ISSN: 2181-3337 | SCIENTISTS.UZ VOLUME 5 ISSUE 7 JULY 2026

CLINICAL PROGRESSION OF RHEUMATOID ARTHRITIS AND HEMOVASCULAR REMODELING: ASSOCIATIONS BETWEEN SEROSTATUS, FUNCTIONAL CLASS, ENDOTHELIAL DYSFUNCTION AND HEMOSTATIC ACTIVITY

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DOI: 10.67620/sai.57d0004

ABSTRACT

Rheumatoid arthritis is a systemic autoimmune disease whose progression is frequently accompanied by vascular inflammation, endothelial dysfunction, and hemostatic imbalance. This study assessed the relationships among disease duration, serological status, American College of Rheumatology functional class, platelet hemostasis, coagulation abnormalities, and endothelial dysfunction. The study included 85 patients with rheumatoid arthritis and 30 healthy controls. Patients were classified into three groups according to disease duration: up to 6 months (n = 24), 6 months to 1 year (n = 33), and more than 2 years (n = 28). Serostatus, functional class, platelet indices, coagulation parameters, and endothelial dysfunction markers were analyzed. The proportion of seronegative rheumatoid arthritis declined from 45.8% in the first group to 39.4% in the second and 28.6% in the third, whereas seropositive disease increased to 71.4% among patients with disease duration exceeding 2 years. The frequency of functional classes I and II decreased as disease duration increased, while classes III and IV became progressively more common. Platelet hemostatic activity was most pronounced during the first year of disease, whereas coagulation abnormalities became more prominent in patients with longer disease duration. Endothelial dysfunction persisted across all groups. These findings indicate that rheumatoid arthritis progression is associated with a transition from early platelet-dominant activation to later coagulation-dominant hypercoagulability, while endothelial dysfunction remains present throughout the disease course. Seropositive status and advanced functional limitation may therefore characterize a more severe hemovascular phenotype..

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Keywords: *rheumatoid arthritis, serostatus, functional class, endothelial dysfunction, hemostasis, D-dimer, endothelin-1, von Willebrand factor.*

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Introduction

Rheumatoid arthritis is a chronic systemic autoimmune disease characterized by persistent synovial inflammation, progressive joint destruction and functional impairment [1,2]. Although joint involvement remains the main clinical feature of rheumatoid arthritis, increasing evidence shows that the disease also affects the vascular endothelium and hemostatic system [3,4,11-13].

Systemic inflammation in rheumatoid arthritis contributes to endothelial activation, platelet stimulation and coagulation imbalance. These changes may increase the risk of microcirculatory disturbances, cardiovascular complications and thrombotic events [3,5-7,11-13,15]. Endothelial dysfunction is reflected by increased endothelin-1, soluble intercellular adhesion molecule and von Willebrand factor, while hemostatic activation is manifested by increased platelet adhesion and aggregation, elevated fibrinogen, increased D-dimer, shortened clotting times and higher prothrombin index [5-7,11-13,15].

Patients with rheumatoid arthritis have an increased risk of venous thromboembolism and cardiovascular complications, especially when systemic inflammation remains active [8-10,14]. Therefore, vascular and hemostatic risk assessment may have additional value in patients with different disease duration, serological status and functional limitation.

The present study was designed to evaluate how serostatus and ACR functional classes change with rheumatoid arthritis duration and how these changes relate to platelet hemostasis, coagulation hemostasis and endothelial dysfunction.

Materials and Methods

This clinical and laboratory study was conducted at the multidisciplinary clinic of Tashkent State Medical University during 2022-2025. The study included 85 patients with rheumatoid arthritis and 30 practically healthy individuals as a control group.

Patients were divided into three groups according to disease duration: group 1 included patients with rheumatoid arthritis up to 6 months, n=24; group 2 included patients with rheumatoid arthritis from 6 months to 1 year, n=33; and group 3 included patients with rheumatoid arthritis lasting more than 2 years, n=28.

Inclusion criteria were confirmed rheumatoid arthritis according to EULAR/ACR criteria, age above 18 years, moderate disease activity according to DAS28 and informed consent. Exclusion criteria included severe somatic diseases, acute infections, uncontrolled arterial hypertension, use of antiplatelet agents, anticoagulants or statins, and refusal to participate.

The following parameters were analyzed: seropositive and seronegative rheumatoid arthritis, ACR functional classes, platelet count, platelet adhesion, platelet aggregation, activated partial thromboplastin time, prothrombin index, thrombin time, fibrinogen, D-dimer, endothelin-1, sICAM and von Willebrand factor.

Quantitative values are presented as M±m. Differences compared with the control group were considered statistically significant at $p<0.05$.

Results

Serostatus and functional classes

Serostatus analysis demonstrated that seronegative rheumatoid arthritis became less frequent as disease duration increased. In group 1, seronegative rheumatoid arthritis was detected in 45.8% of patients. In group 2, this proportion decreased to 39.4%, and in group 3 it decreased further to 28.6%. In contrast, seropositive rheumatoid arthritis increased from 54.2% in group 1 to 60.6% in group 2 and 71.4% in group 3.

Functional status also worsened with disease duration. ACR functional class I was found in 33.3% of group 1 patients, 21.4% of group 2 patients and 14.3% of group 3 patients. Class II decreased from 41.6% to 38.4% and 28.6%, respectively. In contrast, class III increased from 21.0% in group 1 to 34.1% in group 2 and 46.4% in group 3. Class IV increased from 4.1% in group 1 to 6.1% in group 2 and 10.7% in group 3.

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Table 1. Serostatus and ACR functional classes according to disease duration

Parameter	Group 1, n=24	Group 2, n=33	Group 3, n=28
Seropositive RA, %	54.2	60.6	71.4
Seronegative RA, %	45.8	39.4	28.6
ACR class I, %	33.3	21.4	14.3
ACR class II, %	41.6	38.4	28.6
ACR class III, %	21.0	34.1	46.4
ACR class IV, %	4.1	6.1	10.7

Platelet hemostasis and endothelial dysfunction

Platelet count increased from 254±28 in the control group to 332±30 in group 1 and 450±41 in group 2. In group 3, platelet count was 278±29 and did not differ substantially from the control value. Platelet adhesion increased from 30±4 in controls to 46±5 in group 1 and 52±6 in group 2, while in group 3 it was 26±3. Similar changes were observed in platelet aggregation.

Endothelial dysfunction markers showed a different pattern. Endothelin-1 progressively increased from 1.7±0.2 pg/ml in controls to 2.9±0.3 pg/ml in group 1, 3.5±0.4 pg/ml in group 2 and 4.1±0.4 pg/ml in group 3. sICAM increased from 220±24 ng/ml in controls to 298±26, 324±29 and 360±32 ng/ml, respectively. Von Willebrand factor increased from 98±10% to 139±13%, 152±16% and 148±11%.

Table 2. Platelet hemostasis and endothelial dysfunction markers

Parameter	Control, n=30	Group 1, n=24	Group 2, n=33	Group 3, n=28
Platelet count	254±28	332±30*	450±41***	278±29
Platelet adhesion	30±4	46±5*	52±6**	26±3
Maximum aggregation rate	33±4	46±4*	49±5*	30±3
Maximum aggregation degree	38±3	49±4*	52±5*	35±4
Endothelin-1, pg/ml	1.7±0.2	2.9±0.3**	3.5±0.4**	4.1±0.4**
sICAM, ng/ml	220±24	298±26*	324±29**	360±32***
Von Willebrand factor, %	98±10	139±13*	152±16**	148±11**

*Note: *p<0.05; **p<0.01; ***p<0.001 compared with the control group.*

Coagulation hemostasis

Coagulation parameters showed progressive hypercoagulability with increasing disease duration. APTT decreased from 30.0±2.8 s in controls to 24.2±2.2 s in group 1, 21.6±2.0 s in group 2 and 19.5±2.6 s in group 3. Prothrombin index increased from 97±8% in controls to 105±9%, 128±10% and 136±9%, respectively.

Thrombin time shortened from 18.8±1.0 s in controls to 16.6±1.3 s in group 1, 15.3±1.3 s in group 2 and 14.6±1.2 s in group 3. Fibrinogen increased from 2.83±0.22 g/L to 3.55±0.30 g/L, 4.46±0.43 g/L and 4.66±0.24 g/L. D-dimer increased from 254±29 ng/ml to 380±43, 460±41 and 450±49 ng/ml.

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Table 3. Coagulation hemostasis according to rheumatoid arthritis duration

Parameter	Control, n=30	Group 1, n=24	Group 2, n=33	Group 3, n=28
APTT, s	30.0±2.8	24.2±2.2	21.6±2.0*	19.5±2.6**
Prothrombin index, %	97±8	105±9	128±10*	136±9**
Thrombin time, s	18.8±1.0	16.6±1.3	15.3±1.3*	14.6±1.2**
Fibrinogen, g/L	2.83±0.22	3.55±0.30	4.46±0.43**	4.66±0.24***
D-dimer, ng/ml	254±29	380±43*	460±41***	450±49***

*Note: *p<0.05; **p<0.01; ***p<0.001 compared with the control group.*

Figure 1 is provided below to visually summarize the central quantitative findings described in the Results section.

Figure 1. Disease progression, serostatus, and hemovascular remodeling in rheumatoid arthritis

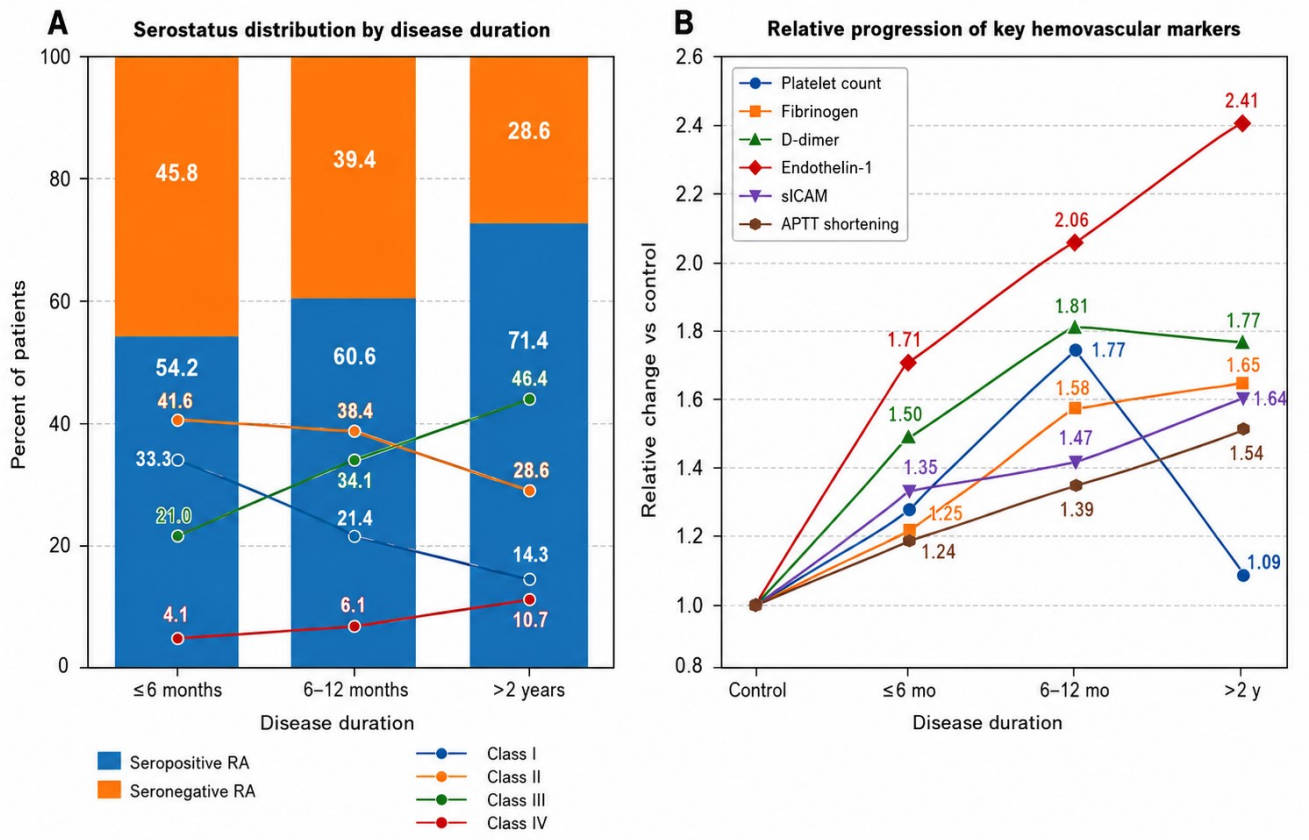


Figure 1. Disease progression, serostatus, and hemovascular remodeling in rheumatoid arthritis.

Note. Panel A shows the distribution of seropositive and seronegative rheumatoid arthritis together with ACR functional classes across disease-duration groups. Panel B illustrates relative changes versus the control group for selected platelet, coagulation, and endothelial markers. The figure was prepared from the summarized numerical data reported in Tables 1–3.

Discussion

The present study demonstrates that clinical progression of rheumatoid arthritis is accompanied by distinct hemovascular remodeling. The decrease in seronegative rheumatoid arthritis and increase in seropositive forms with disease duration suggest that longer disease course is associated with a more immunologically defined phenotype [1,2].

The worsening of ACR functional classes confirms progressive functional impairment. The proportion of patients with ACR classes III-IV increased with disease duration, while classes I-II

decreased. This functional deterioration occurred in parallel with persistent endothelial dysfunction and increasing coagulation abnormalities.

The hemostatic pattern was not uniform. In patients with disease duration up to one year, platelet count, adhesion and aggregation were increased, indicating prominent platelet activation in early rheumatoid arthritis. In patients with disease duration longer than two years, platelet parameters were less pronounced, while coagulation disturbances became dominant. This suggests a transition from platelet-driven hemostatic activation to coagulation-dominant hypercoagulability [3,7,15].

Endothelial dysfunction persisted in all disease-duration groups. Endothelin-1, sICAM and von Willebrand factor were elevated even in the earliest group and remained increased in long-standing disease. This confirms that vascular endothelial involvement is not secondary only to late complications but is an early and persistent component of rheumatoid arthritis [3-7,11-13].

The combination of advanced seropositive disease, higher ACR functional classes, persistent endothelial dysfunction and coagulation activation may define a subgroup of patients with increased vascular and thrombotic risk. Therefore, assessment of endothelial and hemostatic markers may have practical value in addition to conventional rheumatologic evaluation [8-10,14].

Conclusions

1. Rheumatoid arthritis progression is associated with changes in serostatus, functional status and hemovascular parameters.

2. Seronegative rheumatoid arthritis decreased from 45.8% to 28.6% with increasing disease duration, while seropositive disease increased to 71.4%.

3. ACR functional classes III-IV became more frequent in long-standing disease, indicating progressive functional limitation.

4. Platelet hemostasis was most activated during the first year of rheumatoid arthritis.

5. Coagulation hyperactivity became more pronounced in patients with disease duration longer than two years.

6. Endothelial dysfunction persisted in all groups and increased with disease duration.

7. Serostatus, ACR functional class, endothelial dysfunction and hemostatic markers should be evaluated together for more complete clinical risk stratification in rheumatoid arthritis.

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