALUES IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Abstract

Objective: To examine the disease activity score, the values of Rheumatoid factor and Lipoprotein (a) in patients with active and untreated Rheumatoid Arthritis (RA) before and after treatment with Methotrexate (MTX). **Material and methods**: 50 patients with active and untreated RA were treated with MTX therapy. The age of patients varied from 32 to 59 years old. The average age was 45.7 years old and the average disease duration was 6.2 years. The diagnosis was determined according to ARA (American Rheumatology Association) criteria of 1988. Before the treatment, all patients had done clinical and laboratory examinations. Drugs were prescribed according to the protocol for treatment, while Rheumatoid factor (RF) and Lipoprotein a (Lp(a)) values were recorded at the beginning of the study, the 6-month mark and at the end of study, respectively end of month 12. **Results**: At DAS28 score after 6 month($p<0.01$) there are significant differences in relation beginning, 6 and 12 month. The difference is also significant ($p<0.001$) in the relation beginning/12 month after treatment with MTX therapy. Changes in RF and Lp(a) levels between the start of the study, at 6 months and again in one year after the start of the study were with significant differences. There were noted very weak negative and non significant correlations between the values of RF and Lp(a) at the beginning, 6 and 12 month after treatment with MTX. **Conclusion**: Use of Methotrexat therapy at patients with active and untreated RA had reduced effect on disease activity and inflammation but also had beneficial effect lowering the values of RF and Lp(a) which contribute for lower risk for Cardio vascular disease (CVD) at RA patients.

Keywords: Rheumatoid arthritis, Rheumatoid factor, Lipoprotein (a), Methotrexat.

INTRODUCTION

It's now well established that Rheumathoıd Arthritis is associated with the increase in both morbidity and mortality compared to the general population. RA increases the risk of cardiovascular (CV) mortality by up to 50% compared with the general population and CV disease (CVD) is the leading cause of death in RA patients.(Peters *et al.,* 2010, Meune *et al.,* 2009, Avina Zubieta *et al.,* 2008) The pattern of CVD in RA patients appears to differ from that in general population. RA patients are more likely not only to have silent ischemic heart disease and experience sudden death, but also to develop heart failure and die shortly after thereafter (Solomon *et al.,* 2003).

Inflammation and poor control of this disease during treatment seem to be associated with increased CV events, and when disease control is achieved, CV outcomes have been shown to improve. Traditional CV risk factors may contribute to CV disease in patients with RA but do not adequately explain the overall increased risk in long-term RA registry studies. Inflammation, especially in uncontrolled RA, is thought to play a key role in driving CV disease in RA. (Yusuf *et al.*, 2008).

Histological data provided evidence that coronary arteries from autopsied RA patients have more inflammation in the media and adventitia and more fragile atherosclerotic plaques, but

less atherosclerosis, when compared to coronary arteries from age-and sex-matched controls who died from CV diseases. Despite this, the number of acute coronary lesions and grades of stenosis were similar (Maradit-Kremers et al., 2005, Gabriel SE 2008, Aubry et al., 2007). A possible interpretation of these differences is that the mechanisms responsible for cardiovascular morbidity and mortality are likely to be different in patients with RA. The value of MTX in preventing cardiovascular (and all-cause cardiovascular) morbidity and mortality has been investigated by several groups. A variety of composite endpoints have been used, including fatal and nonfatal MI, stroke and transient ischemic attack.

Strong evidence of CVD benefit for MTX comes from Choi and colleagues, who reported a significantly reduced incidence of CVD mortality in a study of 1240 patients. Patients receiving MTX therapy were 70% less likely to suffer a fatal CV event [hazard ratio (HR) 0.3; 95% confidence interval (CI) 0.2–0.7] during the study (mean follow up 6 years) compared with those not receiving a DMARD. There was no demonstrable dose-dependent relationship and other non-MTX DMARD usage was not associated with a decreased risk of CVD mortality. Further evidence of benefit has been provided by several other studies also showing statistically significant reductions in CVD mortality. The reductions in CVD morbidity and mortality range from 85% to 15% (Choi *et al.,* 2002, Van Halm *et al.,* 2006).

One possible mode of action may be through alterations in adenosine concentrations. Extracellular adenosine levels are increased by methotrexate and are known to mediate its anti-inflammatory effect (Naranjo *et al.,* 2008, Tian *et al.* 2007). To accompany this, there is evidence that adenosine enhances the effects of insulin on glucose transport and metabolism, and may also alter aspects of lipid metabolism. A recent study has also provided evidence that MTX may offer an atheroprotective effect, through activation of the adenosine A2A, thus promoting reverse cholesterol transport (Narano *et al.*, 2008). Another possible mode of action may be indirect, in that it may occur not as a consequence of methotrexate use per se, but as a consequence of concurrent folic acid supplementation. Folic acid has been shown to suppress plasma homocysteine levels. This may be particularly important in the context of the metabolic syndrom, which is known to be associated with high homocysteine levels (Joost *et al.,* 1982, Reiss *et al.,* 2008).

The presence of autoantibodies such as rheumatoid factor (RF) and possibly anticyclic citrullinated protein antibodies (ACPA) is associated with an increased CVD risk in RA and in the general population possibly by direct endothelial injury. Antibodies directed against oxidized low-density lipoprotein (LDL) have also been associated with CVD and occur more frequently in RA than the general population (Goodson *et al.*, 2002), though they have not yet been proven to be pathogenic (Wallberg-Jonsson *et al.*, 2002).

In addition to an inflammatory burden, RA may contribute to the thrombotic aspects of CVD through its promotion of a hypercoagulable state. Increased levels of fibrinogen, von Willebrand factor and tissue plasminogen activator, factors that are all associated with an increased cardiovascular risk, have been noted in patients with RA (Mc Entegard *et al.,* 2001).

In terms of serology, RF and ACPA are useful variables for determining the prognosis. The presence of RF at baseline has significant predictive value for the development of erosions; RF seropositivity also predicts persistent synovitis and the necessity for intensive treatment. However, there is disagreement regarding the value of RF as a predictor of remission and loss of function.(Praresi *et al.,* 2014). On the other hand, RF and ACPA are not associated with any of the extra-articular manifestations of the disease (Giles *et al.,* 2014).It is unclear whether joint destruction and the persistence of RA are due to the same mechanisms. Factors clearly associated with both are ACPA and RF positivity, HLA shared epitope (SE) status, and the duration of symptoms. Inflammatory markers are associated with the severity of joint damage but not with the persistence of the disease. Nonetheless, taken together these variables account

for 32% of the total variance in predicting joint destruction and disease progression, leaving 68% of the variance unaccounted for.(Praresi *et al.,* 2014, DeRooy *et al.,* 2011)
Lipoprotein (Lp)(a) is a cardiovascular risk factor and is known to promote thrombosis, inflammation, and coronary artery disease. As an LDL-like particle consisting of an apoB100 molecule linked to a glycoprotein, Lp(a) has been recognized to be in a very weak correlation with other lipid and non-lipid parameters. This particle's function remains largely uncertain; Lp(a) binds proinflammatory-oxidized phospholipids and is a preferential carrier of oxidized phospholipids (ox-PL) in human plasma.(De rooy *et al.*, 2011, AltanOnat *et al.,* 2015)
Since the lipid contents of Lp (a) and LDL-C were similar, they might have similar mechanisms in atherosclerosis. It is suggested that the reticulo-endothelial system became over stimulated in active rheumatoid arthritis and then the lipid elimination by scavenger receptors of macrophages increased. For that reason, Lp (a) may have a role as an important atherogenic factor. Dyslipoproteinemia in rheumatoid arthritis includes lower HDL-C, higher Lp (a), and higher TG and is related to atherosclerosis.(K.P.Shiva *et al.*, 2015)

AIM OF STUDY

The purpose of this study is to examine the disease activity and RF and Lp(a) values in 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 them in this period of time.

MATERIAL AND METHODS

A group of 50 patients with active and untreated RA patients at a time of one year, and a group of 30 healthy individuals who will serve as a control group, will be followed during this study. The study was conducted at the Rheumatology Clinic at the Clinical Center of Skopje. All patients were female, age range between 32 to 59 years old. The average age was 45.7 years old and the average disease duration was 6.2 years. All met the revised criteria by ARA (American Rheumatology Association) of 1987 for the classification of acute RA. Those criteria are: morning stiffness, arthritis in three or more sets of joints, arthritis in the joints of the hands, symmetrical arthritis, rheumatoid nodule, the serum Rheumatoid factor and typical radiological changes. The study did not include patients with disease or condition that directly or indirectly may affect the status of lipids, such as: sin. Cushing, cancer, diabetes mellitus, acute infections, vegetarians, diseases of liver, kidney, thyroid, cerebrovascular insults, cardiovascular disease, patients undergoing therapy with beta blockers, vitamin E, antilipid drugs, oral contraceptives, pregnant women, patients with excessive body weight, etc. (AltanOnat *et al.*, 2015, Georgiadis *et al.*, 2006).
Laboratory tests were done at the Institute of Biochemistry in Skopje. In all patients, the serum levels of RF were determined through test of agglutination (IU/ml), Lipoprotein (a) were determined through Bohring Turbi-timer methods (mg/dl) and were treated with MTH, mean dose 7.5-15 mg once weekly. Clinical disease activity of patients with RA is measured by: duration of morning stiffness of the joints, number of swollen joints, number of deformed joints, questions modified to improve the health (MHAQ), visual analog scale for pain (VAS) and the general definition of physician.
Blood samples were taken in the morning, at least 12 hours of fasting, as well as after consumption of greasy food the day before giving blood.
Statistical processing: statistical processing is extracted with 7.1 Statistic statistical programs.

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 (1-4), morning stiffness, the affected joints, swollen joints, VAS index, global doctor assessment, sedimentation of Er, CRP and RF. These parameters show disease activity in early studies. (Table 1).

Table 1. Characteristics of patients and controls

	RA (n=50)	Controls (n=30)
Age (year)	45.7 +-9.8	45.2 +-9.8
Sex: M/F	50 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)	41.4 +-29.4	
RF (positive/negative)	47/3	

BMI: Body Mass Index; MHAQ: Question modified to improve health,
VAS: visual pain score; CRP: C-reactive protein.

During the study, 50 patients with newly discovered active and untreated RA were treated with Methotrexate. These 50 patients were selected according to those who have responded the therapy. The patients who did not respond to the therapy (7 in number) were excluded from the study.

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

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

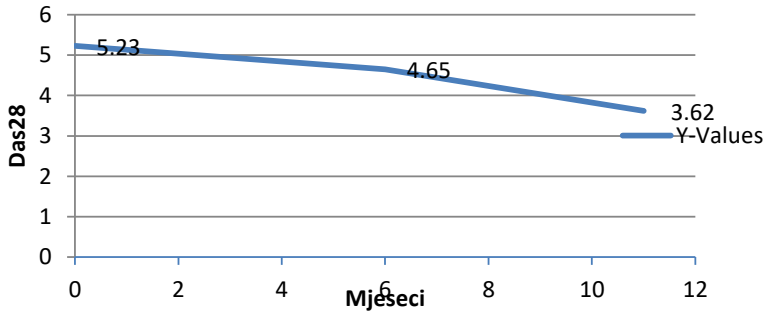


Figure 1. DAS28 index at the beginning, after 6 and 12 month of therapy

Table 2 presents values of RF at the beginning of the study, after 6 months and after a year from starting the study. RF at the beginning of the study was in the range 96,86 IU/ml. The minimum value was 0,00 while the maximum 708 IU/ml.
After 6 months of study, RF had lower values ranging between 90,99 + -111,86, with a 0.00 minimum value and a maximum value of 605,00 IU/ml.
After a year of commencement of the study interval, RF values were between 80,08 with a 0,00 minimum value and maximum values were 474,00 IU/ml. SD (Standard deviation) values were between 95,24

Table 2. Values of RF at the beginning of the study, after 6 months and after a year

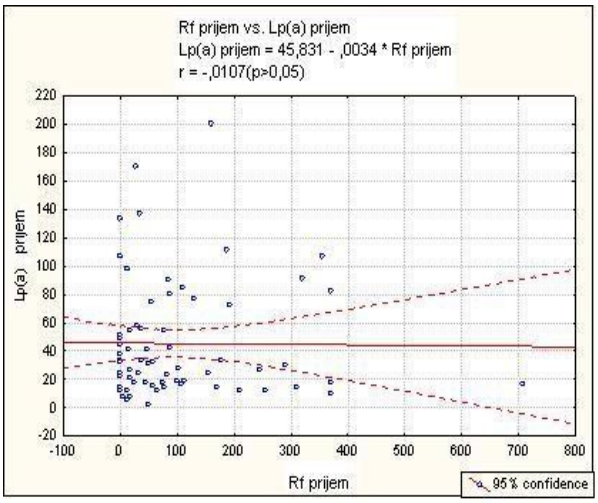
Timeframe	Valid N	Mean	Confidence -95,00%	Confidence +95,00%	Minimum	Maximum	Std.Dev.
Rf beginning	80	96,86	66,80	126,91	0,00	708,00	127,88
Rf after 6 m.	80	90,99	64,70	117,27	0,00	605,00	111,86
Rf after 12 m.	80	80,08	57,70	102,46	0,00	474,00	95,24

Table 3 presents Lipoprotein (a) research at the beginning of the study, after 6 months and one year of starting the study. Lp (a) at the beginning of the study was in the range of 45,50 + - 41,22 mg/dl, the +/-95.0% Confid.int. was between - 35,81 and + 55,18., while the minimum value was 1,80 mg/dl and the maximum at 200,00 mg/dl.
After 6 months of starting the study, Lp (a) ranged between1.5 + and -0.4 mmol / l, the +/- 95.0% Confid.int. was between 34,77 and 57,44 while the minimum value was 1.60 mg/dl and maximum at 286 mg/dl.
After a year of starting the study, Lp (a) was in the range between 38.70 + and -35,56 mg/dl, the +/-95.0% Confid.int. was between 30,35 and 47,06 with a minimum value of 1,50 mg/dl and the maximum value of 200,00 mg/dl.

Table 3. Lipoprotein research at the beginning of the study, after 6 months and one year

Timeframe	Valid N	Mean	Confidence -95,00%	Confidence +95,00%	Minimum	Maximum	Std.Dev.
Lp(a) beginning	80	45,50	35,81	55,18	1,80	200,00	41,22
Lp(a) after 6 m.	80	46,10	34,77	57,44	1,60	286,00	48,22
Lp(a) after 12 m.	80	38,70	30,35	47,06	1,50	200,00	35,56

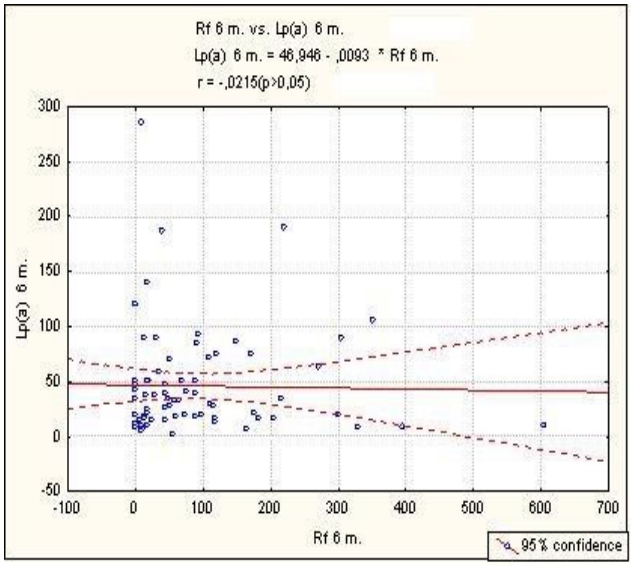
Correlation between the values of RF and Lp (a)
RF beginning / Lp(a) beginning
In figure nr.2 are shown the results of relation (correlation) between the values of RF and values of Lp (a) at the beginning of the study. For r = - 0,01 and p>0.05 there is very weak and negative nonsignificant correlation between the values of RF and Lp(a). Increasing the value of RF for 1 IU/ml has been followed with the decrease of the values of Lp(a) for 0,003 mg/dl.



RF 6 month / Lp(a)6 month

Figure 2. Correlation between the values of RF and values of Lp(a) at the beginning of the study

In figure nr.3 are shown the results of relation (correlation) between the values of RF and values of Lp(a) after 6 month of the study. For r = - 0,02 and p>0.05 there is very weak and negative nonsignificant correlation between the values of RF and Lp(a). Increasing the value of RF for 1 IU/ml has been folloved with the decrease of the values of Lp(a) for 0,009 mg/dl.



RF 12 month / Lp(a) 12 month

Figure 3. Correlation between the values of RF and values of Lp(a) after 6 months

In figure nr.4 are shown the results of relation (correlation) between the values of RF and values of Lp(a) after 12 month of the study. For r = - 0,009 and p>0.05 there is extremely very weak and negative nonsignificant correlation between the values of RF and Lp(a). Increasing the value of RF for 1 IU/ml has been followed with the decrease of the values of Lp(a) for 0,003 mg/dl.

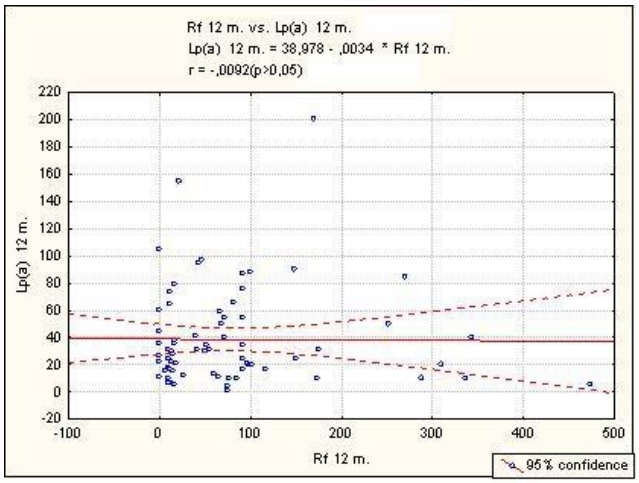


Figure 4. Correlation between the values of RF and values of Lp(a) after 12 months

DISCUSSION

Our goal was to determine the values of RF and Lp (a) in patients with active and untreated RA and variations in RF and Lp(a) values after treatment with drugs that modulate the progress of the disease, such as methotrexate. According to our results, these patients with active and untreated RA had high levels of RF and Lp(a). After 6 months and one year treatment with MTX, patients with RA showed significantly lower levels of RF and Lp(a) compared to RF and Lp(a) levels at the beginning of the study. This suggests that lowering levels of Lp(a) are followed with decreasing of inflammation at the end of the study. Or, in other words it tells us that inflammation in some way interact proatherogenic lipid profile, the metabolism of lipoproteins and high disease activity is associated with higher values of Lp(a) and other lipid changes. Conventional therapy with MTX has positive effects on Lp(a) and RF values and with that in lipid profile in patients with RA and this enables us to conclude that treatment with immunomodulators affect the mechanisms that influence cardiovascular morbidity and mortality of these patients. (Peters *et al.,* 2010, Yusuf *et al.*, 2008, Choi *et al.*, 2002, Durusonogllu *et al.,* 2005,) According the correlation between RF and Lp(a) during the study there was very weak, negative and nonsignificcant correlation in the beginning, after 6 and 12 month of study.

Lipid profile in patients with RA was investigated in several studies. Some have reported lower values of HDL cholesterol and total cholesterol (TC), and increased the concentration values of Lp (a) and increase the proportion of TC / HDL and LDL / HDL in patients with active and untreated RA patients, compared with the general population. (Georgiadis *et al.,* 2006, Lee *et al.*, 2000, Garcia-Gomez *et al.*, 2009) Meanwhile, several other studies have not shown significant differences in lipid profile of RA patients compared with the healthy population. There are also studies that show a decline across the lipid fraction in the acute phase of illness. Such differences that arise in different cases can be explained by the size of samples, type of study (prospective or cross sectional), differences in the disease type (early or established) or disease activity, etc.(Von halm *et al.*, 2006, Naranjo *et al.,* 2008, Myasoedova *et al.,* 2011, Situnayake *et al.,* 1997).

In his study, Taysi S. et al., presents significantly higher values of Lp (a) in serum of patients with RA compared with those of control group ($p < 0.01$) and HDL cholesterol values, Apolipoprotein A1 (Apo A1) values were significantly lower in patients with RA ($p < 0.01$). Sedimentation values and the CRP have been higher in these patients and these parameters have correlated positively with the values of Lp (a) in serum of RA patients, and negatively

with HDL-C. She emphasizes that these patients, with these lipid values are at risk for developing cardiovascular disease and atherosclerosis.(Taysi *et al.,* 2004)
Van Halm et al. support the observations that patients with RA have a atherogenic lipid profile even 10 years before the clinical onset of RA, which in itself may explain the increase of cardiovascular risk in patients with RA. The study was conducted on 79 patients, blood donors who later have developed RA. These patients had low levels of HDL cholesterol and high levels of TC, Trygliceride (TG), Apolipoproteins B (Apo B) compared with controls, even the 10 years before the disease appears. This suggests that lipid changes can make people more susceptible to the appearance of RA or these patients are genetically in predisposition for dyslipidaemia, or the transcription of these genes are altered by the presence of inflammation.(Van Halm *et al.*, 2007)
In the latest study of Cho SKdisease-modifying anti-rheumatic drugs (DMARDs) (OR = 0.79) were protective against CVD, and biologic DMARDs were not significantly associated with CVD risk (OR = 0.85). Corticosteroids (OR = 1.26) and NSAIDs (nonselective NSAIDs: OR = 1.32, Cox-2 inhibitors: OR = 1.31) were risk factors for CVD in RA patients. (Cho SK *et al.*, 2018).
According to the presence of RF appears to have a clear association with higher levels of disease activity, whereas the presence of ACPAs is associated with lower disease activity, although this was observed only as a trend. The data further imply that therapeutic strategies in RA should focus not only on classic variables of disease activity but also on the presence of RF. As seroconversion into an autoantibody-negative state is attainable for RF, this should be a therapeutic goal, and lack of seroconversion a potentially decision-driving situation.(Aletaha *et al.*, 2015)
Management of dyslipidaemies should be considered as part of cardiovascular risk at patients with RA. It is clear that good controlling managing and taking control of the disease has positive effects on lipid profile and thereby reduces cardiovascular events in these patients. Good and adequate treatment of cardiovascular risk factors is most necessary in these patients but taking into account other epidemiological research in this area as well as more precise and comprehensive guidelines for tackling this issue.(Avina-Zubieta *et al.*, 2008, Yusuf Yazici *et al.*, 2008, Van Halm *et al.,* 2006, Nranjo *et al.,* 2008)

CONCLUSION

Use of Methotrexat therapy at patients with active and untreated RA had reduced effect on disease activity and inflammation but also had beneficial effect lowering the values of RF and Lp(a) which contribute for lower risk for Cardio vascular disease (CVD) at RA patients.

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