

Original article

Duration of rheumatoid arthritis changes blood levels of angiotensin and aldosterone

Boris A. Rebrov, Elena B. Komarova, Antonina K. Knyazeva

St. Luke State Medical University of Lugansk, Lugansk, Russia

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Abstract: The article presents data on the influence of rheumatoid arthritis (RA) duration on changes in blood levels of angiotensin (ATII) and aldosterone (ALD).

Objective — To examine the changes in the activity of the renin-angiotensin-aldosterone system (RAAS) depending on the time elapsed from the onset of RA (i.e., on the stage of the disease development).

Methods — We examined 184 patients diagnosed with RA (*sensu* the ACR/EULAR 2010 criteria) without concomitant pathology. The control group (CG) consisted of 34 virtually healthy individuals. The serum concentrations of ATII and ALD were determined by the enzyme-linked immunosorbent assay (ELISA).

Results — When assessing the studied parameters of the RAAS, we discovered that in all examined RA patients, the level of ATII and ALD in the blood was more than twice as high as that in the CG ($p < 0.001$; $p < 0.010$). ATII concentration decreased unevenly with increasing disease duration. The differences of the group of patients with a duration of RA less than 6 months were not statistically significant with the groups of patients of 0.6-1.0 and 2.1-3.0 years ($p > 0.050$), while the differences with patients with a disease duration of 1.1-2.0, 3.1-4.0, and > 5 years were statistically significant ($p < 0.050$). Further comparative analysis of the indicators revealed statistically significant differences between the group of patients of 0.6-1.0 years and patients with RA duration of 3.1-4.0 and > 5 years ($p < 0.050$), as well between patients with RA duration of 1.1-2.0 and 4.1-5.0 years ($p < 0.050$). The blood content of ALD increased unevenly in patients: from the minimum to the maximum disease duration. In individuals with a duration of RA < 0.5 years, the differences were significant ($p < 0.05$), with the exception of the group of 0.6-1.0 years ($p > 0.05$). In patients with a disease duration of 0.6-1.0 and 1.1-2.0 years, the differences were statistically significant with all subsequent groups of RA duration ($p < 0.05$). Further mathematical processing of data using multiple regression analysis and determination of correlations showed the presence of a linear inverse relationship between the ATII level and the duration of the disease ($R = -0.44$, $p < 0.001$; $F = 10.98$, $p = 0.001$). Data processing also revealed strong direct correlations between the level of ALD in the blood and the duration of the disease ($R = 0.4999$, $p < 0.001$; $F = 58.27$, $p < 0.001$).

Conclusion — The RAAS is heterogeneous and its integration into a single system is ambiguous. The significance of various components of the RAAS in RA is determined by the pathophysiological processes in the patient's body. Blocking of various components of the RAAS should be differentiated and either correspond to some specific levels of indicators for each patient, or match to the stages of RA associated with the duration of the disease.

Keywords: renin-angiotensin-aldosterone system, rheumatoid arthritis, angiotensin, aldosterone.

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Correspondence to Antonina K. Knyazeva. E-mail: antonina-vifanskaya@yandex.ru.

Introduction

Up to 40% of the population suffers from joint diseases. Rheumatic diseases include more than 80 nosologic variants. However, first of all, rheumatoid arthritis (RA) is associated with a medical, social and economic burden on society [1]. The number of potent medicines for RA is increasing, but their widespread use is limited by high cost [2]. Therefore, the search for new, more effective approaches to treatment is urgent.

The effect of the renin-angiotensin-aldosterone system (RAAS) on the course of RA was confirmed in many studies [3]. However, it is not used in practical medicine and was not confirmed in clinical studies, although the possibility of effective blocking of the RAAS is obvious *in vitro* [4, 5, 6]. There is conflicting evidence regarding the effectiveness of RAAS blocking drugs in RA. For

instance, the positive effect of treatment with angiotensin-converting enzyme inhibitors (ACE inhibitors) was noted by M.F. Martin et al. [7], while the efficacy of angiotensin receptor blockers was established by D. Wang et al. [6]. However, H.A. Bird et al. [8] and A.J. Flammer et al. [9] observed no improvement in RA patients with a blocked RAAS.

In recent years, no new evidence was revealed that ATII receptors should be the best choice for the treatment of hypertension in patients with RA. Consequently, the previous (EULAR 2010) preferences for ATII receptors and receptor blockers were excluded from the EULAR 2015/2016 recommendations for the management of patients with RA and cardiovascular risk [10].

Pathological processes occurring in the early and late periods of RA have different directions [11]. Therefore, RA is usually

structured into phases (active and inactive), stages (exacerbation and remission), degrees of activity, and time periods.

The objective of our study was to examine the changes in the activity of some components of the RAAS depending on the time elapsed from the onset of RA (i.e., on the stage of the disease development).

Material and Methods

Research design and study population

We examined 184 patients with a diagnosis of RA (*sensu* the ACR/EULAR 2010 criteria) without concomitant pathology in the Department of Rheumatology settings.

Our exclusion criteria were as follows: blood pressure >140/90 mmHg, acute cerebrovascular accidents, myocardial infarction, heart failure, diabetes, chronic kidney disease, malignant neoplasms, active bacterial or viral infection, use of ACE inhibitors, ATII receptor blockers, and mineralocorticoid receptor antagonists within the past 6 months.

The control group (CG) included 42 individuals [34 women (81%) and 8 men (19%)] without clinical signs and laboratory confirmation of acute or chronic diseases of internal organs, not taking any medications, and 34 to 56 years of age [median 46.8 (46; 51) years].

The majority of respondents were women [168 patients (86.6%)]. There were 26 men (13.4%). The mean age of women was 47.9±9.6 years, while men were on average 46.3±13.7 years ($t=1.13$, $p=0.13$). The mean duration of the disease was 3.82±3.43 years in women and 3.42±3.34 in men ($t=0.44$, $p=0.33$). The mean duration of the disease for both genders combined was 3.72±3.43 years.

Based on the duration of the disease, the following groups of RA patients were identified: with early course (<2 years), medium course (2-5 years) and late course of the disease (>5 years) [26]. We observed no significant differences in this parameter between genders ($\chi^2 = 1.9$, $p = 0.17$).

Laboratory studies

The concentrations of ATII and ALD in blood serum were determined by the enzyme-linked immunosorbent assay (ELISA) manufactured by BCM Diagnostic, Canada.

Statistical data processing

Statistical processing of data was carried out by parametric and nonparametric methods, correlation, univariate and multivariate (ANOVA/MANOVA) analyses of variance on a personal computer using licensed software packages (Microsoft Excel and STATISTICA 10, StatSoft, USA). The mean, median (Me), lower and upper quartiles (LQ and UQ), standard deviation (σ), and statistical validity (p) were assessed. Normality of the distribution was tested by W-test and Shapiro-Wilk test. Student's t test was employed to determine the significance of differences between the means of continuous numerical parameters. The Mann-Whitney test (Z , U) was used when the data were unevenly distributed. Spearman's rank correlation coefficients (R), Friedman test (χ^2), Kruskal-Wallis (KW), Fisher's (F) and statistical significance (p) were assessed. The results were considered statistically significant at $p < 0.05$.

Results

Before assessing the RAAS indicators, we determined the concentrations of the main electrolytes that significantly affect the state of the RAAS (Table 1).

As can be seen from the table, the levels of K^+ and Na^+ in the blood serum did not differ significantly between the patients with RA and the CG ($p > 0.05$) (Table 1). The levels of ATII and ALD in the blood of patients with RA were more than twice as high as the values in the CG. All examined RA patients were split among three groups depending on the duration of the disease (Table 2 and Table 3).

The level of ATII decreased unevenly with increasing disease duration (Table 2). Differences between groups were not always statistically significant.

Differences in ATII levels between patients with disease duration of 1.1-2.0, 3.1-4.0 and >5 years were statistically significant ($p=0.034$), whereas differences in ATII levels between groups of patients with RA duration <0.5, 0.6-1.0 and 2.1-3.0 years were not significant ($p > 0.050$).

When comparing the indicators, we detected statistically significant differences between the group of patients of 0.6-1.0 years and the groups of patients with RA duration of 3.1-4.0 and >5 years ($p=0.042$), as well as between patients with RA duration of 1.1-2.0 and 4.1-5.0 years ($p=0.027$).

Changes in blood ALD concentration vs. the duration of RA are presented in Table 3.

The level of ALD in patients increased unevenly with increasing duration of the disease (Table 2). In case of the group with RA duration <0.5 years, the differences were significant with all groups ($p=0.019$) except the group of 0.6-1.0 years ($p > 0.050$). In case of the groups of patients with disease duration of 0.6-1.0 and 1.1-2.0 years, the differences with all subsequent groups of RA duration were statistically significant ($p=0.024$). At the same time, no significant differences were noted between the groups with RA duration of 3.1-4.0, 4.1-5.0, and >5 years ($p > 0.050$). Hence, Table 3 shows an increase in blood ALD content with an increase in the duration of RA with a relatively steady concentration over a period of disease duration from two to five years.

The unevenness of the curve and statistical insignificance of differences between some groups could be caused by a large standard deviation in individual groups (scattered data, insufficient number of observations). However, in the period between the years 2 and 4 of the disease, there is a fairly noticeable decrease in the ATII content, as compared with the level of its relative steadiness (from 0.5 to 2 years).

The correlation analysis yielded an inverse linear relationship between the level of ATII and the duration of the disease ($R=-0.44$, $p < 0.001$; $F=10.98$, $p=0.001$), and graphical interpretation showed a linear and uniform exponential curve gradually declining over the course of the disease (Figure 1).

Table 1. RAAS parameters in examined patients with RA, Me (LQ; UQ)

Parameter	Patients with RA (n=184)	Control group (n=42)	p
K^+ , mmol/L	4.3 (4.1; 4.5)	4.5 (4.2; 4.7)	0.662
Na^+ , mmol/L	140 (138; 141)	138 (137; 140)	0.752
ATII, pg/mL	16.39 (12.41; 22.99)	7.44 (6.32; 8.54)	<0.001
ALD, pg/mL	146.7 (99.56; 215.02)	68.25 (54.4; 100.1)	0.002

RA, rheumatoid arthritis; RAAS, renin-angiotensin-aldosterone system; ATII, angiotensin II; ALD, aldosterone.

Table 2. Changes in the level of ATII depending on the disease duration in examined patients with RA, Me (LQ; UQ), σ

Parameter	Disease duration (years)						
	<0.5 (n=18)	0.6-1.0 (n=30)	1.1-2.0 (n=34)	2.1-3.0 (n=8)	3.1-4.0 (n=7)	4.1-5.0 (n=6)	>5 (n=29)
ATII, pg/mL	23.42 (18.99; 29.12) 7.47	21.30 (15.35; 28.19) 8.014	17.68 (12.95; 21.82) 5.25	21.20 (14.89; 21.30) 9.67	12.35 (11.11; 13.52) 2.11	15.65 (13.04; 16.76) 4.18	14.73 (11.02; 15.30) 7.18

RA, rheumatoid arthritis; ATII, angiotensin II.

Table 3. Changes in the level of ALD depending on the disease duration in examined patients with RA, Me (LQ; UQ), σ

Parameter	Disease duration (years)						
	<0.5 (n=19)	0.6-1.0 (n=31)	1.1-2.0 (n=37)	2.1-3.0 (n=8)	3.1-4.0 (n=8)	4.1-5.0 (n=12)	>5 (n=62)
ALD, pg/mL	75.26 (39.99; 111.56) 44.59	89.84 (50.89; 120.30) 47.29	126.45 (71.26; 178.67) 67.79	175.76 (111.53; 231.60) 70.90	180.20 (145.08; 217.88) 58.67	169.49 (152.21; 197.99) 40.54	188.80 (128.10; 252.11) 68.79

RA, rheumatoid arthritis; ALD, aldosterone.

Strong direct correlation was also established between the level of ALD in the blood and the duration of the disease ($R=0.4999$, $p<0.001$; $F=58.27$, $p<0.001$). The Fisher's criterion (F) confirmed the high degree of quality and the authenticity of the discovered pattern; this finding implied that the detected pattern was not a consequence of random fluctuations in the data scatter (Figure 2). The ALD change curve was also uniform, with a gradual rise in its level with the duration of the disease.

Our data processing showed that as the duration of disease increased, distinct changes in ATII and ALD levels occurred. In the period of time between the years 2 and 5, there was an almost steady level of ALD (mostly without statistically significant differences).

In medical practice, the clinical course of RA is often subdivided into periods of time before year 2 and after year 2 of the disease duration (unstable RA and progressive RA, correspondingly) [1, 11]. Therefore, we decided to divide the examined patients into three groups depending on the duration of RA (Table 4 and Table 5).

Table 4 shows that ATII levels decreased with increasing disease duration. Statistically significant differences in patient indicators were established between groups with RA duration of <2, 2-5 and >5 years ($p=0.037$).

The ALD level clearly increased with increasing duration of the disease, and statistically significant differences were observed between all indicators, as can be seen from Table 5.

The dynamics of the studied components of the RAAS is more clearly visible in Figure 3 when plotting the data presented in Table 4 and Table 5.

Initially, high levels of ATII and low values of ALD (similar to control values) were noted. Then ATII content decreased, while ALD concentration increased. The graph lines converge and intersect in the period of 2-5 years of RA duration. Further, ATII decreases to minimum values (without significant differences from the control), whereas ALD increases to its maximum values. This occurs if the duration of the disease significantly exceeds five years.

Analysis of variance demonstrated that the duration of the disease affected the levels of ATII and ALD in the blood of patients with RA ($KW=21.68$, $p<0.001$; $KW=78.66$, $p<0.001$, respectively). With increasing duration of RA, the content of ATII in the blood declined ($R=-0.44$, $p<0.001$), while the concentration of ALD increased ($R=0.59$, $p<0.001$).

Discussion

Treatment of RA is important. It is necessary to find more affordable means and methods of treatment [2]. The RAAS and its main elements, ATII and ALD, are of interest to rheumatologists, since they have been well studied in cardiology, and stable therapeutic algorithms have been developed [12, 13, 14].

It is known that ATII, in addition to vasoactive effect, exhibits anti-inflammatory and antiproliferative effects, reduces endothelial dysfunction, and increases apoptosis of synovocytes [3]. At the same time, ALD has a more pronounced profibrotic effect: it triggers amplified growth of connective tissue [14], proliferative processes, and inflammation in general. These properties of ATII and ALD, as well as the effect of blocking the RAAS in vitro [4, 5, 6], should hypothetically give a good clinical result of blocking the RAAS.

However, in clinical trials, the effectiveness of RAAS blockades was considered controversial [6, 7]; there was no clear clinical evidence of their usefulness [8, 9]. Accordingly, the EULAR 2015/2016 recommendations for the management of patients with RA and cardiovascular risk did not confirm their previous treatment preferences regarding ACE inhibitors and ATII receptor blockers [10].

Typically, among rheumatological recommendations, the regulation and suppression of the RAAS is prescribed solely for lupus nephritis. Consequently, joint recommendations of rheumatologists and nephrologists (EULAR/ERA-EDTA 2019) proposed that nephroprotective effect of the RAAS blocking contributed to limiting the development of renal vasculopathies [15].

RAAS inhibitors are an important component of standard therapy for antiphospholipid syndrome, prescribed to provide a vasodilatory effect. They significantly influence pathogenesis [16]. The important role of vascular lesions in the development of RA was confirmed by a number of studies [17, 18].

There are some assumptions. Perhaps the different clinical results of using RAAS blockers, which were not always comparable with laboratory data, could be explained by 'non-standard' clinical material. Then the patients need to be standardized. Typically, RA patients are grouped by phases, stages, degree of activity, and time elapsed from the onset of the disease. Pathological processes and changes occurring in the body of patients with RA in the early and late stages have different directions [11, 19].

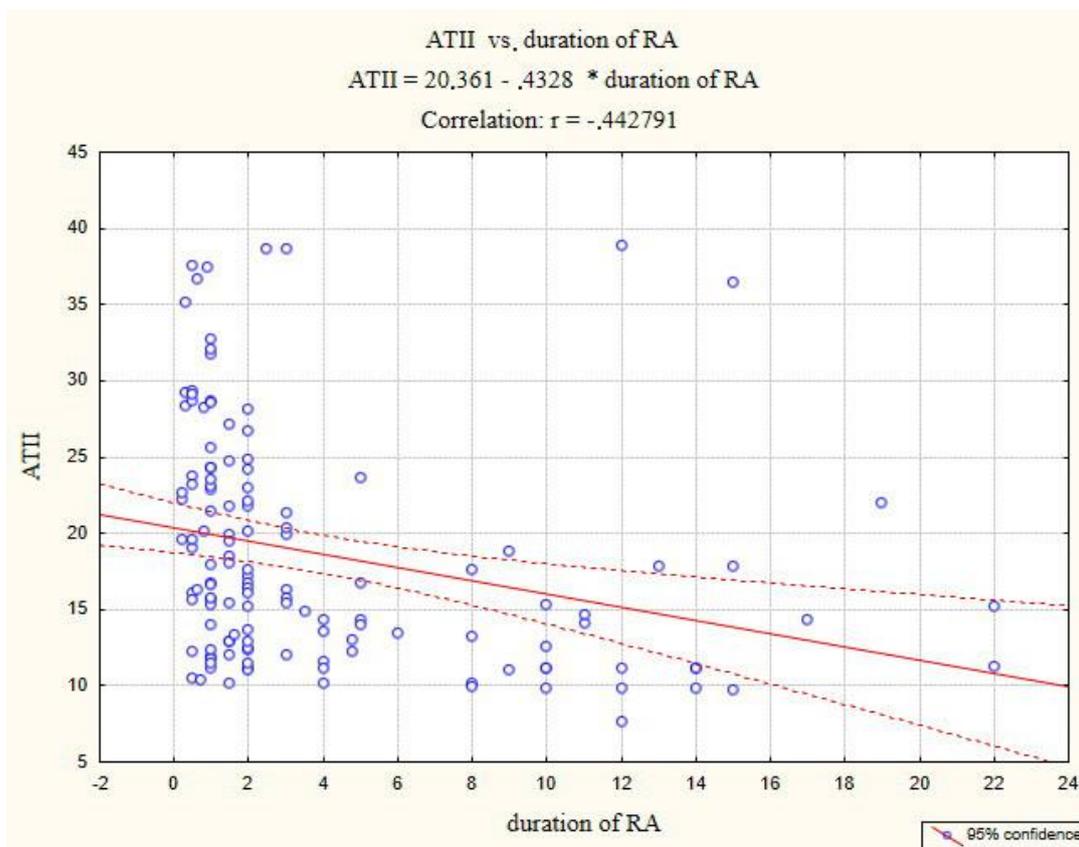


Figure 1. Relationship between the duration of RA (years) and blood level of ATII in examined patients. RA, rheumatoid arthritis; ATII, angiotensin II.

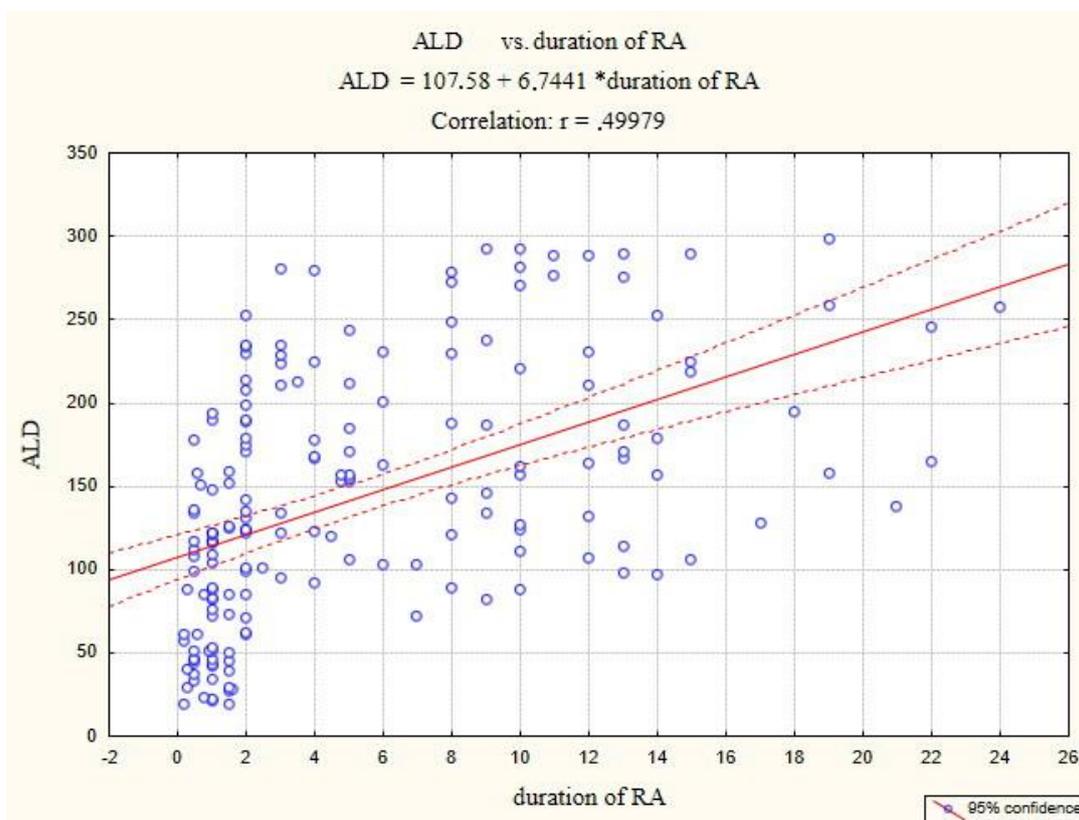


Figure 2. Relationship between the duration of RA (years) and blood level of ALD in examined patients. RA, rheumatoid arthritis; ALD, aldosterone.

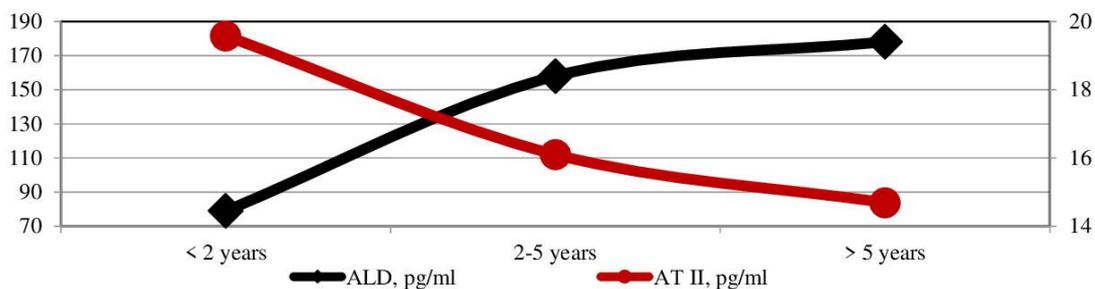


Figure 3. Dynamics of ATII and ALD blood levels vs. RA duration in examined patients (three groups) (Me, pg/mL). RA, rheumatoid arthritis; ATII, angiotensin II; ALD, aldosterone.

Table 4. Changes in ATII level depending on the duration of RA in examined patients, Me (LQ; UQ)

Parameters	Disease duration (years)		
	<2 (n=81)	2-5 (n=22)	>5 (n=29)
ATII, pg/mL	20.31 (18.72; 21.91)	17.46 (14.39; 20.53)	14.73 (12.06; 17.40)

RA, rheumatoid arthritis; ATII, angiotensin II.

Table 5. Changes in ALD level depending on the duration of RA in examined patients, Me (LQ; UQ)

Parameters	Disease duration (years)		
	<2 (n=86)	2-5 (n=28)	>5 (n=63)
ALD, pg/mL	100.48 (49.70; 135.05)	179.57 (143.08; 223.90)	187.49 (126.80; 252.11)

RA, rheumatoid arthritis; ALD, aldosterone.

It can be assumed that the ambiguity of clinical data on the effectiveness of blocking the RAAS in RA depends on the pathophysiological stage of the disease. It is also possible that the elements of the RAAS are not so strongly related to each other.

In this study, ATII and ALD were selected as the main and most significant components of the RAAS. Their availability for a practicing physician, along with an opportunity to analyze and correct them, if necessary, were important factors determining their choice.

At the initial stage of the study, we established that ATII and ALD levels in patients were higher than control values. This finding complied with the data of other researchers indicating increased activity of the RAAS in RA [3, 9].

The electrolyte composition of the blood was within normal limits and did not differ significantly between patients with RA and those with chronic hepatitis. Although the absolute values of K⁺ and Na⁺ did not provide a complete understanding of water-and-salt metabolism, the lack of changes in electrolyte balance, and the absence of fluctuations in blood pressure and heart rate allowed excluding the influence of volumetric and sympathoadrenal effects, which was a significant factor in case of these patients.

When considering possible time intervals for dividing patients into groups, we took into account, first of all, the usual classification of the disease: early RA and protracted (late) RA, with different corresponding diagnostic and treatment approaches. According to international recommendations, early RA is a disease lasting more than 6 weeks but less than 6 months (ACR 2015) [19, 20]. The practical value of any research lies in its significance for the average doctor. Practicing medics divide patients with RA

according to the duration of the disease into three stages: early (forming) RA (up to 2 years), steady RA (from 2 to 5 years) and late (difficult-to-treat) RA (more than 5 years).

Subdivision of the RA course three stages in our study accounted for different pathophysiological processes occurring at its early stage, advanced stage and late stage (completely formed pathological condition). Various immune, biochemical and endocrine shifts cause changes in the course of the disease. One of the most important symptoms noted during this period and most often forcing patients and primary care doctors to diagnose the disease and contact rheumatologists is the dysfunction of the joints. It takes about two years from the onset of the disease for the patient and the attending physician to understand the irreversibility of the articular syndrome. Many studies carried out by various researchers facilitated the identification of major morphological changes in joint tissues, intense angiogenesis, and synovial hyperplasia with a pronounced vascularization [21]. In RA patients, inflammatory exudative processes and angiogenesis predominated from its onset to two years of the disease [22]. During this period, high levels of ATII were observed. The latter was actively involved in vascular inflammation via inducing the expression of IL-1, IL-18, and TNF α [23]. Previous studies confirmed that the blood level of ATII in patients with highly active RA was 1.5 times higher than in patients with low or moderate RA activity. Analysis of variance demonstrated that the degree of RA activity was associated solely with the blood level of ATII [17].

As the active inflammatory process subsided over a period of 2 to 5 years from the onset of RA, active angiogenesis and inflammation were replaced by the growth and development of connective tissue. Proliferative and atrophic changes in RA became predominant after 5 years [21, 24, 25]. The thickness of the synovium, pannus, atrophic changes, mucinous edema, and fibrinoid changes increase with the formation of osteochondral lesions, characterizing proliferative and destructive processes [26]. During this period, there is an increase in ALD concentration, which plays an active role in the development of fibrosis. This pattern is characteristic for diseases of the kidneys, heart and lungs [12, 15]. Simultaneously, ATII content decreases. Mathematical processing and comparison of indicator values between the study groups clearly showed that the ATII level declined with increasing duration of the disease, and there were statistically significant differences in the indicators of patients between the groups of RA duration <2 years, 2-5 years and >5 years ($p < 0.05$). Moreover, the level of ALD clearly increased with increasing duration of the disease, and statistically significant differences between groups were exhibited by all indicators. When graphically displaying the data presented in [Table 4](#) and [Table 5](#)

(Figure 2), the dynamics of the studied components of the RAAS was more explicit than in Figure 1. High values of ATII and low concentrations of ALD (virtually indistinguishable from the control values) were present at an early stage of RA. Subsequently, ATII declined to a minimum (also statistically indistinguishable from the control values) with a long course of the disease; simultaneously, ALD values increased, and the curves intersected during the period of 2-5 years from the onset of RA.

The different patterns of changes in ATII and ALD can be explained by the fact that, despite the integration of the RAAS into a single system, all its components are more or less autonomous. For instance, the phenomenon of aldosterone escape was established and, consequently, in heart failure, it is advisable to prescribe simultaneously an ACE inhibitor and an angiotensin receptor blocker (ARB) [12, 27].

Hence, the discrepancy between theoretical and laboratory data on the effect of the RAAS and the effectiveness of its blockade in RA, along with conflicting clinical data obtained by various research groups, can be explained by the fact that the activity of the RAAS, as well as the course of RA, varies depending on the duration and stage of the disease development. Significant changes in the RAAS are observed up to two years and after five years of illness. RA has different stages of progression and differs significantly in morphogenesis in the early (up to 2 years) and late (more than 5 years) periods.

The RAAS is heterogeneous; hence, its integration into a single system is ambiguous. The significance of various components of the RAAS in RA is determined by the pathophysiological processes in the patient's body. Blockades of various RAAS components should be differentiated and either correspond to the individual level of indicator values for each patient, or match the stages of RA associated with the duration of the disease.

Limitations

Our data and actual conditions did not allow observing a sufficient number of desirable patients, which was associated with the late detection of RA, the small number of patients and, as a consequence, the low representativeness of the groups. Definitive diagnosis and the start of regular follow-up for most practicing rheumatologists begins when RA has lasted two to three years. Of course, the activity of the RAAS can also be influenced by the state of other systems, including the sympathoadrenal system, natriuretic peptides, vasopressin, thyroid hormones, sex hormones, etc. It would be interesting to investigate in detail water-and-salt metabolism, taking into account the clearance of electrolytes and peptides. It is possible that subclinical changes in internal organs, which can be detected during a comprehensive laboratory and instrumental examination, may have some effect on the state of the RAAS. However, it is problematic to conduct such extensive study within one research project. It should be noted that we studied some indicators that influence the state of the RAAS and, in particular, vascular endothelial growth factors, vascular tone, the morphological and functional state of blood vessels, the entire cardiovascular system, etc., which was partially presented in our previous publications. At the same time, it is not possible to present our full results in a separate article, because we plan to include them in a monograph we are currently working on. Our results require further investigation on a much larger sample, especially in the early stages of RA disease.

Conclusion

The RAAS is heterogeneous and its integration into a single system is ambiguous. The significance of various components of the RAAS in RA is determined by the pathophysiological processes in the patient's body. Blocking of various components of the RAAS should be differentiated and either correspond to some specific levels of indicators for each patient, or match to the stages of RA associated with the duration of the disease.

Conflict of interest

The authors report no conflicts of interest.

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Authors:

Boris A. Rebrov – MD, DSc, Professor, Head of Department of Internal Medicine, Graduate School, St. Luke State Medical University of Lugansk, Lugansk, Russia. <https://orcid.org/0000-0003-1303-9142>.

Elena B. Komarova – MD, DSc, Professor, Department of Internal Medicine, Graduate School, St. Luke State Medical University of Lugansk, Lugansk, Russia. <https://orcid.org/0000-0002-3476-3351>.

Antonina K. Knyazeva – MD, PhD, Assistant Professor, Department of Internal Medicine, Graduate School, St. Luke State Medical University of Lugansk, Lugansk, Russia. <https://orcid.org/0000-0003-0247-5328>.