Effect of Methotrexate on Lipid Profile and Cardiovascular Atherosclerosis in patients with Rheumatoid Arthritis

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Abstract: Background: rheumatoid arthritis is a common disease with subsequent disability. Different treatments were present. However, the effects of these drugs on lipid profile are not well investigated. **Aim of the work:** investigate the possible role of methotrexate therapy in rheumatoid arthritis with or without dyslipidemia and/or atherosclerosis. **Methodology:** the present work included 150 patients with rheumatoid arthritis, divided into two main groups. **The first group** included patients who had no dyslipidemia nor atherosclerosis with methotrexate only therapy; **the second group** included patients with dyslipidemia and/or carotid atherosclerosis; **the second group were subdivided into three subgroups** according to the treatment. The first subgroup included those treated with methotrexate only; the second subgroup treated with methotrexate and statins and the third subgroup treated by other DMARDs. **Results:** There was statistically significant decrease of disease severity and quality of life, CRP and ESR in all studied groups after treatment when compared to corresponding values before treatment. Lipid profile showed heterogeneity in results, for example post-treatment cholesterol was significantly increased in GI, GIIb, and GIIc and significantly decreased in GIIa. Triglycerides significantly decreased in GI, but significantly increased in GIIa, GIIb, GIIc after treatment. HDL results were similar to triglycerides. However, lipoprotein A had no significant changes after treatment in group GI; while there was statistically significant decrease in the other 3 subgroups. There was significant correlation between pre-treatment cholesterol and pre-treatment CRP. Post-treatment cholesterol was significantly correlated with disease severity (post), CRP (Post) and ESR (post). In addition, each of post-treatment triglycerides and LDL was significantly correlated with disease severity (post) and ESR (post). In addition, there was significant correlation between either pre- or post-treatment Carotid intima median thicknesses with each of total cholesterol (pre), HDL post and DAS28 (post). **Conclusion:** methotrexate and other included therapies in the present study exert a heterogeneous effect on lipid profile. However, there was a significant correlation between lipid profile and inflammatory markers linking both in the pathogenesis and response to treatment of rheumatoid arthritis.

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1. Introduction

The overall world prevalence of rheumatoid arthritis (RA) ranges from 0.5% to 1%, qualifying as the most common chronic inflammatory condition **(Gibofsky, 2012).** RA is a chronic inflammatory polyarthritis that often leads to joint destruction, deformity and loss of function. In addition, patients with RA have an increased risk of cardio-vascular disease or events and reduced survival **(Avina-Zubieta et al., 2012).** The risk of RA patients developing chronic heart failure was approximately twice that of controls **(Nicola et al., 2005).** The increased prevalence of CVD is probably due to an increase in both the traditional risk factors for atherosclerosis and the presence of chronic inflammation **(Sattar et al., 2003).** Active systemic inflammation is a risk factor that accelerates athero-sclerosis by several mechanisms. These include: changes to the endothelium induced by CRP and cytokines; induction of secondary dyslipidemia, altered glucose metabolism and creation of a hypercoagulable state due to platelet activation **(van Leuven et al., 2008).** Given the importance of inflammation in the development of CVD, therapies aimed at reducing disease activity in RA may also have a positive impact on CVD risk by reducing the

burden of systemic inflammation.

Methotrexate (MTX) has become the most frequently used disease modifying anti-rheumatic drugs (DMARD) in RA and the cornerstone in most DMARD and biologic combinations **(Edwards et al., 2005).** Although the side effects of MTX can be serious, its long-term safety has been established in patients with RA. MTX improves the mobility of patients with RA, judging from questionnaires for health assessment and other global measures of quality of life **(Ridker, 2014).**

The carotid ultrasonography is a non-invasive imaging techniques offer a unique opportunity to identifying the Carotid intima-media thickness (cIMT) and presence of plaques **(Laczik et al., 2012).** cIMT is a simple, reliable, inexpensive, non-invasive marker that is increasingly being used to detect subclinical atherosclerosis and has been recommended by the American Heart Association (AHA), American Society of Echocardiography (ASE) and Society for Vascular Medicine (SVM) as a screening test for heart disease in apparently healthy individuals **(Greenland et al., 2010).** The importance of abnormally high cIMT and plaques as predictors of CV events in patients with RA has been emphasized **(Simonetti et al., 2014).**

The present study designed to investigate the effect of methotrexate on lipid profile and cardiovascular atherosclerosis in rheumatoid arthritic patients.

2. Patients and methods

This study was carried out on 150 patients with new or old onset RA who were naïve to methotrexate (MTX). Diagnosis of RA was made by the ACR 1987 criteria for the diagnosis of RA **(Arnett et al., 1988)** and the 2010 ACR/ EULAR Classification criteria **(Aletaha et al., 2010)** for early arthritis. Patients were recruited from the Rheumatology and Rehabilitation clinic, Al-Azhar University Hospital (New Damietta). This study was done during the period extending from August 2016 through August 2017. Patients who their age less than 50 years, had no history of previous MTX therapy before enrolment in the study, and had no history of cardiovascular disease (CVD), diabetes mellitus DM or hypertension; were enrolled in the present work. On the other hand, patients with age ≥ 50 years, had MTX therapy before enrollment in the study, had cardiovascular disease, diabetes mellitus or hypertension, had history of pulmonary fibrosis injury, had pregnancy or currently lactating were excluded from the study. All patients were underwent full history taking and clinical examination (general and musculoskeletal). Pain was assessed by visual analogue scale as described elsewhere **(Langley and Sheppeard, 1985).** In addition, disability was assessed by Health Assessment Questionnaire–Disability Index (HAQ-DI), and disease activity was evaluated by disease Activity Score 28(DAS) 28as described by **Van Riel and Schumacher (2001).** Blood samples were drawn and the following laboratory investigations were done: 1) Rheumatoid factor, 2) serum anti-cyclic citrullinated peptide-2 antibodies, 3) C-reactive protein **(Mackiewicz et al., 1985),** 4) Erythrocyte sedimentation rate levels **(Westergren, 1957),** 5) Lipid profile **(Richmond, 1973),** and 6) lipoprotein A **(Mohieldein et al., 2014).** Finally, carotid duplex was done to determine intimal thickness as a direct measure of atherosclerosis. Both carotid arteries were scanned, with the subject in supine position with slight hyperextension of the neck. The greatest distance between lumen-intima and media-adventitia interface was measured. Mean value of 2 sides (right and left) was taken and included in statistical analysis **(Persson et al., 1992).**

According to the results of the lipid profile and/or the carotid duplex, patients were divided into the following groups: **Group I:** RA patients without dyslipidemia or carotid artery atherosclerosis. This group was treated with MTX only. **Group II:** RA patients with dyslipidemia and/or carotid artery atherosclerosis. This group will be subdivided into two groups: **Group IIa:** this group will be treated with MTX only. **Group IIb:** this group will be treated with MTX and statin. **Group IIc:** this group treated with other DMARDs. All patients after 3 months from treatment were re-evaluated by lipid profile and carotid duplex to evaluate the effect of MTX on lipid profile and cardiovascular atherosclerosis.

Statistical analysis of data: the collected data were organized, tabulated and statistically analyzed using statistical package for social science version 22 (IBM, SPSS Inc., USA). Quantitative data were presented as mean and standard deviation, while qualitative data were presented as relative frequency and percent distribution. Comparison between groups was done using one analysis of variance, independent samples (t) test, Chi square or Mann-Whitney test. P values < 0.05 was considered significant.

3. Results

In the present work, age ranged from 27 to 49 years, and there was statistically non-significant difference between studied groups. In addition, 39 subjects (26.0%) were males and 111 (74.0%) were females; and there was no significant difference between studied groups as regard to sex distribution (females presented 77.8%, 77.1%, 77.1% and 62.9% of GI, GIIa, GIIb and GIIc respectively). BMI ranged from 24.91 to 32.39 and there was no significant difference between studied groups. Disease duration (week) ranged from 6 to 11weeks, and there was no

significant difference between studied groups. Finally, there was no significant difference between studied groups as regard to pre-treatment disease severity. In addition, there was no statistically significant difference between studied groups as regard to pretreatment value of ESR, CRP, RF and anti-CCP (table 1).

Table (1): Pretreatment data in studied populations

Variable		**GI**	**GIIa**	**GIIb**	**GIIc**	**P value**
Age		43.80±5.30	45.34±4.09	44.40±5.11	46.25±2.76	0.09(ns)
Sex	**Male**	10(22.2%)	8(22.%)	8(22.%)	13(37.1%)	0.39(ns)
	Female	35(77.8%)	27(77.1%)	27(77.1%)	22(62.9%)	
BMI		27.09±1.43	27.49±1.47	27.17±0.84	27.42±0.93	0.41(ns)
Duration		5.33±0.92	5.36±0.97	5.33±0.99	5.39±1.01	0.99(ns)
DAS28		5.80±0.47	5.69±0.42	5.59±0.34	5.74±0.41	0.19(ns)
ESR		35.40±5.68	34.11±5.41	36.44±5.26	34.41±5.74	0.27(ns)
CRP		3.09±0.40	3.05±0.46	3.06±0.38	3.14±0.42	0.83(ns)
R.F		27.60±4.51	28.40±5.06	28.16±5.42	26.61±6.39	0.51(ns)
R.F +ve		43(95.6%)	33(94.3%)	33(91.7%)	30(88.2%)	0.63(ns)
Anti-CCP +ve		35(77.8%)	26(74.3%)	24(66.7%)	23(67.6%)	0.64(ns)

GI: RA without dyslipidemia or carotid atherosclerosis; **GIIa:** RA with dyslipidemia and/or carotid atherosclerosis treated with methotrexate only; **GIIb:** RA with dyslipidemia and/or carotid atherosclerosis treated with methotrexate and statin; **GIIc:** RA with dyslipidemia and/or carotid atherosclerosis treated with other DMARDs

Table (2): comparison between different pre- and post-treatment values in studied groups

	Time	GI	GIIa	GIIb	GIIc
DAS28	Pre-	5.80±0.47	5.69±0.42	5.59±0.34	5.74±0.41
	Post-	2.14±0.52	2.95±0.32	2.89±0.26	2.98±0.13
	P	**<0.001***	**<0.001***	**<0.001***	**<0.001***
QoL-DI	Pre-	0.82±0.25	0.81±0.16	0.79±0.27	0.75±0.16
	Post-	0.33±0.09	0.49±0.13	0.46±0.16	0.41±0.16
	P	**<0.001***	**<0.001***	**<0.001***	**<0.001***
CRP	Pre-	3.09±0.40	3.05±0.46	3.06±0.38	3.14±0.42
	Post-	0.90±0.32	1.44±0.20	1.10±0.15	1.0±0.20
	P	**<0.001***	**<0.001***	**<0.001***	**<0.001***
ESR	Pre-	35.40±5.68	34.11±5.41	36.44±5.26	34.41±5.74
	Post-	10.68±1.86	15.25±2.38	13.30±2.79	14.0±3.18
	P	**<0.001***	**<0.001***	**<0.001***	**<0.001***
Cholesterol	Pre-	149.93±18.11	194.00±13.07	150.19±12.37	152.26±12.36
	Post-	150.93±17.08	182.34±8.52	186.36±9.18	187.50±7.22
	P	**0.027***	**<0.001***	**<0.001***	**<0.001***
TG	Pre-	121.24±11.66	122.91±17.69	123.30±15.09	122.82±12.25
	Post-	120.22±11.71	131.62±13.19	132.33±8.54	132.64±8.16
	P	**0.001***	**<0.001***	**<0.001***	**<0.001***
HDL	Pre-	53.62±4.82	51.68±5.64	52.50±6.36	51.52±5.54
	Post-	54.28±4.85	60.22±4.13	68.41±4.39	68.64±1.82
	P	**<0.001***	**<0.001***	**<0.001***	**<0.001***
LDL	Pre-	127.80±33.97	143.31±46.52	135.00±25.71	139.02±26.20
	Post-	126.55±34.15	114.08±10.74	103.63±6.81	114.85±14.39
	P	**<0.001***	**<0.001***	**<0.001***	**<0.001***
Lipoprotein A	Pre-	326.82±28.19	325.20±29.46	321.58±30.85	320.91±34.21
	Post-	326.80±28.93	246.45±17.64	220.47±16.83	240.88±12.87
	P	0.66	**<0.001***	**<0.001***	**<0.001***
mCIMT	Pre-	0.581±0.027	0.589±0.039	0.590±0.039	0.600±0.037
	Post-	0.582±0.027	0.50±0.040	0.591±0.038	0.602±0.035
	P	0.18	0.80	0.32	0.18

As regard to disease severity (measured by DAS28), the disease severity was significantly reduced after treatment when compared to corresponding values before treatment in each of studied groups. Quality of life-disability index revealed that, it was significantly decreased after treatment when compared to corresponding values before treatment in each of studied groups. In addition, CRP was significantly reduced after treatment when compared to corresponding values before treatment in each of studied groups. In addition, results of ESR showed that, ESR was significantly decreased after treatment when compared to corresponding values before treatment in each studied group. As regard to total cholesterol, it was significantly increased after treatment when compared to corresponding values before treatment in each of studied group. TG was significantly increased after treatment when compared to corresponding values before treatment in each of IIa, IIb and IIc group, while the values in group GI was significantly decreased after treatment when compared to corresponding value before treatment. HDL was significantly increased after treatment when compared to corresponding values before treatment in each of studied group. LDL was significantly decreased after treatment when compared to corresponding values before treatment in each of studied group. Lipoprotein A was significantly decreased after treatment when compared to corresponding values before treatment in each of groups IIa, IIb and IIc; while there was no statistically significant difference between values after and before treatment in group GI. Carotid intima media thickness showed statistically non-significant difference between values after treatment when compared to corresponding values before treatment in each of studied groups (table 2).

In the present work, there was significant correlation between pretreatment cholesterol and pretreatment CRP. On the other hand, post-treatment cholesterol was significantly correlated with disease severity (post), CRP (Post) and ESR (post). In addition, each of post-treatment triglycerides and LDL was significantly correlated with disease severity (post) and ESR (post) (table 3). In addition, there was significant correlation between either pre- or post-treatment Carotid intima median thicknesses with each of total cholesterol (pre), HDL post and DAS28 (post) (table 4).

Table (3): Correlation between lipid profile and other studied variables

		Chol. pre	Chol. Post	TG pre	TG post	HDL Pre	HDL post	LDL Pre	LDL Post
Disease duration	r	.04	-.01	.03	.01	.03	.03	.06	-.12
	p	.59	.88	.64	.91	.71	.76	.42	.12
DAS28 pre	r	.05	-.05	-.08	-.03	.04	-.16	-.04	.09
	p	.50	.54	.28	.67	.65	.04	.60	.24
DAS28 post	r	-.10	.50	.02	.32	.03	.53	.08	-.10
	p	.21	.00	.76	.00	.68	.00	.30	.22
Rh. F	r	.03	.02	-.05	-.00	-.11	-.14	-.01	-.03
	p	.63	.78	.48	.98	.15	.08	.95	.66
Anti-CCP	r	-.04	.04	-.07	-.05	-.16	.06	-.03	-.12
	p	.58	.59	.34	.50	.05	.42	.66	.06
CRP-pre	r	-.20	-.06	-.09	-.06	.01	0-.02	.09	.02
	p	.01	.41	.23	.45	.91	.80	.26	.78
CRP post	r	-.01	.32	.05	.25	-.01	.09	.10	-.01
	p	.94	.00	.47	.01	.81	.26	.20	.82
ESR pre	r	.01	.04	-.03	.00	-.13	-.09	-.01	-.01
	p	.88	.57	.64	.99	.10	.27	.89	.94
ESR post	r	.04	.40	.06	.25	-.02	.19	.11	-.11
	p	.60	.00	.46	.02	.84	.02	.06	.17

4. Discussion

While RA therapy may have a role in decreasing cardiovascular risk in RA patients through control of disease activity, its potential impact through lipid profile modification is not well-established. Thus, the present study was designed to investigate the possible role of methotrexate therapy in rheumatoid arthritis with or without dyslipidemia and/or atherosclerosis.

In the present study, 39 subjects (26.0%) were males and 111 (74.0%) were females; and there was no significant difference between studied groups as regard to sex distribution (females presented 77.8%, 77.1%, 77.8% and 61.8% of GI, GIIa, GIIb and GIIc respectively). These results are comparable to those

reported by **Galarza-Delgado et al. (2016)** who reported that, sixty-two patients were included in the final analysis. Fifty five (88.7 %) were women, which reflected the female predominance in rheumatoid arthritis as in the present work. In addition, **Li et al. (2017)** reported that, among the 2013 RA subjects, 79.1% were women. All subjects were Chinese with mean age of 55.5 year.

Table (4): Correlation between carotid intima median thickness and other variables

	CIMT		CIMT Post	
	r	p	r	p
Cholesterol pre	0.177	0.031	0.176	0.032
Cholesterol post	0.058	0.482	0.052	0.529
Triglycerides pre	0.013	0.879	0.047	0.565
Triglycerides post	0.142	0.084	0.171	0.037
HDL pre	0.067	0.419	0.046	0.573
HDL post	0.200	0.014	0.210	0.010
LDL Pre	-0.107	0.193	-0.103	0.208
LDL post	-0.067	0.413	-0.078	0.343
Lipoprotein A pre	-0.155	.00057	-0.139	0.089
Lipoprotein A post	-0.111	0.177	-0.109	0.183
Disease duration	-0.029	0.724	-0.048	0.556
DAS28- pre	0.063	0.445	0.058	0.483
DAS28- post	0.206	0.012	0.199	0.014
Rheumatoid F	0.058	0.482	0.042	0.606
Anti-CCP	0.009	0.909	0.030	0.714
CRP pre	0.031	0.710	0.002	0.977
CRP post	-0.002	0.981	-0.024	0.772
ESR pre	0.030	0.715	0.035	0.667
ESR post	0.044	0.597	0.024	0.768
Age	-0.136	0.098	-0.115	0.163
BMI	0.133	0.105	0.146	0.075

Regarding RF, there was no statistically significant difference between studied groups either before or after treatment. In addition, there was no significant difference between values after treatment when compared to corresponding values before treatment in each group. In addition, 95.6%, 94.3%, 91.7% and 88.2% of groups I, IIa, IIb and IIc were RF positive; and there was no significant difference between studied groups. These results are in accordance with **Muller et al. (2017)** who reported that, the majority of RA patients were seropositive, and 50 % had moderate disease activity.

As regard to Anti-CCP antibodies, it was positive in 77.8%, 74.3%, 66.7% and 67.6% in groups I, IIa, IIb and IIc respectively, and there was no statistically significant difference between studied groups. Anti-CCP antibodies usually used for diagnosis of RA. It had been reported that, assays for anti-citrullinated protein antibody (ACPA; often tested as anti-CCP) are now being used clinically for diagnosing RA. ACPA-positive and ACPA-negative RA may be 2 distinct disease subsets, with different underlying pathogeneses and risks for developing RA **(Daha and Toes, 2011; Scott et al., 2011).** ACPA-positive patients may have a more erosive RA disease course than ACPA-negative patients **(van Venrooij et al., 2011).**

Regarding BMI in studied populations, it ranged from 24.91 to 30.86 and there was no significant difference between studied groups. These results are in comparable to those reported by **Muller et al. (2017)** who reported that, BMI was not significantly different between studied groups.

As regard to disease severity (measured by DAS28), there was no significant difference between studied groups before treatment; while after treatment, the disease severity was significantly higher in each of groups IIa, IIb and IIc when compared to GI. In addition, the disease severity was significantly reduced after treatment when compared to corresponding values before treatment in each of studied groups. These results are in agreement with those reported by **Parveen et al. (2017)** who reported that, the DAS28 showed significant improvement after treatment by DMARDs ($p<0.0001$).

In the present work, lipid profile showed decreased levels of total cholesterol, triglycerides, HDL and elevated LDL in patients with rheumatoid arthritis before treatment, with significant elevation of cholesterol, triglycerides, HDL and reduction of LDL

after treatment by methotrexate alone, or with statin and with other DMARDs. In addition, disease severity, disability index, and inflammatory markers were significantly reduced 3 months after treatment, but carotid intima media thickness showed non-significant increase after 3 months of therapy (denoting stoppage of atherosclerosis progression); the pronounced effect was observed in subgroup of methotrexate with statin treatment, then methotrexate alone or other DMARDs come in the second position. Results of the present study are comparable to those reported by **Myasoedova et al. (2010)** who in a retrospective case–control study found that, cholesterol and LDL were lower in RA cases than in controls. Furthermore, the study reported that that LDL levels decreased significantly in the 5 years before RA diagnosis. However, these lower levels of Tchol and LDL associated with the inflammatory process in RA resulted in a paradoxically higher risk for CVD **(Myasoedova et al., 2011; Robertson et al., 2013)** and, interestingly, successful reduction in RA disease activity following anti-inflammatory treatment had increased serum lipid levels **(Daien et al., 2012).** These results go in agreement with that of the present work. These observations imply that the traditional interpretation of lipid profiles for predicting CV risk in the general population may be confounded by disease activity in RA patients **(Myasoedova et al., 2011).**

Going with results of the present work, traditional DMARDs, such as MTX, SSZ and HCQ, have a protective role against CV risk possibly by reducing inflammation. MTX increases total cholesterol (TCh), LDL, HDL and triglyceride levels in RA **(Navarro-Millan et al., 2013).** However, it is believed that these changes are likely to be due to the inflammatory-dampening effect of the drug and may essentially reflect normalization of the lipid levels to those seen in the general population **(Liao et al., 2013).** These lipid increases are therefore not generally believed to increase CV risk. On the contrary, there is evidence that MTX therapy may decrease CV morbidity and mortality in RA patients **(Westlake et al., 2010).** Potential mechanisms of CV risk reduction with MTX are not well understood, although suppression of inflammation is likely to partially explain the cardio-protective effects of MTX **(Greenberg et al., 2012).** In an observational study in patients with RA taking MTX or leflunomide, there was no significant difference in the levels of LDLc, HDLc, and TG **(Rho et al., 2009).** In contrast, another study reported that MTX may induce increments in both TC and TG levels **(Saiki et al., 2007).**

Regarding effects of statin therapy in RA patients, **Tam et al. (2011)** reported that, their results showed that a 10-mg dose of rosuvastatin lowered LDL-C concentration by 35.8%, which is comparable to previous studies reporting 35–50% LDL-C reduction **(Weng et al., 2010).** Statin has good efficacy in lowering TC, LDL-C, and Apo B levels in RA patients with a normal lipid profile, similar to non-RA subjects published elsewhere **(Crouse et al., 2007).**

Going with results of the present work, previous studies have demonstrated a slower progression of IMT in the statin group compared to placebo in patients with established CAD **(Yu et al., 2007)** or borderline hyperlipidemia **(Probstfield et al., 1995).** In low-risk patients with subclinical atherosclerosis, rosuvastatin 40 mg daily resulted in a significant reduction in the rate of progression of maximum IMT, in the Measuring Effects on Intima–Media Thickness: an Evaluation of Rosuvastatin (METEOR) study **(Crouse et al., 2007).**

In conclusion, methotrexate and other included therapies in the present study exert a heterogeneous effect on lipid profile. However, there was a significant correlation between lipid profile and inflammatory markers linking both in the pathogenesis and response to treatment of rheumatoid arthritis. Future case-controlled studies are needed to elucidate the situation.

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