Assessment of Adipokines, CXCL16 Chemokine Levels in Patients With Rheumatoid Arthritis Combined With Metabolic Syndrome

Lyudmila Gennadyevna Turgunova1, Anna Andreevna Shalygina1, Janis Pavlovich Zalkalns2, Dmitriy Anatolyevich Klyuyev1, Lyudmila Leonidovna Akhmaltdinova1 and Raushan Sultanovna Dosmagambetova1

1Karaganda Medical University, Karaganda, Kazakhstan. 2Riga Stradins University, Latvia.

ABSTRACT

OBJECTIVE: Rheumatoid arthritis (RA), which is a chronic systemic inflammatory disease, is associated with accelerated atherosclerosis and an increased risk of cardiovascular disease (CVD), but the causal factors have yet to be completely elucidated. The studies show that the prevalence of metabolic syndrome (MS) was significantly higher in RA patients compared to the population. In RA and MS inflammation and atherosclerosis are closely linked. The level of chemokines and adipokines, which may play a role in the development of atherosclerosis in RA with MS patients is currently unknown. In this study, we investigated the level of chemokine C-X-C motif chemokine ligand 16 (CXCL16) and adipokine in RA with MS patients and assessed the association of biomarkers with clinical and biochemical activity scores of RA and components of MS.

METHODS: Blood serum of 298 people (48—patients with RA and MS, 82—with RA without MS, 105—with MS, 63—control group without both RA and MS) was tested for (CXCL16), Resistin, Leptin and Fibroblast Growth Factor 21 (FGF21) levels by fluorescent antibody technique. Statistical analysis was performed using SPSS version 18.0.

RESULTS: The biomarker study showed the highest level in the RA with MS patient group; but as compared with the RA group the differences were insignificant. CXCL16 (Me = 426.2 pg/ml (Q25-75: 250.5-527.6), resistin (Me = 8685.4 pg/ml (Q25-75: 6480.8-13629.1), and FGF21 (Me = 443.6 pg/ml (Q25-75: 772.9-916.3) proved to be significantly augmented in RA with MS patients group, and in RA without MS patients group (Me = 312.7 (Q25-75: 199.4-517.7) pg/ml; Me = 8265.3 (Q25-75: 577.9-13340.5) pg/ml; Me = 412.4 (Q25-75: 300.4-497.4) pg/ml, respectively) as compared with MS patients group (Me = 189.4 (Q25-75: 130.3-280.6) pg/ml; Me = 5364.8 (Q25-75: 2368.9-10160.9) pg/ml; Me = 133.2 (Q25-75: 76.2-268.6) pg/ml, respectively; P = <.001). Leptin level in all groups was higher than in the control group, but there were no differences between groups. The correlation analysis found a positive relationship between the leptin level and the waist circumference (rs = 0.39; P = .007) in the RA with MS patients, the association of biomarkers with DAS28 score and ESR did not have any statistical significance.

Conclusions: The augmented chemokine, resistin and FGF21 in the RA with MS patients prove the systemic inflammation which is the basis of RA; the augmented leptin is linked to the abdominal obesity. These data are somewhat of an explanation of the increased risk of the CVD development in RA with MS people. A differentiated specification can be useful to assess the cardiovascular risk of patients and justify prompt personalized treatment.

KEYWORDS: Rheumatoid arthritis, metabolic syndrome, biomarkers, CXCL16, Leptin, Resistin, FGF21

Introduction

Cardiovascular disease (CVD) continues to be a pressing global health problem. In Kazakhstan’s healthcare system, the circulatory diseases (CD) are also the dominants in the morbidity and mortality rates, totaling 2595.7 and 174.8 instances per 100,000 population respectively in 2017, with the myocardial infarction and stroke taking up 74% of the CD-associated deaths.1 The inflammation proved to be crucial in the development and progression of atherosclerosis, which is the key factor of cardiovascular complications.

Rheumatoid arthritis (RA) being a chronic systemic inflammatory disease associates with an increased cardiovascular risk (CVR) which is comparable to the risk of type 2 diabetes.2 The link between atherosclerosis and RA is still incompletely understood. Circulating biomarkers in the pathophysiology of atherosclerosis, including inflammation, are the subject of study in rheumatoid arthritis.3-5

Metabolic syndrome is a cluster of traditional risk factors for CVD, including abdominal obesity, hypertension, high triglycerides, and low levels of high-density lipoprotein cholesterol.6,7 The meta-analysis has shown that the metabolic syndrome is associated with a 2-fold increase in cardiovascular outcomes and a 1.5-fold increase in all-cause mortality rates.8 Several studies report that patients with RA have a
significantly higher prevalence of the metabolic syndrome (MtS) compared to the general population.9 The metabolic syndrome (MtS) is believed to increase the risk of CVR in patients with RA.10 The metabolic syndrome has also been found to increase the risk of having moderate-to-high disease activity in RA patients.11

Systemic inflammation is assumed to be a common patho-genetic link of rheumatoid arthritis and metabolic syndrome. The exact pathogenesis of chronic inflammation is not yet completely studied. The adipocytokines and chemokines have been found to be among the major hallmarks for the pathogenesis of chronic inflammation. Chemokines play an important role in recruitment and functioning of immune cells, and angiogenesis in rheumatoid arthritis.12 The stimulation of chemokine receptors aggravates an inflammatory response in adipose tissue. By regulating macrophage recruitment and M1/M2 phenotype switch they cause the insulin resistance.13 Inhibition of CCR5 expression reduces the aggregation of pro-atherogenic cytokines to the site of arterial injury. Adipokines produced by white adipose tissue contribute to hepatic insulin sensitivity, skeletal muscle, and adipose tissue insulin sensitivity and to metabolic syndrome. Proinflammatory adipokines also participate in the regulation of the immune response and endothelial function, and have an effect on the synovial membrane and cartilage.14

The link between metabolic syndrome and rheumatic diseases is complex. Several studies have shown that there was no association between leptin and resistin levels and the RA disease activity,15,16 other studies report about association of leptin and resistin levels and the clinical and laboratory scores of RA disease activity.17-19 Increased FGF21 levels in RA patients compared to osteoarthritis patients was associated with BMI but not with RA disease activity.20

Since the biomarkers may have several participation roles and ways, we can assume that the RA together with the MtS enhances the biological effects of biomarkers. The are few studies on adipokine status in RA patients with MtS.21,22 We did not find any comprehensive study of adipokine and CXCL16 chemokine levels in RA patients with MtS compared to RA patients without MtS, and MtS patients.

Thus, the objective of our study was to investigate the level of chemokine CXCL-16 and adipokines (leptin, resistin, FGF21) in RA patients with MtS.

Material and Methods

Subjects

We carried out an observational cohort study. The study was carried out at the level of 2 municipal outpatient clinics (#1 and #3) in Karaganda city (Kazakhstan). Inclusion criteria: age from 25 to 65 years, patients with verified rheumatoid arthritis, metabolic syndrome. The control group consisted of persons without metabolic syndrome and rheumatoid arthritis, corresponding to gender and age. Exclusion criteria: previous myocardial infarction, history of acute cerebrovascular accident, end-stage cardiac, renal, liver failure, pregnancy.

In total, the study included 299 people. Of these, 48 are patients with rheumatoid arthritis in combination with metabolic syndrome (RA with MtS), 84 people are patients with rheumatoid arthritis without metabolic syndrome (RA without MtS), 105 people are people with metabolic syndrome without rheumatoid arthritis (MtS), 62 people made up a control group (Control).

Patients were examined in the setting of the Karaganda Medical University. All participants submitted a written informed consent prior to any study-associated procedure. The study was approved by the Institutional Review Board of the Karaganda Medical University (registration number 47 of August 10, 2018). The study was carried out in accordance with the Good Clinical Practice Guidelines (GCP) and the Declaration of Helsinki.

Diagnosis of rheumatoid arthritis and determination of activity

The diagnosis of rheumatoid arthritis was made on the basis of the 2010 ACR/European League Against Rheumatism (EULAR)/American College of Rheumatology criteria for RA.21,24 RA activity was determined by the Disease Activity Score 28-ESR (DAS28-ESR).

Metabolic syndrome

Metabolic syndrome was classified according to the criteria of the International Diabetes Federation (IDF, 2009) based on the presence of central obesity (waist circumference (WT) ≥94 cm for Caucasian males and ≥80 cm for women in combination with any 2 of the following 4 factors: triglycerides (TG): ≥150 mg/dl (1.7 mmol/l), or specific treatment for the disorder; a decrease in the content of high density lipoproteins (HDL cholesterol): <40 mg/dl (1.03 mmol/l) in men and <50 mg/dl (1.29 mmol/l) in women, or specific treatment for this disorder; increased blood pressure (BP): systolic blood pressure (SBP) ≥130 or diastolic blood pressure (DBP) ≥85 mm Hg, or treatment of previously diagnosed hypertension; increased fasting plasma glucose: ≥100 mg/dl (5.6 mmol/l), or previously diagnosed type 2 diabetes mellitus.25

Questionnaire

The questionnaire was comprised of questions about gender, age of the respondent, socio-demographic aspects (nationality, marital status, education background, occupation). The “employed” category of the “occupation” line included the civil servants, private sector workers, and entrepreneurs. The “unemployed” category included pensioners and actually unemployed people. The questionnaire also comprised the questions about daily 30-minute physical activity (PA), active smoking at that point.
Physical examination

We measured the waist circumference (WC) by standard method to verify the metabolic syndrome. Blood pressure (BP) was measured 3 times in both hands after 15 minutes of rest. The final result of the measurement was the arithmetic mean of the 3 measurements. The BMI was calculated in all patients.

Laboratory diagnostics

Glucose was measured using the Accu-Chek Active system in capillary blood after 12 hours of fasting. The high-density lipoprotein cholesterol was determined by selective precipitation method. Blood samples for laboratory evaluation of biochemical parameters were obtained after participants’ overnight fast. Cholesterol, (TG), uric acid levels in the blood were determined by enzymatic colorimetric method with selective protection without precipitation. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald Equation. The erythrocyte sedimentation rate was determined (ESR) by Panchenkov’s method.

To determine soluble CXCL16, Leptin, Resistin and FGF21 in blood serum, a multiplex immunofluorescence assay was performed using XMap technology (examination on the surface of fluorescently coded magnetic particles known as MagPex—microspheres). For this, a Bioplex 3D device and a set of reagents Millipex Human Cardiovascular disease Magnetic Bead, Bio-Plex Pro Human Diabetes, Bio-Plex RBM Hu Metab Panel 2 were used. A variant with a 16-hour incubation was used. The results were evaluated using the patented Luminex Xponent v. 4.0.846.0 and Bioplex Manager 6.1.

FGF21 in blood serum, a multiplex immunofluorescence assay CV 20%. FGF-21 low limits of qualification 11.5 pg/ml low limits detection 3.1 pg/ml intra-assay CV 16% inter-assay CV 19%. Leptin Low limits of qualification 25 pg/ml low limits detection 11 pg/ml intra-assay CV 16% inter-assay CV 19%. Leptin Low limits of qualification 11.5 pg/ml low limits detection 3.1 pg/ml intra-assay CV 3% inter-assay CV 4%. Resistin Low limits of qualification 2.3 pg/ml low limits detection 1.3 intra-assay CV 3% inter-assay CV 4%.

Statistical processing

Statistical processing of the material was carried out using the statistical package for social sciences (SPSS for Windows, version 23.0, SPSS Inc., Chicago, Illinois, USA). All continuous variables were checked for normal distribution using the Kolmogorov–Smirnov criterion. In our study, all variables had an abnormal distribution, so the data is presented as median and IQR. Categorical values were represented as numbers and percent. Comparisons between groups were made using the Kruskal–Wallis test. Significance level was calculated by the following formula: \( P = 1 - .951/n \), where n is the number of comparisons made. The number of paired comparisons between the 4 groups was 6, so the significance level is \( P = 1 - .951/6 = .0085 \). The 2-tailed correlation analysis was carried out using Spearman’s method. The significance level for correlation analysis assumed to be \( P \leq .005 \).

Study results

The characteristics of the surveyed are presented in Table 1. Females dominated in all groups, the mean of age did not differ significantly in the groups RA with MtS, RA without MtS and MtS. The mean of age in the Controls was lower than in the other groups. The analysis of socio-demographic points showed that married people predominated in all groups. The proportion of people with higher education was higher in the MetS group (49.4%) compared to other groups. Persons with disabilities were noted in RA with MtS—41.6% and in RA without MtS—41.5%. Despite the presence of rheumatoid arthritis, we found no differences between groups in the frequency of daily 30-minute PA. The percentage of active smoking in the groups did not differ and did not exceed 18%. It should be noted that in the RA without MtS group, the median BMI did not belong to normal values and amounted to 25.9 kg/m².

An analysis of the parameters of carbohydrate and lipid metabolism and biomarkers is presented in Table 2. Perhaps, due to the “lipid paradox” in rheumatoid arthritis, we did not find changes in lipid metabolism, while in the MtS group there were the highest blood glucose, triglycerides, low density lipoproteins and the lowest high density lipoproteins. Cholesterol levels did not differ between groups.

Analysis of biomarker levels showed the following results: adipokine levels have the lowest values in Control. It is clearly seen that the levels of biomarkers increase from the Control group to the RA with MtS group and acquire the highest rates in the RA with MtS group.

In a pairwise comparison between groups Table 3, it was found that in the group of patients with RA with MtS, the glucose level was higher in patients with RA without MtS and was lower than in patients with MtS. Comparison of lipid metabolism indices showed that the HDL-C level in patients with RA with MtS and RA without MtS was higher than in the group with MtS and Controls. The triglyceride level in all groups was higher than the level of the control group, but in patients with MtS it was higher than in the group with RA without MtS. The level of biomarkers had the highest values in the group of patients with RA with MtS, but compared with the group of patients with RA without MtS, this increase in biomarkers did not have statistically significant differences. When comparing biomarkers of the group with RA with MtS with the group of patients with MtS, it was found that the level of chemokine CXCL16, resistin and FGF21 was significantly higher in RA with MtS.

Correlation analysis of biomarkers with clinical and laboratory parameters showed that in the RA with MtS group, the leptin level had a positive relationship with WC, the resistin level—with the age of the patients (Table 4). FGF21 levels were negatively associated with HDL. We found no correlations
between CXCL16 and adipokines with DAS28, ESR. As well as in the RA with MtS group, in the RA without MtS group, a significant positive correlation was found between the level of leptin and WC (Table 5). HDL levels were accompanied by increases in CXCL16 and resistin. We did not find significant correlations of biomarkers with activity on the DAS 28-ESR scale and ESR level.

**Discussion**

Our study was the first to compare such biomarkers as CXCL16, leptin, resistin, and FGF21 in RA patients with MetS compared to RA patients without MetS, and MetS patients.

We found a high level of CXCL16 in the RA with MetS group compared to MetS group and no difference in RA without MetS group. Studies of CXCL16 levels in RA patients are conflicting: some authors have found highly elevated CXCL16 levels in serum and in synovial fluid in RA patients compared to osteoarthritis patients, and the control group.26,27 In another study, the chemokine CXCL16 levels were the same as in the control group,28 but the authors noted that CXCL16 was highly elevated in patients with seropositive RA compared to seronegative ones. We have not found any significant correlation relationship between CXCL16 and ESR, the RA disease activity score. While Zhang et al, Li et al in their independent studies have shown a correlation of the CXCL16 levels with...
Table 2. Indicators of carbohydrate, lipid metabolism and the level of biomarkers in patients with RA with MtS, RA without MtS, MtS and controls.

| PARAMETER, Ме (Q25-Q75) | RA WITH MTS (N=48) | RA WITHOUT MTS (N=82) | MTS (N=105) | CONTROL (N=63) | χ² | P |
|--------------------------|---------------------|-----------------------|-------------|----------------|-----|---|
| Serum cholesterol, mmol/l | 5.3 (4.7-6.8)       | 5.9 (4.7-7.5)         | 5.5 (4.6-6.9) | 5.4 (4.5-6.7) | 1.79 | .616 |
| Glucose, mmol/l           | 5.7 (5.2-6.0)       | 5.2 (5.0-5.7)         | 6.1 (5.6-7.9) | 5.4 (5.1-5.7) | 74.2 | <.001 |
| TG, mmol/l                | 1.2 (0.8-2.3)       | 1.06 (0.6-1.4)        | 1.5 (0.9-2.1) | 0.7 (0.5-1.1) | 45.0 | <.001 |
| HDL-C, mmol/l             | 1.43 (1.07-2.93)    | 1.6 (1.3-2.6)         | 0.96 (0.81-1.12) | 0.99 (0.19-1.45) | 97.0 | <.001 |
| LDL-C, mmol/l             | 2.5 (2.0-3.9)       | 3.0 (2.3-4.0)         | 3.3 (2.9-4.5) | 1.3 (1.1-1.5) | 13.9 | .003 |
| CXCL16, pg/ml             | 426.2 (250.5-527.6) | 312.7 (199.4-517.7)   | 189.4 (130.3-280.6) | 274.4 (221.0-362.9) | 72.9 | <.001 |
| Leptin, pg/ml             | 16 536.8 (8148.6-31 648.4) | 12 186.5 (5207.1-25 070.1) | 11 184.0 (6100.7-31 916.1) | 4230.6 (1799.6-8129.4) | 46.8 | <.001 |
| Resistin, pg/ml           | 8685.4 (6480.8-13 629.1) | 8265.3 (5779.7-13 340.5) | 5364.8 (2368.9-10 160.9) | 4886.9 (3127.2-6730.9) | 40.3 | <.001 |
| FGF21, pg/ml              | 443.6 (772.9-916.3) | 412.4 (300.4-497.4)   | 133.2 (76.2-268.6) | 126.1 (45.1-232.4) | 89.8 | <.001 |

Abbreviations: CXCL16, C-X-C motif chemokine ligand 16; FGF21, fibroblast growth factor 21; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; TG, triglycerides.

Table 3. Comparative analysis between groups in terms of carbohydrate and lipid metabolism and the level of biomarkers.

| PARAMETER | RA WITH MTS AND RA WITHOUT MTS | RA WITH MTS AND MTS | RA WITH MTS AND CONTROL | RA WITHOUT MTS AND MTS | RA WITHOUT MTS AND CONTROLS | MTS AND CONTROL |
|-----------|---------------------------------|---------------------|-------------------------|-------------------------|-----------------------------|-----------------|
|           | U                               | P                   | U                       | P                       | U                           | P               |
| Serum cholesterol, mmol/l | 1714.0 .311 | 2404.0 .786 | 1496.0 .924 | 3788.0 .35 | 2233.0 .243 | 3120.5 .68 |
| Glucose, mmol/l       | 1275.5 .001* | 1671.0 .001* | 1082.5 .01 | 1504.5 <.001* | 2430.6 (1799.6-8129.4) | 46.8 <.001 |
| TG, mmol/l            | 1438.0 .011 | 2288.0 .41 | 793.0 <.001* | 2652.5 <.001* | 1957.0 .018 | 1425.5 <.001* |
| HDL-C, mmol/l         | 1776.5 .414 | 936.0 <.001* | 1003.0 .003* | 1054.0 <.001* | 1203.0 <.001* | 1858.0 <.001* |
| LDL-C, mmol/l         | 1840.0 .67 | 1284.0 .04 | 986.0 .04 | 2341.0 .002* | 1770.0 .033 | 2061.0 .61 |
| CXCL16, pg/ml         | 1465.0 .15 | 844.0 <.001* | 304.0 <.001* | 2259.0 <.001* | 1008.0 <.001* | 2706.0 .096 |
| Leptin, pg/ml         | 1540.5 .09 | 2203.0 .428 | 458.0 <.001* | 3755.0 .357 | 1121.0 <.001* | 1302.0 <.001* |
| Resistin, pg/ml       | 1836.0 .826 | 1520.0 <.001* | 623.0 <.001* | 2572.0 <.001* | 1093.0 <.001* | 2721.5 .401 |
| FGF21, pg/ml          | 525.5 .034 | 301.0 <.001* | 111.0 <.001* | 1048.0 <.001* | 436.0 <.001* | 2838.0 .222 |

Abbreviations: CXCL16, C-X-C motif chemokine ligand 16; FGF21, fibroblast growth factor 21; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; TG, triglycerides.

*Significance level P <.0086.
BMI, RA disease activity and bone erosion. The positive correlation that we have found between the CXCL16 and WC and the negative one with the HDL-C levels in MetS is confirmed by studies of other authors who have found the correlation between CXCL16 and WC, triglyceride levels and diastolic blood pressure. In the RA, a direct correlation relationship between chemokine and CXCL16, and HDL-C can be associated with a “lipid paradox” where the HDL-C does not perform its usual positive role in the prevention of atherosclerosis, but becomes a proinflammatory marker.

Over the last few years, the role of the adipokines in the RA pathogenesis has been studied, but the results remain conflicting. We have found the elevated leptin levels in RA patients compared to the controls. Leptin is assumed to be a proinflammatory adipokine, since it promotes production of cytokines, such as tumor necrosis factor, IL-6 reactive oxygen species, and is a cause for production of macrophage-derived chemokine. Some studies have shown the relationship between elevated leptin level and RA disease activity, RA disease duration, radiographic joint damage. We have not found an association of leptin levels with RA disease activity indicators. In our study we have found positive correlation relationship between leptin levels and WC in all groups, which is stronger in RA patients with MetS group (r = 0.39; P = 0.007). We believe that our findings stress the negative role of central obesity, found to be in most patients with RA and in all patients with MetS. In contrast, a study by Fioravanti A, et al. no correlations between leptin levels and clinical and biochemical parameters were found.
Our findings on the elevated resistin levels in the RA patients with or without MetS, are consistent with the findings of Kontunen et al.\textsuperscript{14} We have not found more comparative data of resistin levels in the RA patients with MetS. Meta-analysis have shown that in most studies the resistin level in RA patients is higher than that in the control group.\textsuperscript{35} Several studies have shown the association of resistin level with inflammation indicators such as C-reactive protein, erythrocyte sedimentation rate, IL-6, IL-1, as well as with white blood cells count in RA patients.\textsuperscript{30,34-38} We have not found any correlation between the resistin levels and the DAS28 activity score. We have also shown that resistin levels do not correlate with WC, unlike leptin levels, what coincides with the findings of other researchers.\textsuperscript{39} A positive correlation relationship between resistin and patients’ age was found in RA with MetS group. The age seems not affect the resistin levels regardless of body fat mass, but the elevated level of that adipokine is associated with an increased risk of CVD in older men and women.\textsuperscript{40}

The FGF21 studies at RA are few. The increase in the FGF21 level in RA, regardless of the presence of MetS, coincides with the results of a study in which the authors note that serum FGF-21 levels were significantly higher in RA patients and did not correlate with the disease activity.\textsuperscript{20} In contrast to this work, we have not found any positive correlation between the FGF-21 and the BMI, but have found a negative relationship with the HDL-C level. It is assumed that an augmented FGF-21, especially in seropositive RA patients, can indicate a compensatory response to inflammation, as well as a manifestation of co-morbidity.\textsuperscript{41} It can be assumed that elevated FGF-21 in the RA with MetS group is due to high comorbidity rates as compared to other groups of patients.

The study has some limitations. Firstly, the study was a cross-sectional one, therefore the cause-effect relations have not been considered. Secondly, the study included just part of all RA disease activity indicators, visual signs of joint damage, which hinders the identification of a close relationship between biomarkers and the disease activity. Thirdly, the study included a relatively small number of RA with MetS patients.

Conclusion

Thus, the results of our study made it possible for the first time to evaluate the features of changes in the level of inflammation biomarkers, adipokine status in patients with RA and MS compared with patients with RA without MS and with patients with MS. An increase in the level of chemokine CXCL16, resistin, and FGF21 in patients with RA, regardless of the presence of MS, confirms the importance of systemic inflammation, which underlies RA; an increase in the level of leptin is more associated with the presence of abdominal obesity. These data may, to a certain extent, explain the existing increased risk of CVD in RA with MS. Differentiated refinement can be useful in assessing patients’ CVRs and justifying early personalized treatment.

Author Contributions

LGT invented and developed the research, formulated the hypothesis and the purpose of the research, supervised the analytical part of the research, wrote part of the manuscript text. AAS recruited patients into the study, questioned patients, formed a database of the obtained results, carried out statistical processing of the results obtained, and participated in writing the text of the manuscript. DAK participated in the processing of the results obtained, in the formation of the presentation of the obtained data in the form of tables. JPY reviewed the final version of the manuscript. LLA guided the process of determining the laboratory parameters and writing the corresponding section in the Materials and Methods of the manuscript. RSD supervised the results of this work, reviewed the final version of the manuscript. All authors participated in the discussion of the results and the formation of the final version of the manuscript.

ORCID iD

Lyudmila Gennadievna Turgunova (https://orcid.org/0000-0002-6962-4247)

REFERENCES

1. Health of the population of the Republic of Kazakhstan and the activities of health organizations in 2017. The statistical collection. Astana: 22 (Almaty), No. 3 (189), 2018 public health, pp. 35-39. http://www.ms.gov.kz/sites/default/files/pages/boesnuk2018.pdf
2. Van Halm VP, Peters MJL, Yoskui AE, et al. Rheumatoid arthritis versus diabetes as a risk factor for cardiovascular disease: a cross-sectional study, the CARRE Investigation. Ann Rheum Dis. 2009;68:1395-1400.
3. Martinez E, Martorell R, Rambau V. Review of serum biomarkers in caridio-vascular risk. J. Vasc. Surg. 2020;71:329-341.
4. Södergren A, Karp K, Bengtsson C, Möller B, Rantapää-Dahlqvist S, Wållberg-Jonsson S. Biomarkers associated with cardiovascular disease in patients with early rheumatoid arthritis. PLoS One. 2019;14:e0220531.
5. Gobbi CA, Aibert P, Alba PB, et al. Marcadores subclínicos de aterosclerosis y factores de riesgo cardiovascular en artritis temprana. [Subclinical markers of atherosclerosis and cardiovascular risk factors in early arthritis]. Rev. Fac. Cienc. Med. Univ. Nac. Cordoba. 2019;76:174-179 (Spanish).
6. Glucic Z, Zalic B, Resanovic I, et al. Link between metabolic syndrome and insulin resistance. Curr Vasc Pharmacol. 2017;15:30-39.
7. McCracken E, Monaghan M, Sreenivasan S. Pathophysiology of the metabolic syndrome. Clin Dermatol. 2018;36:14-20.
8. Sherling DH, Perumareddi P, Hennechek CH. Metabolic syndrome. J Cardiovasc Pharmacol Ther. 2017;22:365-367.
9. Hallajzadeh J, Safi S, Mansournia M, et al. Metabolic syndrome and its components among rheumatoid arthritis patients: a comprehensive updated systematic review and meta-analysis. PLoS One. 2017;12:e0170361.
10. Dessein P, Tobias M, Veller M. Metabolic syndrome and subclinical atherosclerosis in rheumatoid arthritis. J. Rheumatol. 2006;33:2425-2432.
11. Kavouniaris SA, Sidropoulos PI, Papadakis JA, et al. Metabolic syndrome is common among middle-to-older aged Mediterranean patients with rheumatoid arthritis and correlates with disease activity: a retrospective, cross-sectional, controlled, study. Ann Rheum Dis. 2007;66:28-33.
12. Vergunst CE, Van de Sande MG, Lebre MC, Tikk PP. The role of chemokines in rheumatoid arthritis and osteoarthritis. Scand J Rheumatol. 2005;34:415-425.
13. Zhang Z, Wang Q, Yao J, et al. Chemokine receptor 5, a double-edged sword in metabolic syndrome and cardiovascular disease. Front Pharmacol. 2020;11:146.
14. Francisco V, Ruiz-Fernández C, Pino J, et al. Adipokines: linking metabolic syndrome, the immune system, and arthritic diseases. Biochem Pharmacol. 2019;165:196-206.
15. Oner SY, Valkan O, Oner C, Mengi A, Direskeneli H, Tasan DA. Serum leptin levels do not correlate with disease activity in rheumatoid arthritis. Acta Reumatol Port. 2015;40:50-54.
16. Hammad MH, Nasef S, Muslum D, Ahmed MM, Osman I, Hammad MH. Resistin, an adipokine, its relation to inflammation in Systemic Lupus Erythematosus and Rheumatoid Arthritis. Middle East J Intern Med. 2014;7:3-9.
17. Lee YH, Bae S-C. Circulating leptin level in rheumatoid arthritis and its correlation with disease activity: a meta-analysis. *Z Rheumatol.* 2016;75:1021-1027.

18. Migita K. The serum levels of resistin in rheumatoid arthritis patients. *Clin Exp Rheumatol.* 2006;24:698-701.

19. Rivera-Bahena CB, Xibillé-Friedmann DX, González-Christen J, Carrillo-Vásquez SM, Montiel-Hernández JL. Peripheral blood leptin and resistin levels as clinical activity biomarkers in Mexican Rheumatoid Arthritis patients. *Rheumatol Clin.* 2016;12:323-326.

20. Huléjová H, Andrés Cerezo L, Kuklová M, et al. Novel adipokine fibroblast growth factor 21 is increased in rheumatoid arthritis. *Physiol Res.* 2012;61:489-494.

21. Del Rincón I, Polak JF, O’Leary DH, et al. Systemic inflammation and cardiovascular risk factors predict rapid progression of atherosclerosis in rheumatoid arthritis. *Ann Rheum Dis.* 2015;74:1118-1123.

22. Kononoff A, Vuolteenaho K, Hämäläinen M, et al. Metabolic syndrome, disease activity, and adipokines in patients with newly diagnosed inflammatory joint diseases. *J Clin Rheumatol.* Published online May 21, 2020. doi:10.1097/RHU.0000000000001412.

23. Aleta D, Neogi T, Silman AJ, Funovits J, Felton 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;62:2569-2581.

24. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum.* 1988;31:315-324.

25. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome: a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabetes Med.* 2006;23:469-480.

26. Zhang X, Zhao JX, Sun L, Liu XY. Expression of CXCL16/CXCR6 in fibroblast-like synoviocytes in rheumatoid arthritis and its role in synoviocyte proliferation. *Beijing Da Xue Xue Bao Yi Xue Ban.* 2017;49:663-668 (Chinese).

27. Li CH, Xu LL, Zhao JX, et al. CXCL16 upregulates RANKL expression in rheumatoid arthritis synovial fibroblasts through the JAK2/STAT3 and p38/MAPK signaling pathway. *Inflammation Res.* 2016;65:193-202.

28. Muhsein HY, Kadri ZHM, Ad’hiah AH, Mayouf KZ. Predictive significance of CXCL8, CXCL10 and CXCL16 in juvenile idiopathic and rheumatoid arthritis Iraqi patients. *Egypt Rheumatol.* Published online June 13, 2019. doi:10.1016/j. ejr.2019.06.002.

29. Collado A, Marquez P, Escudero P, et al. Functional role of endothelial CXCL16/CXCR6-platelet-leucocyte axis in angiotensin II-associated metabolic disorders. *Cardiovasc Res.* 2018;114:1764-1775.

30. Yoshino T, Kusunoki N, Tanaka N, et al. Elevated serum levels of resistin, leptin, and adiponectin are associated with C-reactive protein and also other clinical conditions in rheumatoid arthritis. *Intern Med.* 2011;50:269-275.

31. Olama SM, Senna MK, Elraman R. Synovial/serum leptin ratio in rheumatoid arthritis: the association with activity and erosion. *Rheumatol Int.* 2012;32:683-690.

32. Rho YH, Soh J, Sokka T, et al. Adipocytokines are associated with cardiovascular joint damage in rheumatoid arthritis. *Arthritis Rheum.* 2009;60:1906-1914.

33. Fioravanti A, Tenti S, Bacarelli MR, et al. Tocilizumab modulates serum levels of adiponectin and chemerin in patients with rheumatoid arthritis: potential cardiovascular protective role of IL-6 inhibition. *Clin Exp Rheumatol.* 2019;37:293-300.

34. Kontunen P, Vuolteenaho K, Nieminen R, et al. Resistin is linked to inflammation, and leptin to metabolic syndrome, in women with inflammatory arthritis. *Scand J Rheumatol.* 2011;40:256-262.

35. Abella V, Sorcece M, Conde J, et al. Adipokines, metabolic syndrome and rheumatic diseases. *J Immunol Res.* 2014;2014:343746.

36. Šenolt L, Housa D, Vernerová Z, et al. Resistin in rheumatoid arthritis synovial tissue, synovial fluid and serum. *Ann Rheum Dis.* 2007;66:458-463.

37. Klein-Wieringa IR, Van der Linden MPM, Knevel R, et al. Baseline serum adipokine levels predict radiographic progression in early rheumatoid arthritis. *Arthritis Rheum.* 2011;63:2567-2574.

38. Fadda SM, Gamal SM, Elsaid NY, Mohy AM. Resistin in inflammatory and degenerative rheumatologic diseases. Relationship between resistin and rheumatoid arthritis disease progression. *Z Rheumatol.* 2013;72:594-600.

39. Montazerifar F, Bolouri A, Paghalea RS, Mahani MK, Karajibani M. Obesity, serum resistin and leptin levels linked to coronary artery disease. *Arg Braz Cardiol.* 2016;107:348-353.

40. Mancuso P, Bouchard B. The impact of aging on adipose function and adipokine synthesis. *Front Endocrinol (Lausanne).* 2019;10:137.

41. McCoy D, Sturrock RD. Comparison of cardiovascular risk in ankylosing spondylitis and rheumatoid arthritis. *Clin Exp Rheumatol.* 2009;27:SI24–SI26.