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

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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%]) and 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 0.76 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 disability in 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 in 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 Euripid 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 ≤ 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 | 57.0 (52.0–60.0) | 53.5 (47.2–60.0) | 0.062 |
| Gender n, % | 22 (78) | 48 (80) | 0.813 |
| Male | 9 (32) | 12 (20) | 0.482 |
| Current smoker, n (%) | 6 (14.6) | 6 (10) | 0.482 |
| Alcohol use, n (%) | 20 (48.8) | 30 (50) | 0.905 |
| Systolic blood pressure (mm/Hg), Me (Q25-Q75) | 140.0 (122.0–150.0) | 120.0 (115.0–130.0) | <0.0001 |
| Total cholesterol (mmol/L), Me (Q25-Q75) | 5.6 (4.8–7.2) | 6.2 (4.8–7.6) | 0.535 |
| HDL-C (mmol/L), Me (Q25-Q75) | 1.3 (1.0–2.8) | 1.6 (1.3–2.3) | 0.597 |
| Triglycerides (mmol/L), Me (Q25-Q75) | 3.0 (2.4–3.9) | 3.2 (2.5–4.1) | 0.425 |
| Non-fasting glucose (mmol/L), Me (Q25-Q75) | 5.7 (5.2–6.1) | 5.2 (5.0–6.6) | <0.0001 |
| CIMT (mm), Me (Q25-Q75) | 23.5 (9.0–60.0) | 16.0 (10.0–28.5) | 0.465 |
| CRP (mg/L), Me (Q25-Q75) | 5.0 (5.0–11.0) | 5.0 (5.0–10.0) | 0.827 |
| Erythrocyte sedimentation rate (mm/h), Me (Q25-Q75) | 3.7 (3.0–4.4) | 4.3 (3.6–5.0) | 0.406 |
| RA disease duration (years), Me (Q25-Q75) | 10.0 (5.0–23.0) | 6.0 (5.0–11.0) | 0.056 |
| Current corticosteroids use, n (%) | 18 (43.9) | 19 (48.8) | 0.597 |
| Current DMARDs use, n (%) | 20 (48.8) | 28 (68.3) | 0.529 |

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 ($Q2 = 10.0$; $Q7 = 23.0$) years than in RA group (Me = 6.0; $Q2 = 5.0$; $Q7 = 11.0$) 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 drugs used 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 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 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 ($r_s = 0.427$), SBP ($r_s = 0.336$), or RA disease duration ($r_s = −0.292$) in RA group.

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

| Parameter | RA+ MetS (n = 101) | RA (n = 160) | RA without MetS (n = 60) | p     |
|-----------|-------------------|-------------|--------------------------|-------|
| Age | 0.377 | 0.012 | 0.0001 | 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 |
| Systolic blood pressure | 0.111 | 0.267 | 0.008 | 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 | −0.371 | 0.479 | −0.187 | 0.341 | 0.022 | 0.866 |
| LDL-C | −0.158 | 0.117 | −0.15 | 0.355 | −0.143 | 0.277 |
| Triglycerides | 0.138 | 0.094 | 0.048 | 0.766 | 0.147 | 0.264 |
| Non-fasting glucose | 0.016 | 0.087 | −0.063 | 0.697 | −0.063 | 0.631 |
| Erythrocyte sedimentation rate | 0.17 | 0.115 | 0.13 | 0.463 | 0.154 | 0.277 |
| 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 | 0.087 | 0.045 | 0.782 | 0.0 | 1.0 |
| Current DMARDs use | 0.126 | 0.21 | 0.101 | 0.529 | 0.2 | 0.125 |

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

The univariate logistic regression model was established 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% Cl  |
|---------------------------|---------|-------------------|--------|---------|---------|---------|
| 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  | 0.599             | 1.319  | 0.251   | 1.9    | 0.633   | 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% Cl  |
|---------------------------|---------|-------------------|--------|---------|---------|---------|
| Model for RA with MetS    | 0.768   | 0.376             | 4.186  | 0.041   | 2.156  | 1.033   | 4.503  |
| MIS DAS28-ESR             | 0.14    | 0.05              | 6.66   | 0.01    | 1.15   | 1.03    | 1.27   |
| Model for RA without MetS |         |                   |        |         |         |         |
| DAS28-ESR                 | 0.506   | 0.219             | 5.364  | 0.021   | 1.659  | 1.081   | 2.546  |

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, NLRP-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 ($0.644 \pm 0.136$ mm, $0.767 \pm 0.233$ mm, respectively, $p < 0.05$). Furthermore, the effects of...
methotrexate on CIMT were correlated with its dosage ($\beta = -0.029, p < 0.01$) [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.

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