

ВЛИЯНИЕ ПОЧЕЧНОЙ ДИСФУНКЦИИ НА УРОВЕНЬ СЫВОРОТОЧНЫХ АНГИОПОЭТИН-ПОДОБНЫХ БЕЛКОВ И АНТИТЕЛ К ФОСФОЛИПИДАМ У БОЛЬНЫХ РЕВМАТОИДНЫМ АРТРИТОМ С МЕТАБОЛИЧЕСКИМ СИНДРОМОМ

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Резюме. Ревматоидный артрит (РА) является частым фоном для развития почечной патологии. Хроническая болезнь почек (ХБП) определяется более чем у 30% пациентов с РА. Наряду с воспалением и другими факторами прогрессирования основного заболевания развитию почечного поражения при РА способствует наличие метаболического синдрома (МС).

Цель исследования – оценить взаимосвязь сывороточных концентраций ангиопоэтин-подобных белков (АППБ) и антител к фосфолипидам (аФЛ) с развитием почечной дисфункции у больных РА.

Было обследовано 158 пациентов с РА (91,8% – женщин и 8,2% – мужчин) в возрасте от 21 до 80 лет и средней длительностью заболевания – 9 (4-15) лет. Преобладали пациенты серопозитивные по ревматоидному фактору и по антителам к циклическому цитруллинированному пептиду, с развернутой клинической стадией и умеренной активностью ($3,2 < DAS28 \leq 5,1$) патологического процесса.

ELISA-тест был использован для количественного определения в сыворотке крови больных РА ангиопоэтин-подобного белка 3-го типа и 4-го типа и антител к фосфолипидам (аФЛ-IgG/IgM) для суммарного выявления антител к кардиолипину, фосфатидилсерину, фосфатидилинозитолу, фосфатидиловой кислоте и комплексу отрицательно заряженного фосфолипида и β_2 -гликопротеина-I.

Более половины обследованных больных РА имели расчетную скорость клубочковой фильтрации (рСКФ) в пределах от 89 до 60 мл/мин/1,73 м² (распределение по стадиям ХБП: С1 – 21,5%; С2 – 58,9%; С3 – 19,6%). Признаки МС (сочетания повышенного АД, повышения уровня триглицеридов и нарушений углеводного обмена на фоне центрального ожирения) были диагностированы у 68 (43%) больных РА.

Был выполнен многофакторный дисперсионный анализ по сравнению изучаемых показателей (АППБ3, АППБ4, аФЛ) в зависимости от рСКФ в группах больных РА без признаков метаболи-

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ческого синдрома и больных РА с МС. Между больными РА с различной степенью выраженности метаболических нарушений были установлены существенные различия в уровне АППБЗ ($F = 8,86$, $p = 0,0034$) и АППБ4 ($F = 29,6$, $p < 0,001$), но не аФЛ ($p > 0,05$). Проведение многофакторного дисперсионного анализа показало достоверное увеличение АППБ4 в сыворотке крови больных РА со сниженной рСКФ (< 89 мл/мин) ($F = 18,5$, $p < 0,001$) и выраженными метаболическими изменениями ($F = 24,2$, $p < 0,001$). Таким образом, на содержание АППБ4 у больных РА непосредственное влияние оказывали только два фактора (почечная дисфункция и наличие МС), способные более чем в 30% случаев описать изменчивость данного признака. Квадрат множественного коэффициента корреляции (R^2) в данной модели составил 0,33. АППБ 4-го типа следует рассматривать в роли ключевого фактора, связывающего развитие почечной дисфункции и метаболические изменения, вызванные ревматоидным воспалением.

Ключевые слова: ревматоидный артрит, почечная дисфункция, ангиопоэтин-подобные белки, метаболический синдром

INFLUENCE OF RENAL DYSFUNCTION ON THE LEVEL OF SERUM ANGIOPOIETIN-LIKE PROTEINS AND ANTI-PHOSPHOLIPID ANTIBODIES IN PATIENTS WITH RHEUMATOID ARTHRITIS AND METABOLIC SYNDROME

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Abstract. Rheumatoid arthritis (RA) is a frequent background for the development of renal pathology. Chronic kidney disease (CKD) is determined in more than 30% of patients with RA. Along with inflammation and other factors in the progression of the underlying disease, the development of renal damage in RA is facilitated by the presence of metabolic syndrome (MetS).

The aim of this study is to assess the relationship of serum concentrations of angiopoietin-like proteins (ANGPTL) and antiphospholipid antibodies (aPL) with the development of renal dysfunction in patients with RA.

We examined 158 patients with RA (91.8% – women and 8.2% – men) aged 21 to 80 years old and an average duration of the disease – 9 (4-15) years. The majority of patients were seropositive for rheumatoid factor and for antibodies to cyclic citrullinated peptide, with an advanced clinical stage and moderate activity ($3.2 < DAS28 \leq 5.1$) of the pathological process.

The ELISA test was used for the quantitative determination of angiopoietin-like protein type 3 and type 4 and antibodies to phospholipids (aPL-IgG/IgM) for total detection of antibodies to cardiolipin, phosphatidylserine, phosphatidylinositol, phosphatidylic acid and a complex of negatively charged phospholipid and β_2 -glycoprotein-I.

More than half of the examined RA patients had the calculated glomerular filtration rate (eGFR) ranging from 89 to 60 ml/min/1.73 m² (allocation by CKD stages: C1 – 21.5%; C2 – 58.9%; C3 – 19.6%). Signs of MetS (a combination of increased blood pressure, increased triglyceride levels and carbohydrate metabolism disorders against the background of central obesity) were diagnosed in 68 (43%) RA patients.

Multivariable analysis of variance was performed to compare the studied parameters (ANGPTL3, ANGPTL4, aPL) depending on eGFR in groups of RA patients without signs of metabolic syndrome and RA patients with MetS. Significant differences in the level of ANGPTL3 ($F = 8.86$, $p = 0.0034$) and ANGPTL4 ($F = 29.6$, $p < 0.001$), but not aPL ($p > 0,05$) were found between RA patients with varying degrees of severity of metabolic disorders. Multivariable analysis of variance showed a significant increase in ANGPTL4 in the blood serum of RA patients with reduced eGFR (< 89 ml/min) ($F = 18.5$, $p < 0.001$) and pronounced metabolic changes ($F = 24.2$, $p < 0.001$). Thus, only two factors (renal dysfunction and the presence of MetS) had a direct

effect on the ANGPTL4 content in RA patients, which could describe the variability of this sign in more than 30% of cases. The squared multiple correlation coefficient (R^2) in this model was 0.33. ANGPTL type 4 should be considered as a key factor linking the development of renal dysfunction and metabolic changes caused by rheumatoid inflammation.

Keywords: rheumatoid arthritis, renal dysfunction, angiotensin-like proteins, metabolic syndrome

Introduction

Rheumatoid arthritis (RA) is a frequent comorbidity for developing renal pathology [5, 15]. Chronic kidney disease (CKD) is determined in more than 30% of patients with RA, and the hyperfiltration (C1) stage predominates in such patients, being considered as the most important indicator of the subsequent progression of renal dysfunction and an increase in related cardiovascular risk [14].

Along with inflammation and other factors in the progression of the underlying disease, the development of renal damage in RA is facilitated by the presence of metabolic syndrome (MetS). The prevalence of MetS among patients with RA according to Hallajzadeh J. et al. (2017) is 30.65%, but it ranges from 14.32 to 37.83%, depending on factors related to the characteristics of the studied population and the method used for determining MetS [9].

Obviously, there is a close relationship between MetS course and the severity of articular syndrome in RA, especially in newly diagnosed and untreated patients, as well as evidence to consider MetS as an independent risk factor for chronic kidney disease [7].

The improvement of the methods of nephroprotective strategy aimed at inhibiting the progression of CKD in RA should include not only the study of hemodynamic mechanisms of CKD progression, but also immunoinflammatory aspects. In addition, the asymptomatic course in the early stages of CKD accounts for to search for new biomarkers that can predict the progression of kidney damage in RA.

Antiphospholipid antibodies (aPL) – a heterogeneous group of autoantibodies directed against negatively charged phospholipids (cardiolipin), protein-phospholipid complexes or plasma proteins (β_2 -glycoprotein-I, β_2 -GP-I) – are characteristic of antiphospholipid syndrome, but they may also be present in diseases not associated with thrombosis (hypertension, diabetic nephropathy) [3, 12].

According to a systematic review by El Hasbani G. et al. (2021), antiphospholipid antibodies can be detected on average in 14% of patients with inflammatory and autoimmune rheumatic and musculoskeletal diseases (in addition to systemic lupus erythematosus) [6]. According to Olech E. et al., the incidence of antiphospholipid antibodies (aPL) in patients with RA is 28% (median – 22%) [13] being slightly lower in systemic scleroderma (> 30%) [6].

Angiotensin-like proteins of types 3 and 4 (ANGPTL3 and ANGPTL4), included in the group of adipokines and participating in the regulation of homeostasis of fat, lipid and glucose metabolism, can become a promising object for studying the pathogenetic mechanisms that determine the manifestations of comorbid pathology in RA. There are indications on the key role of such proteins in the regulation of physiological and multiple pathophysiological processes (regulation of lipid and carbohydrate metabolism, inflammation, hematopoiesis, etc.) [2, 11], which makes them attractive target markers for studying cardiorenal and metabolic complications of RA.

The aim of this study is to assess a relationship between serum concentrations of ANGPTL and aPL and development of renal dysfunction in patients with RA.

Materials and methods

We examined 158 patients with RA (91.8% – women and 8.2% – men) aged 21 to 80 years old, with average duration of the disease – 9 (4–15) years. The majority of patients were seropositive for rheumatoid factor (RF) and for antibodies to cyclic citrullinated peptide (ACPA), at advanced clinical stage and moderate activity ($3.2 < \text{DAS28} \leq 5.1$) of the pathological process (Table 1).

There were not included RA patients with signs of acute bacterial and viral infection at the time of the study, with detected malignant neoplasm of any localization and severe concomitant pathology (myocardial infarction, vascular thrombosis, type 1 or 2 diabetes mellitus) in history, as well as never treated with biological drugs.

Physical examination consisted of interviewing complaints, collecting anamnesis, studying the medical patient documentation, assessing the general condition, measuring blood pressure on both arms, anthropometry, calculating body mass index (BMI) in kg/m², waist / hip ratio (W/H) and calculating the DAS28 index.

The ELISA test was used to quantitate angiotensin-like protein type 3 (Human Angiotensin-like Protein 3 ELISA; Bio Vendor, Czech Republic) and type 4 (RayBio Human ANGPTL4 ELISA; RayBiotech, USA), antibodies to cyclic citrullinated peptide (ACPA) (Anti-CCP hs; Orgentec Diagnostika, Ger-

TABLE 1. CLINICAL CHARACTERISTICS OF PATIENTS WITH RA

Studied indicator	Value
Age, years, M±SD	55.4±10.7
Duration of RA, n (%)	
< 4 years	41 (25.9)
5-9 years	39 (24.7)
> 10 years	78 (49.4)
Seropositivity for RF, n (%)	91 (57.6%)
Seropositivity for ACPA, n (%)	95 (60.1%)
Clinical stage of RA, n (%)	
0 – provisional RA	3 (1.9)
1 – early	16 (10.1)
2 – moderate	38 (24.1)
3 – severe	72 (45.6)
4 – terminal	29 (18.3)
R° stage, n (%)	
I	16 (10.1)
II	61 (38.6)
III	68 (43.1)
IV	13 (8.2)
The presence of erosion, n (%)	
+	126 (79.7)
-	32 (20.3)
RA activity according to DAS28 index, n (%)	
Remission of RA (DAS28 < 2,6)	26 (16.5)
Low (2.6 ≤ DAS28 ≤ 3.2)	26 (16.5)
Moderate (3.2 < DAS28 ≤ 5.1)	92 (58.2)
High (DAS28 > 5.1)	14 (8.8)
Functional class, n (%)	
0	1 (0.6)
I	24 (15.2)
II	108 (68.4)
III	24 (15.2)
IV	1 (0.6)

many) and antibodies to phospholipids (aPL-IgG/IgM) (Anti-Phospholipid Screen IgG/IgM; Orgentec Diagnostika, Germany) for total detection of antibodies to cardiolipin, phosphatidylserine, phosphatidylinositol, phosphatidyl acid and a complex of negatively charged phospholipid and β_2 -glycoprotein I. All serum samples from patients with RA were analyzed simultaneously (in one session) in accordance with the manufacturer's instructions.

A combination of increased blood pressure ($\geq 140/90$ mmHg), increased triglyceride levels (≥ 1.7 mmol/L) and disorders of carbohydrate metabolism (increased fasting plasma glucose ≥ 6.1 mmol/L) along with central obesity (waist volume > 94 cm in men and > 80 cm in women)

served as a rationale for inclusion in the group of RA patients with signs of metabolic syndrome.

To assess renal function in RA patients, the calculated glomerular filtration rate (GFR) was used according to the CKD-EPI formula (Chronic Kidney Disease Epidemiology Collaboration, 2009), taking into account the height and weight of any patient without indexing by body surface area (CKD-EPI_{height / weight}). According to the recommendations of KDIGO (Kidney Disease: Improving Global Outcomes, 2012), GFR values < 60 ml/min/1.73 m² were regarded as a certain decrease, and GFR values from 60 to 89 ml/min/1.73 m² – as a slight decrease in global kidney function.

Statistical analysis of the obtained sample data was carried out using the computer programs Microsoft

Office Excel 2010 (Microsoft Corp., USA) and STATISTICA 10.0 (StatSoft Inc., USA). Depending on the distribution of the studied variables, the data are presented as mean \pm standard deviation of the mean ($M \pm SD$) or median and interquartile interval ($Me (Q_{0.25}-Q_{0.75})$). While comparing two independent groups, the methods of analysis of variance were used: with a normal distribution of characteristics – analysis of variance ANOVA, with a non-normal distribution – the Kruskal–Wallis analysis (H-test). The relationship between quantitative traits, the distribution of which obeyed the normal law, was determined by the Pearson correlation coefficient (r). In case of abnormal and/or rank distribution of features, the data of correlation analysis by Spearman's coefficient (r_s) were used. The results were considered statistically significant at $p < 0.05$.

Results and discussion

More than half of the examined RA patients had eGFR ranging from 89 to 60 ml/min/1.73 m² (distribution by CKD stages: C1 – 21.5%; C2 – 58.9%; C3 – 19.6%). There was no sharply decreased renal function (GFR < 30 ml/min/1.73 m²), corresponding to CKD C4-5 stages.

Signs of MetS (a combination of increased blood pressure, increased triglyceride levels and carbohydrate metabolism disorders along with central obesity) were diagnosed in 68 (43%) RA patients.

The level of ANGPTL3 in the blood serum of patients with RA ($n = 158$) was 641.9 ± 224.5 ng/ml, and the level of ANGPTL4 ($n = 158$) was $3.15 (0.77-12.1)$ ng/ml. 74.7% of patients with RA ($n = 118$) were found to be positive for ANGPTL3, and 49.4% ($n = 78$) for ANGPTL4.

The upper limit of normal concentration ($< M + 3SD$) for ANGPTL3 (472 ng/ml) and for ANGPTL4 (3.24 ng/ml) was established after determining these parameters in the serum of 33 healthy individuals.

Correlations of varying strength were found between ANGPTL3 and age ($r = 0.23, p = 0.03$), CRP level ($r = 0.21, n = 100, p = 0.031$), blood calcium level ($r = 0, 32, p = 0.014$); between ANGPTL4 and clinical stage of RA ($r_s = 0.21, p = 0.008$), the number of swollen joints ($r_s = 0.19, p = 0.03$), CRP level ($r_s = 0.29, n = 100, p = 0.002$), the level of circulating immune complexes ($r_s = 0.31, n = 126, p = 0.01$).

The level of aPL-IgG in the blood serum of RA patients ($n = 158$) was $5.91 (3.47-7.25)$ U/ml; aPL-IgM – $6.62 (4.37-9.11)$ U/ml. Positive aPL-IgG of low or medium level (ranged 10 – 40 U/ml) were found in 14 (8.9%), aPL-IgM – in 23 (14.6%) patients with RA. Moreover, 7 (4.4%) patients had an increased level of both aPL-IgG and aPL-IgM. There was a correlation of average strength between aPL-IgG and the duration (number of months) of glucocorticosteroid intake ($r_s = 0.31, n = 78, p = 0.006$), as well as a weak strength correlation between aPL-IgM and ANGPTL4 level ($r_s = 0, 26, p = 0.037$), RF-IgM level ($r_s = 0.28, p = 0.007$), DAS28 index ($r_s = 0.19, p = 0.015$).

We studied a relation between the indicators (ANGPTL3, ANGPTL4 and aPL-IgG/IgM) and the incidence of renal dysfunction (according to the level of $eGFR_{\text{growth/weight}}$) in RA patients with varying degrees of severity of metabolic changes. $eGFR_{\text{growth/weight}}$ indices in RA patients ($n = 158$) had a normal distribution (K-S $d = 0.064, p > 0.2$; Lilliefors $p < 0.15$; Shapiro–Wilk $W = 0.98573, p = 0.1$).

The average glomerular filtration rate in RA patients was 74.0 ± 18.6 ml/min. Negative correlations of average strength were revealed between the eGFR indices and the level of ANGPTL3 ($r = -0.32, p < 0.001$) and ANGPTL4 ($r_s = -0.31, p < 0.001$), as well as with age ($r_s = -0.28, p < 0.001$), duration of RA ($r_s = -0.22, p = 0.005$) and an increase in systolic blood pressure ($r_s = -0.25, p = 0.001$).

A negative correlation of weak strength was found between the level of eGFR and the intake (at the time

TABLE 2. CONCENTRATION OF ANGPTL3, ANGPTL4 AND aPL-IgG/IgM IN RA PATIENTS WITH DIFFERENT GFR

Measure	RA patients with different GFR		
	Group I (n = 34)	Group II (n = 93)	Group III (n = 31)
ANGPTL3, ng/ml	$533.4 \pm 161.7^{I-III}$	650.0 ± 223.9	733.2 ± 244.1
ANGPTL4, ng/ml	$0.77 (0.28-3.60)^{I-II, I-III}$	$3.3 (0.93-12.10)$	$6.48 (1.52-19.30)$
aPL-IgG, U/ml	$5.70 (3.46-7.15)$	$6.18 (3.69-7.89)$	$4.97 (2.68-7.08)$
aPL-IgM, U/ml	$5.02 (3.98-8.87)^{I-III}$	$6.37 (4.55-8.98)$	$8.85 (5.67-9.97)$

Note. Upper case indicates intergroup differences at $p < 0.05$.

of the study) of glucocorticoids ($n = 158$, $r_s = -0.16$, $p = 0.048$), but there was no correlation with the dose and frequency of receiving non-steroidal anti-inflammatory drugs ($n = 133$, $p = 0.099$ and $n = 132$, $p = 0.784$).

The patients were divided into three groups according to the measured $eGFR_{\text{growth/weight}}$: group I – optimal renal function, > 90 ml/min; group II – a slight decrease in renal function, from 89 to 60 ml/min; group III – reduced renal function, < 59 ml/min (Table 2).

Significant differences were noted in the level of ANGPTL3 in patients from the first group with RA patients in whom $eGFR_{\text{growth/weight}} < 59$ ml/min (groups I-III: H-test = 6.55, $p = 0.032$). There were no other intergroup differences in the level of ANGPTL3. Significant differences in the level of ANGPTL4 in patients with normal renal function (group I) with groups of RA patients with reduced $eGFR$ (groups I-II: H-test = 10.7, $p = 0.001$; groups I-III: H-test = 20.1, $p < 0.001$) were identified. ANGPTL4 indices also had intergroup differences (groups II-III: H-test = 7.2, $p = 0.007$) with $eGFR_{\text{growth/weight}}$ less than 90 ml/min (Table 2).

ANGPTL types 3 and 4 acting along with C-reactive protein (CRP) as markers of systemic inflammation in RA may indicate a direct effect of chronic inflammation on renal function. It has been reported that inflammation promotes glomerular damage through infiltration of inflammatory cells (monocytes and macrophages), which stimulate the proliferation of mesangial cells. A persistently high CRP level for at least 6 months is a significant risk factor for the development of chronic kidney disease [10]. In addition, Clement L.C. et al. (2014) found that ANGPTL4 is a link between proteinuria and hypertriglyceridemia in nephrotic syndrome [4].

There were no intergroup differences in the concentration of aPL-IgG ($p = 0.23$). The aPL-IgM level in group III was significantly higher than in the group of RA patients with $eGFR_{\text{growth/weight}} > 90$ ml/min (groups I-III: H-test = 5.49, $p = 0.02$) (Table 2).

According to Couderc M. et al. (2016) the development of renal failure in RA is more likely associated with cardiovascular risk factors, which are more often observed in RA (age, gender, smoking, hypertension, hypercholesterolemia) and are risk factors for chronic kidney disease, but not associated with the activity or severity of the disease [5].

Antiphospholipid antibodies can cause prolongation of phospholipid-dependent coagulation disorders, although patients with rheumatic diseases are at higher risk of thromboembolic complications rather than bleeding. The clinical significance of aPL in RA is not determined, although the frequency of detected antibodies to cardiolipin is often higher than

in healthy people. The presence of these antibodies is considered to be a nonspecific marker of the activated immune system [8]. We were unable to establish a reliable relationship between aPL-IgG/IgM and the presence of venous thrombosis in patients with RA in the anamnesis ($p > 0.05$). However, according to Yusuf H.R. et al. (2014), autoimmune diseases, including RA, may be associated with an increased risk of venous thromboembolism among hospitalized patients [16], which may presumably be associated with the intake of glucocorticoids.

At the final stage of the study, a multivariable analysis of variance was performed to compare the studied parameters (ANGPTL3, ANGPTL4, aPL) depending on $eGFR$ in groups of RA patients with/without signs of metabolic. Significant differences in the level of ANGPTL3 ($F = 8.86$, $p = 0.0034$) and ANGPTL4 ($F = 29.6$, $p < 0.001$), but not aPL ($p > 0,05$) were found between RA patients with varying degrees of severity of metabolic disorders.

The study of the influence of several factors (the presence of MetS and renal dysfunction) on the level of ANGPTL3 in RA patients showed that these factors and their interactions can explain an insignificant variability of ANGPTL3 ($R^2 = 0.11$), which indicates a low quality of the model.

While studying the influence of the selected factors on the level of ANGPTL4, a more pronounced difference in the level of ANGPTL4 was noted in the presence of metabolic disorders in groups of RA patients with varying degrees of renal dysfunction. Nevertheless, the considered factors and their interactions, although allowing to explain a significant part of the variability in ANGPTL4 ($R^2 = 0.32$), also did not make this model significant ($p = 0.1$).

We differentiated RA patients into patients with high or optimal $eGFR$ (≥ 90 ml/min) and patients with reduced $eGFR$ (< 90 ml/min) when combining groups of RA patients with varying degrees of renal dysfunction (group II and group III). Multivariable analysis of variance using the new characteristics showed a significant increase in serum ANGPTL4 of RA patients with reduced $eGFR$ ($F = 18.5$, $p < 0.001$) and pronounced metabolic changes ($F = 24.2$, $p < 0.001$). The presence of MetS did not affect the serum ANGPTL4 level in RA patients with normal renal function. The decrease in renal function was accompanied by significantly increased ANGPTL4 that was more noticeable in the group of RA patients with MetS ($F = 5.76$, $p = 0.176$).

Thus, only two factors (renal dysfunction and the presence of MetS) had a direct effect on the ANGPTL4 level in RA patients, which could describe the variability of this sign in more than 30% of cases. The squared multiple correlation coefficient (R^2) in this model was 0.33.

Conclusion

Chronic rheumatoid inflammation and the combination of RA with MetS potentiate development of renal dysfunction, noted according to our data in 78.5% of patients, being accompanied by increased level of serum ANGPTL types 3 and 4 of patients.

ANGPTL type 4 should be considered as a key factor bridging the development of renal dysfunction and metabolic changes caused by rheumatoid inflammation. A better understanding of the actions and mechanisms of ANGPTL may be of high priority

for developing effective therapeutic methods lowering the progression of arthritis, metabolic syndrome and cardio-renal complications, thereby improving the quality of life of RA patients .

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