Metabolic Syndrome as a Factor Affecting on Intima-Media Thickness in Patients with Rheumatoid Arthritis

Lyudmila Gennadievna Turgunova[1] , Anna Andreevna Shalygina[2]*, Lyazat Kataevna Ibrayeva[2], Anar Akylbecovna Turmuhambetova[3]

[1]Department of Internal Medicine, Karaganda Medical University, Karaganda, Kazakhstan; [2]Karaganda Medical University, Karaganda, Kazakhstan; [3]Department of Strategic Development, Karaganda Medical University, Research and International Collaboration, Karaganda, Kazakhstan

Abstract

AIM: The aim of the study was to assess the association of the thickness of the intima-media complex with metabolic syndrome (MetS) and the degree of disease activity in patients with rheumatoid arthritis (RA).

MATERIALS AND METHODS: The study included 101 patients with RA. All patients underwent a biochemical examination, the presence of MetS was determined, and the carotid thickness of the intima-media was determined. Statistical processing was performed using SPSS for Windows, version 18.0.

RESULTS: Among 101 patients with RA, 41 (40.5%) had MetS. The frequency of detecting an increased value of the intima-media complex thickness was significantly higher in the group with MetS (n = 31 [75.6%]) than in the group without MetS (n = 21 [35.0%] p ≤ 0.0001). In the group of patients with MetS, the median carotid intima-media thickness (CIMT) was 1.2 mm, while this indicator in the group without MetS was 0.78 mm (U = 727, p = 0.001). In the regression model, MetS (B = 1.05; p = 0.027) and DAS28-ESR (B = 0.506; p = 0.021) were influenced by CIMT.

CONCLUSIONS: The results of our study show the effect of MetS and RA activity on the increase of intima-media thickness.

Introduction

Rheumatoid arthritis (RA) is a systemic immune-inflammatory disease characterized by early disablement of patients and increased cardiovascular risk [1], [2]. Previous studies have shown that the mortality rate in patients with RA is 1.5 times higher than in the general population [3], [4]. The high prevalence of cardiovascular diseases among patients with RA determines the search for the causes of this fact. The researchers attribute the increased risk of cardiovascular disease in rheumatoid patients to the persistence of chronic systemic inflammation, the higher prevalence of traditional cardiovascular risk factors, and the negative effects of drugs used to treat RA on the cardiovascular system. However, all these factors cannot fully explain the more rapid development and progression of atherosclerosis as the main pathogenetic mechanism of cardiovascular diseases in patients with RA [5], [6].

Metabolic syndrome (MetS), which includes an increase of waist circumference (WC), a decrease in high-density lipoprotein (HDL) cholesterol, an increase in triglycerides, arterial hypertension, and hyperglycemia, is associated with the development of cardiovascular diseases in the general population [7], [8]. In a meta-analysis, Zhang *et al.* have been shown that in patients with RA, the prevalence of MetS is higher than in patients without RA [9]. It was also previously shown that the presence of MetS in patients with RA is associated with higher disease activity and less effective therapy [10], [11].

The intima-media thickness (IMT) is considered as a surrogate marker of cardiovascular risk [12]. Despite the fact that modern methods of IMT imaging, such as carotid magnetic resonance imaging, are currently available, the use of ultrasound to determine carotid IMT remains an actual method in patients with RA [13], [14].

Previously, it was shown that patients with RA have higher IMT than in the control group [15]. There is also evidence of higher IMT scores in patients with MetS [16], [17], [18]. It can be assumed that the simultaneous presence of both MetS and RA in the patient will lead to a faster progression of atherosclerotic artery damage. However, there are not enough studies to determine IMT in patients with comorbidity of RA and MetS, and the results of these studies are different [19], [20]. Thus, the aim of our study is to determine the carotid intima-media thickness

(CIMT) in patients with RA and MetS and to determine the relationship of IMT with RA activity indicators.

Materials and Methods

Patients

The study included 101 patients with RA. The diagnosis of RA was established according to the 2010 ACR/European League Against Rheumatism/American College of Rheumatology 1987 criteria for RA [21], [22]. The exclusion criteria were age are over 50 years old, history of cardiovascular disease such as myocardial infarction, cerebrovascular damage, obliterating atherosclerosis, coronary stenting, and coronary artery bypass surgery. Researchers obtained a patient history and performed a physical examination. The patients were recruited at Karaganda Medical University Clinic. All study participants signed informed consent before any procedures were started.

MetS

The MetS was established according to IDF Consensus Worldwide Definition of the MetS (IDF, 2009) [23]. It included abdominal obesity (defined as WC ≥94 cm in Europid males and ≥80 cm in females) plus any two of the following four factors: Triglycerides raised more than 150 mg/dl (1.7 mmol/l) or specific treatment for this lipid abnormality; HDL cholesterol reduced <40 mg/dL (1.03 mmol/L) in males and <50 mg/dL (1.29 mmol/L) in females or specific treatment for this lipid abnormality; raised systolic ≥130 or diastolic blood pressure ≥85 mmHg or treatment of previously diagnosed hypertension; fasting plasma glucose ≥100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes mellitus.

Laboratory diagnostics

The glucose level was measured using the Accu-Chek Active Blood Glucose Meter in capillary blood. All blood samples were collected after 12 h fasting period. Total cholesterol and triglycerides and low-density lipoproteins (LDL) were measured by an enzymatic colorimetric method with selective protection without sedimentation. LDL cholesterol was calculated using the Friedewald formula [24]. The erythrocyte sedimentation rate was established by the Panchenkov method.

Intima media thickness

The specially trained healthcare professional provided an ultrasound examination of the extracranial part of the carotid artery using EPIC 7 Ultrasound (Philips Ultrasound, 2018, USA). The study was conducted at the patient's back position. The ultrasound images were received using B-mode ultrasound at the distal 1 cm of the far wall of each common carotid artery [25]. The measurements were taken twice on each side. The final result was established as an arithmetic mean of two measurements on each side. The CIMT exceeded 0.87 mm was chosen as cut-off point for IMT abnormality according to the literature sources [26], [27], [28].

RA disease activity

RA disease activity was estimated using the Disease Activity Score with 28 joints counted and the erythrocyte sedimentation rate (DAS28-ESR) [29], [30].

Statistical processing

Statistical Package for the Social Sciences (SPSS for Windows, ver. 18.0, SPSS Inc., Chicago, Illinois, USA) was used to calculate statistical parameters. Continuous variables were tested for normal distribution using the Kolmogorov–Smirnov test. All the variables in the present study were abnormally distributed, thus, the data were present as the median and interquartile range. Categorical variables were present as numbers and percentages. Mann–Whitney U test was used to provide inter-group comparison. Spearman's rank correlation coefficient was used to establish correlations (rs). The results were significant at $p \leq 0.05$. The binary logistic regression model was used to determine the probability of such independent variables as MetS, age, gender, smoking status, systolic blood pressure (SBP), WC, body mass index, C-reactive protein (CRP), total cholesterol, age of RA, and (DAS28-ESR) to predict IMT. The adjusted odds ratios (OR) with corresponding 95% confidence interval (95% CI) were calculated.

Results

The baseline characteristics of patients with RA and MetS and without it are present in Table 1.

There were no differences between groups by age, gender, number of smoking, and alcohol-using people. The number of people with sufficient physical activity was higher in the RA group; however, there was no statistical significance found between variables. The WC and body mass index were increased in both the RA+ MetS group and RA group, which indicates the high prevalence of abdominal obesity among study participants. The presents of MetS contributed to the significant differences among studied groups by arterial

blood pressure (p < 0.0001), non-fasting glucose (p < 0.0001), and triglycerides (p = 0.004).

Table 1: Patients baseline characteristics

Parameter	RA+ MetS (n = 41)	RA (n = 60)	p
Age, years, Me (Q_{25}-Q_{75})	57.0 (52.0–60.0)	53.5 (47.2–59.0)	0.062
Gender n, %			
Female	22 (78)	48 (80)	0.813
Male	9 (32)	12 (20)	
Current smoker, n (%)	6 (14.6)	6 (10)	0.482
Alcohol use, n (%)	20 (48.8)	30 (50)	0.905
Sufficient physical activity, n (%)	20 (48.8)	37 (61.7)	0.193
Body mass index (kg/m^2), Me (Q_{25}-Q_{75})	29.8 (27.2–32.9)	27.3 (22.8–30.8)	0.01
WC (cm), Me (Q_{25}-Q_{75})	100.0 (95.0–108.0)	91.5 (83.2–99.7)	< 0.0001
SBP mm/Hg, Me (Q_{25}-Q_{75})	140.0 (122.0–150.0)	120.0 (115.0–130.0)	< 0.0001
Total cholesterol (mmol/L), Me (Q_{25}-Q_{75})	5.6 (4.8–7.2)	6.2 (4.8–7.6)	0.535
HDL-C (mmol/L), Me (Q_{25}-Q_{75})	1.3 (1.06–2.8)	1.6 (1.3–2.3)	0.597
LDL-C (mmol/L), Me (Q_{25}-Q_{75})	3.0 (2.4–3.9)	3.2 (2.5–4.1)	0.425
Triglycerides (mmol/L), Me (Q_{25}-Q_{75})	1.5 (0.8–2.2)	1.01 (0.6–1.3)	0.004
Non-fasting glucose (mmol/l), Me (Q_{25}-Q_{75})	5.7 (5.2–6.1)	5.2 (5.0–5.6)	< 0.0001
Erythrocyte sedimentation rate (mm/h), Me (Q_{25}-Q_{75})	23.5 (9.0–30.0)	16.0 (10.0–28.5)	0.465
CRP (mg/l), Me (Q_{25}-Q_{75})	5.0 (5.0–11.0)	5.0 (5.0–10.0)	0.827
DAS28-ESR , Me (Q_{25}-Q_{75})	4.9 (3.8–5.4)	4.3 (3.6–5.0)	0.106
≤ 2.6, n (%)	3 (7.3)	12 (20)	
2.6–3.2, n (%)	20 (48.8)	33 (55)	
≥ 3.2, n (%)	18 (43.9)	15 (25)	
RA disease duration (years), Me (Q_{25}-Q_{75})	10.0 (5.0–23.0)	6.0 (5.0–11.0)	0.056
Current corticosteroids use, n (%)	18 (43.9)	30 (50)	0.549
Current DMARDs use, n (%)	28 (68.3)	46 (76.7)	0.353

MetS: Metabolic syndrome, WC: Waist circumference, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, SBP: Systolic blood pressure, CRP: C-reactive protein.

The median of RA duration was higher in the RA+ MetS group Me = 10.0 (Q25 = 5.0; Q75 = 23.0) years than in RA group Me = 6.0 (Q25 = 5.0; Q75 = 11.0) years, however, the median age did not show significant differences. About half of the study participants took corticosteroids to treat RA. The number of disease-modifying antirheumatic drug users was 68.3% in the RA+ MetS group and 76.7% in the RA group. The DAS28-ESR level shows no differences between studied groups, but it is worth mentioning that high RA disease activity (DAS28-ESR≥3.2) was 1.75 folds bigger in RA+ MetS than in the RA group.

The results of our study show that increased IMT was significantly higher in the RA+MetS group (n = 31 [75.6%]), compared with the RA group (n = 21 [35.0%] p ≤ 0.0001).

Figure 1 demonstrated the parameters of quantitative CIMT in RA+ MetS and RA patients. According to the figure median CIMT in RA+ MetS group accounted for 1.2 mm, whereas CIMT in RA group was 0.78 mm (U = 727, p = 0.001).

The results of correlation analysis are demonstrated in Table 2.

The initial characteristics of study participants in the RA group did not include division of study participants by MetS presents or absence. The CIMT thickening has weak positive correlation with age (r_s = 0.207), smoking status (r_s = 0.248), body mass index (r_s = 0.377), WC (r_s = 0.44), SBP (r_s = 0.375), and DAS28 (r_s = 0.277) disease activity index. The weak positive correlation was found between MetS and CIMT thickening (r_s = 0.288, p = 0.003). In our study, no correlation was found between CIMT thickening
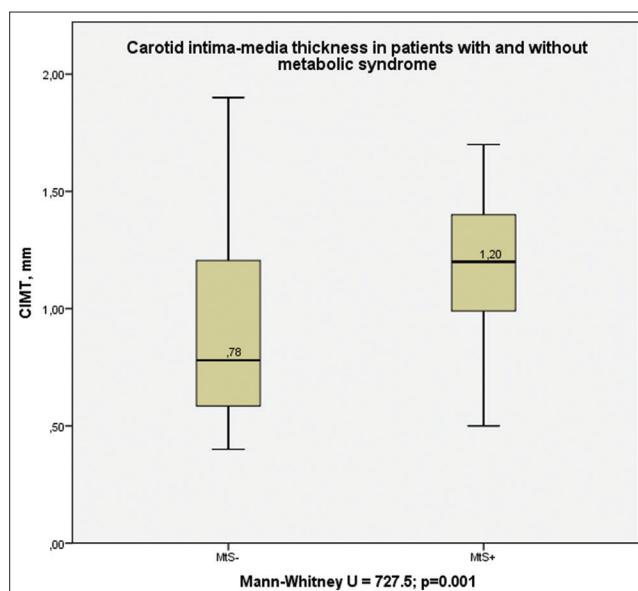

Figure 1: Carotid intima-media thickness in patients with rheumatoid arthritis with and without metabolic syndrome

and traditional cardiovascular risk factors, as well as RA-related parameters in patients with RA+MetS. There were correlations between subclinical atherosclerosis parameters and body mass index (BMI) (r_s = 0.361), WC (r = 0.427), SBP (r = 0.336), or RA disease duration (r_s = −0.292) in RA group.

Table 2: Correlation analysis of CIMT thickening factors and baseline respondents' characteristics

Parameter	Total study group (n = 101)		RA with MetS (n = 41)		RA without MetS (n = 60)	
	rs	p	rs	p	rs	p
Age	0.207	0.038	0.031	0.846	0.23	0.06
Gender	−0.135	0.177	−0.164	0.304	−0.117	0.374
Current smoker	−0.248	0.013	−0.235	0.139	−0.245	0.059
Sufficient physical activity	0.111	0.287	0.088	0.599	0.065	0.632
Body mass index	0.377	0.0001	0.228	0.152	0.361	0.005
WC	0.44	0.0001	0.267	0.091	0.427	0.001
SBP mm/Hg	0.375	0.0001	0.247	0.119	0.336	0.009
Total cholesterol	−0.150	0.136	−0.158	0.323	−0.134	0.312
HDL-C	−0.071	0.479	−0.187	0.241	0.022	0.866
LDL-C	−0.158	0.117	−0.15	0.355	−0.143	0.277
Triglycerides	0.182	0.069	0.048	0.766	0.147	0.264
Non-fasting glucose	0.016	0.877	−0.063	0.697	−0.063	0.631
Erythrocyte sedimentation rate	0.17	0.115	0.13	0.463	0.154	0.27
CRP	0.19	0.057	0.193	0.226	0.214	0.1
DAS28-ESR	0.277	0.005	0.266	0.102	0.22	0.091
RA disease duration	0.122	0.223	−0.036	0.823	−0.292	0.024
Current corticosteroids use	−0.002	0.987	0.045	0.782	0.0	1.0
Current DMARDs use	0.126	0.21	0.101	0.529	0.2	0.125
MetS	0.288	0.003				

CIMT: Carotid intima-media thickness, MetS: Metabolic syndrome, WC: Waist circumference, HDL: High-density lipoprotein, LDL: Low-density lipoproteins, SBP: Systolic blood pressure, CRP: C-reactive protein.

The univariate logistic regression model was created to establish the probable impact of MetS on CIMT thickening in patients with RA. MetS, age, gender, smoking status, WC, CRP, total cholesterol, RA disease duration, and DAS28-ESR were chosen as covariates. The covariates with p ≤ 0.05 were elected for further Multivariate Logistic Regression. The analysis established MetS as an independent predictor of CIMT thickening in RA patients (Table 3, Model 1).

The adjusted regression model established such statistically significant confounders as age, gender, and MetS (Table 3, Model 2). The third regression model included the DAS28-ESR was added

to model 2. MetS and DAS28-ESR show a significant impact on CIMT thickness probability (Table 3, Model 3) for rheumatoid patients.

Table 3: Models of logistic regression for RA patients and CIMT as a dependent variable

Model and depend variable	B	Mean square error	Wald	p-value	Exp (B)	95% CI Lower	95% CI Upper
Model 1							
MetS	1.265	0.446	8.032	0.005	0.282	0.118	0.677
Model 2							
MetS	1.161	0.458	6.429	0.011	0.313	0.128	0.768
Age	0.642	0.032	2.095	0.148	1.048	0.984	1.116
Gender	−1.578	0.559	1.319	0.251	1.9	0.636	5.679
Model 3							
MetS	1.05	0.476	4.869	0.027	0.35	0.138	0.889
Age	0.028	0.034	0.086	0.408	1.028	0.963	1.098
Gender	0.833	0.586	2.023	0.155	2.3	0.73	7.249
DAS28-ESR	0.506	0.219	5.364	0.021	1.659	1.081	2.546

CIMT: Carotid intima-media thickness, MetS: Metabolic syndrome, CI: Confidence interval.

Further analysis using logistic regression was provided separately for MetS+RA and RA groups. The univariate logistic model included age, gender, smoking status, SBP, WC, BMI, CRP, total cholesterol, RA disease duration, treatment regimen, and DAS28-ESR. The covariates with $p \leq 0.05$ were elected for further Multivariate Logistic Regression. The CIMT thickness was influenced by DAS28-ESR disease activity score (Table 4, Model for RA with MetS) in RA patients with MetS.

Table 4: Models of logistic regression for patients with RA with and without MetS and CIMT as a dependent variable

Model and depend variable	B	Mean square error	Wald	P value	Exp (B)	95% CI Lower	95% CI Upper
Model for RA with MtS DAS28-ESR	0.768	0.376	4.186	0.041	2.156	1.033	4.503
Model for RA without MtS BMI	0.14	0.05	6.66	0.01	1.15	1.03	1.27

CIMT: Carotid intima-media thickness, MetS: Metabolic syndrome, RA: Rheumatoid arthritis, CI: Confidence interval, BMI: Body mass index.

There was no significant impact on CIMT thickness found when DAS28-ESR was used as an independent variable of regression analysis in RA patients without MetS (Table 4). Taking into account the early revealed association, BMI, SBP, and RA disease duration were chosen as confounders for the adjusted regression model. The BMI was established as a significant confounder of subclinical atherosclerosis risk in RA patients (Table 4, Model for RA without MetS).

Discussion

The literature, particularly the results of meta-analysis, demonstrated high CIMT in RA patients; however, the studies have not analyzed the prevalence of MetS in those patients [31], [13]. The CIMT in our study was higher in patients with MetS in combination with RA than in RA. Furthermore, we built a few logistic regression models aimed to identify factors that predispose to CIMT thickening in patients with RA and MetS and RA alone. We identified that the presents of MetS in RA patients increased CIMT

thickening risk on 72% according to the adjusted regression model (confounders age and gender). The third regression model for RA patients showed the joint impact of MetS and rheumatoid disease activity score on CIMT thickening. The impact of disease activity score on CIMT had not lost its importance for MetS and RA patients proving the significance of inflammation for subclinical atherosclerosis. It was interesting to see that the BMI as confounder shows an impact on subclinical atherosclerosis in RA alone patients. This fact allows suggesting the increased BMI as a possible factor of cardiovascular risk in RA patients before MetS development; however, further research needed.

The results of our study are correlated with the prospective study of Burggraaf *et al*. where researchers demonstrated that baseline CIMT of RA patients with MetS had was higher compared to those without MetS (0.607 [0.107] vs. 0.556 [0.103] mm; p = 0.001) [20]. It is important to notify that the influence of rheumatoid disease activity on CIMT was demonstrated in several studies of RA alone patients [18], [2], [32]. The study of Uslu *et al*. reported the positive correlation of CIMT and disease activity score of 28 joints (p = 0.002) in 52 patients with RA [18]. The population study of Maradit-Kremers *et al*. demonstrated higher swollen joint counts and higher average CRP were associated with carotid intima medial plaques in RA patients [19]. The authors of another study did not find any correlation between CIMT and DAS28 among RA patients [33]. Despite conflicting reports from the literature, the significance of systemic inflammation is increasingly becoming the main agent for triggering and developing atherosclerosis. According to the latest data, RA is considered not only as an immunoinflammatory disease but also as a model of atherosclerosis fasten progress [34]. The systemic inflammation is a general pathogenetic chain of RA and MetS that realizes their proatherogenic effect through endothelial dysfunction, oxidative stress, macrophage accumulation, toll-like receptor signaling, NLPR-3 formation, and subsequent pro-inflammatory cytokine production, such as TNFa, IL-1β, IL-6, and TNF-like cytokine 1A [35]. Furthermore, inflammation influences several traditional cardiovascular risk factors as dyslipidemia, obesity, and insulin resistance, which are the MetS components simultaneously [36]. The detailed RA and MetS pathogenetic mechanisms and their concomitant impact on atherosclerosis required future study to improve understanding of the process and search for reasonable preventive measures.

Our research team did not reveal any correlation between the type of RA treatment implemented among study participants and CIMT. However, several studies report the opposite trend. In the recent study, authors show that methotrexate use was connected with a lower IMT [31]. The study of Kim *et al*. revealed lower CIMT in RA with methotrexate as compared with RA without methotrexate (0.644 ± 0.136 mm, 0.767 ± 0.233 mm, respectively, p < 0.05). Furthermore, the effects of

methotrexate on CIMT were correlated with its dosage (β = −0.029, p < 0.01) [36]. The absence of correlation between treatment and CIMT was probably connected with the insufficient anti-inflammatory effect of drugs and with a high percentage of corticosteroids in the treatment regimen of patients.

There were several limitations in our study because of a relatively small number of patients and observational study design. Further prospective cohort studies are needed for RA and MetS continuum evaluation.

Thus, the results of our study show more frequent CIMT thickening in RA patients with MetS compared with RA alone patients. Patients with RA and MetS demonstrate the impact of disease activity score on subclinical atherosclerosis. In RA alone patients' study revealed the impact of BMI on CIMT thickening prevalence. We can conclude that the disease management of rheumatoid patients should include activities aimed at early diagnostics of MetS because of its association with increased cardiovascular risk in this patient. In turn, the disease activity score in patients with RA and MetS should be carefully monitored due to the fact that sustainable chronic inflammation leads to atherosclerosis progression and adverse cardiovascular events. Nowadays, many practical questions on MetS management in RA patients rest unsolved. Improving the mechanisms for diagnosing MetS in patients with RA, finding tools for an adequate assessment of cardiovascular risk in patients with RA, and developing and implementing effective lifestyle modification measures may be the key to reducing cardiovascular pathology in patients with RA and increasing their life expectancy and quality.

References

1. van Halm VP, Peters MJ, Voskuyl AE, Boers M, Lems WF, Visser M, _et al_. Rheumatoid arthritis versus diabetes as a risk factor for cardiovascular disease: A cross-sectional study, the CARRE investigation. Ann Rheum Dis. 2009;68(9):1395-400. https://doi.org/10.1136/ard.2008.094151
   PMid:18697775

2. del Rincón I, Polak JF, O'Leary DH, Battafarano DF, Erikson JM, Restrepo JF, _et al_. Systemic inflammation and cardiovascular risk factors predict rapid progression of atherosclerosis in rheumatoid arthritis. Ann Rheum Dis. 2015;74(6):1118-23. https://doi.org/10.1136/annrheumdis-2013-205058
   PMid:24845391

3. Aviña-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: A meta-analysis of observational studies. Arthritis Rheum. 2008;59(12):1690-7. https://doi.org/10.1002/art.24092
   PMid:19035419

4. Fischer LM, Schlienger RG, Matter C, Jick H, Meier CR. Effect of rheumatoid arthritis or systemic lupus erythematosus on the risk of first-time acute myocardial infarction. Am J Cardiol. 2004;93(2):198-200. https://doi.org/10.1016/j.amjcard.2003.09.037
   PMid:14715346

5. Reiss AB, Silverman A, Khalfan M, Vernice NA, Kasselman LJ, Carsons SE, _et al_. Accelerated atherosclerosis in rheumatoid arthritis: Mechanisms and treatment. Curr Pharm Des. 2019;25(9):969-86. https://doi.org/10.2174/1381612825666190430113212
   PMid:31208307

6. Arida A, Protogerou AD, Kitas GD, Sfikakis PP. Systemic inflammatory response and atherosclerosis: The paradigm of chronic inflammatory rheumatic diseases. Int J Mol Sci. 2018;19(7):1890. https://doi.org/10.3390/ijms19071890
   PMid:29954107

7. Jung JM, Kwon DY, Han C, Park MH. Metabolic syndrome and early carotid atherosclerosis in the elderly. J Atheroscler Thromb. 2014;21(5):435-44.
   PMid:24477027

8. Gami AS, Witt BJ, Howard DE, Erwin PJ, Gami LA, Somers VK, _et al_. Metabolic syndrome and risk of incident cardiovascular events and death: A systematic review and meta-analysis of longitudinal studies. J Am Coll Cardiol. 2007;49(4):403-14. https://doi.org/10.1016/j.jacc.2006.09.032
   PMid:17258085

9. Zhang J, Fu L, Shi J, Chen X, Li Y, Ma B, _et al_. The risk of metabolic syndrome in patients with rheumatoid arthritis: A meta-analysis of observational studies. PLoS One. 2013;8(10):e78151. https://doi.org/10.1371/journal.pone.0078151
   PMid:24205134

10. Rostom S, Mengat M, Lahlou R, Hari A, Bahiri R, Hajjaj-Hassouni N. Metabolic syndrome in rheumatoid arthritis: Case control study. BMC Musculoskelet Disord. 2013;14:147. https://doi.org/10.1186/1471-2474-14-147
    PMid:23621997

11. Chung CP, Oeser A, Solus JF, Avalos I, Gebretsadik T, Shintani A, _et al_. Prevalence of the metabolic syndrome is increased in rheumatoid arthritis and is associated with coronary atherosclerosis. Atherosclerosis. 2008;196(2):756-63. https://doi.org/10.1016/j.atherosclerosis.2007.01.004
    PMid:17266963

12. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: A systematic review and meta-analysis. Circulation. 2007;115(4):459-67. https://doi.org/10.1161/circulationaha.106.628875
    PMid:17242284

13. van Sijl AM, Peters MJ, Knol DK, de Vet HC, Gonzalez-Gay MA, Smulders YM, _et al_. Carotid intima media thickness in rheumatoid arthritis as compared to control subjects: A meta-analysis. Semin Arthritis Rheum. 2011;40(5):389-97. https://doi.org/10.1016/j.semarthrit.2010.06.006
    PMid:20889191

14. Wah-Suarez MI, Galarza-Delgado DA, Azpiri-Lopez JR, Colunga-Pedraza IJ, Cardenas-de la Garza JA, Vera-Pineda R, _et al_. The best cardiovascular risk calculator to predict carotid plaques in rheumatoid arthritis patients. Clin Rheumatol. 2018;37(9):2373-80. https://doi.org/10.1007/s10067-018-4181-4
    PMid:29967925

15. Ambrosino P, Lupoli R, Di Minno A, Tasso M, Peluso R, Di Minno MN. Subclinical atherosclerosis in patients with rheumatoid arthritis. A meta-analysis of literature studies. Thromb Haemost. 2015;113(5):916-30. https://doi.org/10.1160/th14-11-0921
    PMid:25716931

16. Zhou PA, Zhang CH, Chen YR, Li D, Song DY, Liu HM, _et al_. Association between metabolic syndrome and carotid atherosclerosis: A cross-sectional study in Northern China.

Biomed Environ Sci. 2019;32(12):914-21.

PMid:31918796

17. Cuspidi C, Sala C, Provenzano F, Tadic M, Gherbesi E, Grassi G, _et al_. Metabolic syndrome and subclinical carotid damage: A meta-analysis from population-based studies. J Hypertens. 2018;36(1):23-30. https://doi.org/10.1097/hjh.0000000000001575

PMid:29035943

18. Uslu AU, Kucuk A, Balta S, Ozturk C, Arslan S, Tekin L, _et al_. The relation between ischemia modified albumin levels and carotid intima media thickness in patients with rheumatoid arthritis. Int J Rheum Dis. 2019;22(1):32-7. https://doi.org/10.1111/1756-185x.12851

PMid:27028097

19. Maradit-Kremers H, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Cardiovascular death in rheumatoid arthritis: A population-based study. Arthritis Rheum. 2005;52(3):722-32. https://doi.org/10.1002/art.20878

PMid:15751097

20. Burggraaf B, van Breukelen-van der Stoep DF, de Vries MA, Klop B, van Zeben J, van de Geijn GM, _et al_. Progression of subclinical atherosclerosis in subjects with rheumatoid arthritis and the metabolic syndrome. Atherosclerosis. 2018;271:84-91. https://doi.org/10.1016/j.atherosclerosis.2018.02.019

PMid:29482038

21. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, _et al_. 2010 Rheumatoid arthritis classification criteria: An American college of rheumatology/European league against rheumatism collaborative initiative. Arthritis Rheum. 2010;62(9):2569-81. https://doi.org/10.1002/art.27583

PMid:20872595

22. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, _et al_. The American rheumatism association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31(3):315-24. https://doi.org/10.1002/art.1780310302

PMid:3358796

23. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome--a new world-wide definition. A consensus statement from the international diabetes federation. Diabet Med. 2006;23(5):469-80. https://doi.org/10.1111/j.1464-5491.2006.01858.x

PMid:16681555

24. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972;18(6):499-502. https://doi.org/10.1093/clinchem/18.6.499

PMid:4337382

25. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, _et al_. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: A consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the society for vascular medicine. J Am Soc Echocardiogr. 2008;21(2):93-111; quiz 189-90. https://doi.org/10.1016/j.echo.2007.11.011

PMid:18261694

26. Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infarction: The Rotterdam study. Circulation. 1997;96(5):1432-7. https://doi.org/10.1161/01.cir.96.5.1432

PMid:9315528

27. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular health study collaborative research group. N Engl J Med. 1999;340(1):14-22. https://doi.org/10.1056/nejm199901073400103

PMid:9878640

28. del Sol AI, Bots ML, Grobbee DE, Hofman A, Witteman JC. Carotid intima-media thickness at different sites: Relation to incident myocardial infarction; The Rotterdam study. Eur Heart J. 2002;23(12):934-40. https://doi.org/10.1053/euhj.2001.2965

PMid:12069447.

29. Prevoo ML, van't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995;38(1):44-8. https://doi.org/10.1002/art.1780380107

PMid:7818570.

30. Fransen J, Welsing P, Keijzer RD, Riel PV. Disease activity scores using C-reactive protein: CRP may replace ESR in the assessment of RA disease activity. Ann Rheum Dis 2004;62:151.

31. Pinto MRC, Kakehasi AM, Souza AJ, Tavares WC Jr., Rocha MA, Trant CG, _et al_. Methotrexate use, not interleukin 33, is associated with lower carotid intima-media thickness in patients with rheumatoid arthritis. Adv Rheumatol. 2019;59(1):15. https://doi.org/10.1186/s42358-019-0060-1

PMid:30944039

32. Targońska-Stepniak B, Drelich-Zbroja A, Majdan M. The relationship between carotid intima-media thickness and the activity of rheumatoid arthritis. J Clin Rheumatol. 2011;17(5):249-55. https://doi.org/10.1097/rhu.0b013e3182290dbf

PMid:21778898

33. Beyazal MS, Erdoğan T, Devrimsel G, Türkyılmaz AK, Cüre MC, Beyazal M, _et al_. Relationship of osteoprotegerin to pulse wave velocity and carotid intima-media thickness in rheumatoid arthritis patients. Z Rheumatol. 2016;75(7):723-8. https://doi.org/10.1007/s00393-015-1675-1

PMid:26555551

34. Adawi M, Firas S, Blum A. Rheumatoid arthritis and atherosclerosis. Isr Med Assoc J. 2019;21(7):460-3.

PMid:31507121

35. Arida A, Protogerou AD, Konstantonis G, Fragiadaki K, Kitas GD, Sfikakis PP. Atherosclerosis is not accelerated in rheumatoid arthritis of low activity or remission, regardless of antirheumatic treatment modalities. Rheumatology (Oxford). 2017;56(6):934-9. https://doi.org/10.1093/rheumatology/kew506

PMid:28160488

36. Kim HJ, Kim MJ, Lee CK, Hong YH. Effects of methotrexate on carotid intima-media thickness in patients with rheumatoid arthritis. J Korean Med Sci. 2015;30(11):1589-96. https://doi.org/10.3346/jkms.2015.30.11.1589

PMid:26539002