ORIGINAL ARTICLE

Prevalence of antiphospholipid antibodies in rheumatoid arthritis patients and relationship with disease activity

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KEY WORDS

anticyclic citrullinated peptide antibodies, antiphospholipid antibodies, immunoglobulin M rheumatoid factor, rheumatoid arthritis

ABSTRACT

INTRODUCTION It is still unclear how important the presence of antiphospholipid antibodies (aPL) is in patients with rheumatoid arthritis (RA).

OBJECTIVES The aim of the study was to assess the prevalence of selected aPL in RA patients and their correlation with the presence of markers for RA antibodies and with disease activity.

PATIENTS AND METHODS The study group consisted of 97 patients with RA who had never been treated with biological agents. In all patients, serum anticardiolipin antibodies (aCL), anti-β_2-glycoprotein I antibodies (a-β_2-GPI), lupus anticoagulant (LAC), immunoglobulin M (IgM) rheumatoid factor (RF), and anticyclic citrullinated peptide antibodies (anti-CCP) were measured and disease activity was assessed.

RESULTS The presence of aPL was observed in 27 patients (27.8%): aCL in 20 patients (20.6%), a-β_2-GPI in 12 patients (12.4%), and LAC in 1 patient (1%). Positive aCL of low or medium levels were detected in the IgM class in 11 patients (11.3%) and in the IgG class in 12 patients (12.5%). Positive a-β_2-GPI of low and medium levels were found only in the IgM class. The presence of LAC was associated with aCL-IgM and a-β_2-GPI-IgM. A significant correlation was observed between the presence of anti-CCP and different types of aPL. There was no correlation between aPL and IgM-RF or disease activity markers.

CONCLUSIONS The prevalence of aPL in patients with RA is relatively high. There is a relationship between the prevalence of aPL and anti-CCP-serological marker of RA, but there are no significant correlations between disease activity and the presence of aPL.

INTRODUCTION It is well known that autoimmune disorders are involved in the pathogenesis of rheumatoid arthritis (RA). Different types of autoantibodies can be detected in the serum of patients with RA[1,2] including immunoglobulin M rheumatoid factor (IgM-RF) and anticitrullinated protein antibodies (ACPA), which are serological markers of RA and play an important role not only in the diagnosis but also in the assessment of disease activity and prognosis.[3-6] ACPA include different types of antibodies such as anticyclic citrullinated peptide antibodies (anti-CCP), citrullinated fibrinogen, citrullinated α-enolase, and mutated citrullinated vimentin.[7] Antiphospholipid antibodies (aPL) are crucial in the pathogenesis of antiphospholipid syndrome (APS). Several types of aPL widely used in diagnosis include lupus anticoagulant (LAC), anticardiolipin antibodies (aCL), and anti-β_2-glycoprotein I antibodies (a-β_2-GPI).[8,9] These antibodies may occur not only in APS, but also in other disorders, particularly in connective tissue diseases, other autoimmune diseases, infections, neoplasms, and as a result of drug use.[10-13] The prevalence and significance of aPL in patients with RA was investigated in several papers; however, there is no agreement as to their clinical role in the course of RA. Some data suggested the potential effect of aCL on extra-articular manifestations of RA. A number of authors indicated that aPL prevalence may vary between different groups of patients depending on disease duration and activity, the age of patients, and laboratory techniques.[1,2,14] In literature, the estimated prevalence of aPL in RA patients varies from 4% to 49%, with the average prevalence of 28% and median prevalence of 22%, based on the data collected from several studies.[1]

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The aim of the current study was to assess the prevalence of selected aPL in RA patients. Moreover, we aimed to analyze the correlations between aPL, marker antibodies of RA, and disease activity.

PATIENTS AND METHODS The study group consisted of 97 consecutive patients with RA treated at the Department of Rheumatology and Connective Tissue Diseases, Medical University of Lublin, Poland. The informed consent was obtained from all patients according to the Declaration of Helsinki. The design of the study was approved by the Ethical Committee of the Medical University of Lublin. All patients fulfilled the American College of Rheumatology criteria for the diagnosis of RA.[15] Patients who had been previously treated with biological agents were excluded from the study.

Data collection Demographic and clinical data were collected using a structured interview, review of medical records, physical examination, and laboratory tests. Disease activity was measured using the Disease Activity Score based on the evaluation of 28 joints (DAS28) calculated with the number of tender and swollen joints, erythrocyte sedimentation rate (ESR), and the patient's global assessment of disease activity on the visual analogue scale (VAS).[16] An erosive form of RA was diagnosed in patients who presented erosions on joint surfaces of the bones on radiograms of the hands or feet or both.

Assessment of antiphospholipid antibodies Blood samples were collected after an overnight fasting. Plasma and serum samples were stored at –70°C for further assessment of antibodies.

TABLE 1 Basic characteristics of patients with rheumatoid arthritis

Variable	Value
sex, female/male	80 (82.5) / 17 (17.5)
age, y	54.2 ±12.2 (range, 20–90)
current smoking	23 (23.7)
disease duration, y	10.4 ±7.7 (range, 0.5–35)
long-standing RA: ≥10 years	41 (42.3)
erosive RA	82 (84.5)
extra-articular symptoms	43 (44.3)
positive IgM-RF	63 (64.9)
positive anti-CCP	83 (85.6)
positive ANA	42 (43.3)
DAS28, score 0–10	5.9 ±1.1 (range, 3.2–8.3)
high disease activity: DAS28 >5.1	69 (71.1)
current therapy with prednisone	73 (75.3)
current therapy with DMARDs	96 (98.9)

Data are presented as mean ± standard deviation or number (%).

Abbreviations: ANA – antinuclear antibodies, anti-CCP – anticyclic citrullinated peptide antibodies, DAS28 – Disease Activity Score with 28-joint counts, DMARDs – disease-modifying antirheumatic drugs, IgM-RF – immunoglobulin M rheumatoid factor, RA – rheumatoid arthritis

The measurement of serum IgM and IgG aCL concentrations was performed using an enzyme-linked inmunosorbent assay (ELISA) with standard diagnostic kits (AUOSTAT II ACA Isotype, HYCOR Biomedical, United States). Serum a-β_2-GPI concentration in the IgG and IgM classes was measured using ELISA with commercial kits: Anti-β_2-Glycoprotein 1 ELISA IgM EA 1632–9601 M and Anti-β_2-Glycoprotein 1 ELISA IgG EA 1632–9601 G (EUROIMMUN, Germany). All immunoenzymatic tests were performed with the use of the Elisa-Mat 3000 device in the laboratory of the Department of Rheumatology and Connective Tissue Diseases, Medical University of Lublin. aCL (IgM or IgG class) was considered positive at the serum concentration of ≥15 MPL/ml or GLP/ml. a-β_2-GPI was considered positive at the concentration above 20 RU/ml.

Assessment of lupus anticoagulant Plasma samples were examined for the presence of LAC using the coagulometric method and based on the standard procedures recommended by the International Society on Thrombosis and Haemostasis in 1995.[17]

Assessment of rheumatoid arthritis-specific antibodies and antinuclear antibodies Serum samples were simultaneously assessed for serological markers of RA, IgM-RF and anti-CCP, and for antinuclear antibodies (ANA) by indirect immunofluorescence (IIF). All serum samples of RA patients were analyzed in a single session according to the manufacturer's instructions.

Anti-CCP were determined using a commercially available third generation ELISA assay (QUANTA Lite CCP3.1 IgG/IgA ELISA, INOVA Diagnostics, United States) with a positive cut-off value of 20 U/ml or higher. IgM-RF was determined using the IgM antirheumatoid factor ELISA (EUROIMMUN, Germany) with the recommended upper limit of the normal range of 20 RU/ml. The analysis of ANA was performed using IIF.

Statistical analysis For statistical analysis, we used the STATISTICA 6.0 software. The results were expressed as mean ± standard deviation or number and percentage. The variables were tested for normality using the Kolmogorov-Smirnov test. Correlations were calculated using the Spearman's rank and the Yule correlation coefficient. For all tests, *P* values of less than 0.05 were considered significant.

RESULTS Demographic and disease-related variables in patients with rheumatoid arthritis The characteristics of patients are presented in TABLE 1. High disease activity (DAS28 >5.1) was noted in 69 patients (71.1%) and low or moderate RA activity (DAS28 ≤5.1) in 28 patients (28.9%). Long-standing RA (disease duration ≥10 years) was observed in 41 patients (42.3%). Most patients were positive for IgM-RF and anti-CCP and had erosions on radiographs. ANA were detected

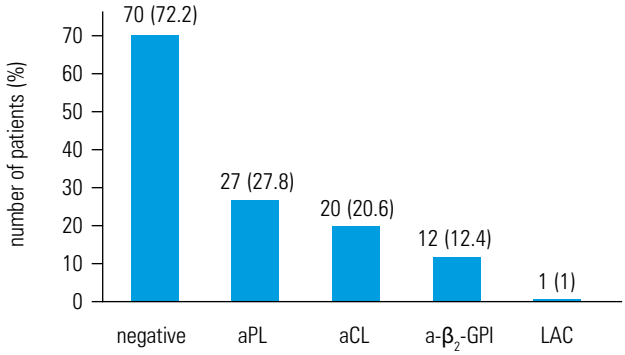

FIGURE Incidence of antiphospholipid antibodies in patients with rheumatoid arthritis
Abbreviations: a-β_2-GPI – anti-β_2-glycoprotein I antibodies, aCL – anticardiolipin antibodies, aPL – antiphospholipid antibodies, LAC – lupus anticoagulant

TABLE 2 Prevalence and coexistence of different types of antiphospholipid antibodies in patients with rheumatoid arthritis

Patients with positive antibodies	
at least 1 type of aPL positive	27 (27.8)
aCL	20 (20.6)
a-β_2-GPI	12 (12.4)
LAC	1 (1)
2 of 3 types of aPL positive	7 (7.2)
aCL + a-β_2-GPI	7 (7.2)
aCL + LAC	0
a-β_2-GPI + LAC	0
3 types of aPL positive	1 (1)
aCL + a-β_2-GPI + LAC	1 (1)

Data are presented as number (%).

Abbreviations: see FIGURE

TABLE 3 Prevalence and titers of anticardiolipin antibodies in patients with rheumatoid arthritis

Antibodies	Total	Level		
		high (>80 IU/ml)	medium (40–80 IU/ml)	low (15–39 IU/ml)
aCL IgM	11 (11.3)	0	3 (3.1)	8 (8.2)
aCL IgG	12 (12.4)	0	1 (1)	11 (11.3)

Data are presented as number (%).

Abbreviations: IgG – immunoglobulin G, others – see TABLE 1 and FIGURE

TABLE 4 Prevalence and titers of anti-β_2-glycoprotein I antibodies in patients with rheumatoid arthritis

Antibodies	Total	Level		
		high (>90 RU/ml)	medium (40–89 RU/ml)	low (20–39 RU/ml)
a-β_2-GPI IgM	12 (12.4)	0	4 (4.1)	8 (8.2)
a-β_2-GPI IgG	0	0	0	0

Data are presented as number (%).

Abbreviations: see, TABLES 1, 2, and FIGURE

in 42 patients (43.3%). At the time of the examination almost all patients (except 1) were treated with disease-modifying antirheumatic drugs (DMARDs) and 75% of the patients additionally with low-dose prednisone (≤10 mg/day). None of the patients were treated with biological DMARDs. The group of patients treated with DMARDs included patients who had previously received: 1 DMARD (10 patients; 10.3%), 2 DMARDs (18; 18.6%), 3 DMARDs (24; 24.7%), 4 DMARDs (27; 27.8%), 5 DMARDs (10; 10.3%), 6 DMARDs (6; 6.2%), and 8 DMARDs (1; 1%).

Extra-articular symptoms during the course of RA were reported in 44 patients and included rheumatoid nodules (22 patients), sicca syndrome (11 patients), amyloidosis (8 patients), interstitial lung disease (7 patients), and APS (1 patient). Clinical signs of thrombosis were documented in the history of 4 patients (venous thrombosis of the lower limbs); 2 patients experienced spontaneous abortion. However, the diagnosis of APS according to the classification criteria[18] was confirmed only in 1 patient.

Current smoking was reported in 23 patients (23.7%). None of the patients were positive for antihepatitis C antibodies.

Prevalence of antiphospholipid antibodies in patients with rheumatoid arthritis At least 1 type of aPL was found in 27 patients (27.8%) (FIGURE, TABLE 2). aCL antibodies were detected in 20 patients (20.6%), of which aCL-IgM were found in 11 patients (11.3%) and aCL-IgG in 12 patients (12.4%) (TABLE 3). The titer of antibodies was medium or low; there was no patient with high aCL level (TABLE 3). Two patients (2.1%) had elevated levels of aCL in both classes (IgM and IgG): in 1 patient low levels in both classes were observed and in the other – low levels in the IgG class and medium levels in the IgM class.

a-β_2-GPI antibodies were positive in 12 patients (12.4%; in all patients in the IgM class; TABLE 4).

In a number of patients, the coexistence of different types of aPL was observed (TABLE 2). All 3 types of antibodies were detected in 1 patient. The coexistence of 2 types of aPL was noted in 7 patients (aCL and a-β_2-GPI).

Associations between antiphospholipid antibodies and rheumatoid arthritis and disease activity markers Positive aCL were observed only in women. The difference was statistically significant (P = 0.02; Yule's coefficient = 0.235).

Significant negative correlations were found between the presence of anti-CCP and aCL and a-β_2-GPI in the IgM class (TABLE 5).

In patients treated with low-dose glucocorticoids, there was a tendency for lower incidence of different types of aPL; however, differences were not statistically significant (aCL: P = 0.09; Yule's coefficient = –0.175; a-β_2-GPI: P = 0.08; Yule's coefficient = –0.182).

There was no correlation between the presence of different types of aPL and patients' age,

TABLE 5 Correlations between anticyclic citrullinated peptide antibodies and antiphospholipid antibodies in patients with rheumatoid arthritis

Antibodies	*P*	Yule's coefficient
aCL and anti-CCP	0.003	–0.338
a-β_2-GPI IgM and anti-CCP	0.03	–0.256
(a-β_2-GPI IgM + aCL) and anti-CCP	0.006	–0.315

Abbreviations: see **TABLE 1** and **FIGURE**

current smoking, disease duration, extra-articular symptoms, erosive form of RA, and activity of the disease measured by DAS28. The occurrence of aPL in RA was not associated with the positivity for IgM-RF (n = 63; *P* = 0.883; Yule's coefficient = 0.150) or with the presence of ANA (n = 42; *P* = 0.145; Yule's coefficient = 0.174).

DISCUSSION Various reports on the prevalence of aPL in patients with RA are available in the literature. The estimated incidence ranges between 4% and 49%,[1,2,13,19-21] which is probably due to different patient selection criteria, disease duration and activity, methods of treatment, and diagnostic techniques. aCL in the IgG class were detected in 11% to 21% of the patients[1,19,20] and in the IgM class in 1% to 4.4% of the patients.[21] The presence of a-β_2-GPI was noted in up to 21% of the patients with RA,[22] while LAC could be detected in 3.8%.[21] In the group of 184 patients with RA, Seriolo et al.[21] observed the medium titers of aCL in the IgG and IgM classes. Del Pino-Montes et al.[19] reported the presence of aPL in 19% of the patients with RA, mainly as aCL-IgG.[19] a-β_2-GPI were not detected in any of the above studies.[19,21] A higher prevalence of aPL (49%) in 90 patients with RA was observed by Keane et al.[14] Elevated levels of aCL were detected in 32% of 173 patients with RA in the study by Wolf et al.[23] They reported that the presence of aCL was correlated with more frequent occurrence of rheumatoid nodules, livedo reticularis, leukocytoclastic vasculitis, and thrombophlebitis. However, they did not observe any correlations between the elevated levels of aCL and the signs and symptoms of APS. They suggested that aCL could have different specificity in RA compared with other systemic diseases.[23] Palomo et al.[22] examined 84 patients with RA and found aPL in 19.1% of the patients, with aCL present in 8.3%, a-β_2-GPI in 7.2%, and LAC in none of the patients.[22]

The prevalence of aPL in RA patients reported in the present study is consistent with the available data. In comparison, in our previous studies, we observed a greater prevalence of aCL in the group of 40 patients with systemic lupus erythematosus (SLE) without clinical manifestations of APS (in 35% of the patients). In the same group of SLE patients, a-β_2-GPI antibodies in the IgM class were found in 30% and in the IgG class in 7.5% of the patients.[24]

The main components of the current management of RA include synthetic and biological DMARDs.[25,26] The potential effect of treatment with DMARDs (mainly biological agents) on an increase in aPL levels has been widely discussed in the literature. A number of authors believe that the presence of aCL could worsen the response to treatment with antitumor necrosis factor (anti-TNF) drugs. One of the theories explaining the phenomenon of the increased production of antibodies in patients treated with anti-TNF drugs is focused on the hyperactivity of autoreactive B-cells due to a decrease in interleukin 10 caused by lower TNF concentration. Another theory suggests that an increase in aCL concentrations during anti-TNF therapy might be caused by latent infections.[2] Ferraccioli et al.[27] reported elevated aCL levels in RA patients treated with etanercept. A possible explanation was higher incidence of infections during biological treatment and persistence of bacterial DNA, which could induce the production of ANA and aCL.[27] It was reported that the prevalence of aCL in RA patients increased significantly with prolonged time of anti-TNF treatment (etanercept, infliximab).[28] It might be associated with advanced patients' age, high disease activity, and a large number of DMARDs used. Patients treated with infliximab and having elevated aCL levels more often suffered from allergic reactions during the biological therapy and the therapeutic response was more often insufficient.[28]

In our study, we included only RA patients who had never been treated with biological drugs. However, in most patients, high disease activity was observed and they were treated with several DMARDs before entering the study. Most patients were also treated with glucocorticoids and there was a tendency for lower incidence of aPL in those patients.

It has been reported that the presence of aCL is associated with worse RA prognosis, with extra-articular manifestations such as vasculitis, chronic infections, and higher cardiovascular and cancer risk. That is why the assessment of aCL is thought to be useful as a marker of unfavorable prognosis in RA patients with an aggressive form of the disease.[2,29] In RA patients with aPL, Keane et al.[14] reported more frequent extra-articular manifestations and higher C-reactive protein (CRP) concentrations. A significant correlation between aPL and CRP or ESR was described in RA patients by Rebee et al.[30] A similar correlation between CRP and aCL was reported by Del Pino-Montes et al.[19] However, they did not find any correlations either between aCL and articular destruction or between aCL and disease activity assessed with DAS28. Vittecoq et al.[31] observed significant correlations between aCL and CRP levels and ANA presence. However, there was no association between aCL and RF presence or clinical symptoms of RA. In a study by Walewska et al.[29] in RA patients who were aCL positive, ANA were detected more often and in higher titers, and also more advanced destruction of joints was observed. There were no correlations between aPL

and RF level, CRP concentration, ESR, and DAS28. The possible role of aPL in the pathogenesis of atherosclerosis and increased cardiovascular risk in RA patients is still being investigated.[32,33] Implications of aPL presence in RA patients without any other features of APS are still unknown.[34]

The results of our study are consistent with the available data reporting the lack of a relationship between aPL presence and patients' age, disease duration, DAS28, clinical signs of APS, and the presence of ANA and IgM-RF. However, we presented significant negative correlations between aPL (aCL, a-β_2-GPI) and anti-CCP antibodies, suggesting different types of immune disorders in the course of RA. To our knowledge, there have been no reports so far concerning the relationship between ACPA and aPL.

ACPA are highly specific and sensitive diagnostic markers of RA.[35] According to the current view on RA pathogenesis, there are 2 subgroups of patients: ACPA-positive and ACPA-negative (constituting 2 different subsets of the disease).[36-38] ACPA-positive patients are characterized by a more aggressive course of the disease; thus, ACPA may be useful not only in the diagnosis of RA but also as a prognostic marker.[37,38] ACPA are thought to be an important marker of early RA.[39-41] However, Lee et al.[42] reported that anti-CCP titers are increased in RA patients with exposure to tobacco and not associated with the clinical parameters of the disease.

The strengths of the present study are as follows: detailed immunological characteristics of the patients; a large number of patients included in the study; no biological DMARDs used in any of the patients (such treatment may induce aPL production). Most importantly, our study has been the first in the literature to report the association between the presence of aPL and anti-CCP antibodies in patients with RA.

Our study also have some limitations. First, high disease activity was observed in the majority of patients. Second, further evaluation should be performed in similar groups of patients. Third, the size of the study population was limited. Finally, measurements were conducted at a single time point.

In conclusion, the prevalence of aPL is relatively high in patients with RA. There is a relationship between aPL and anti-CCP-serological marker of RA; however, we did not confirm any correlations between aPL and disease activity.

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ARTYKUŁ ORYGINALNY

Częstość występowania przeciwciał antyfosfolipidowych u chorych na reumatoidalne zapalenie stawów i ich związek z aktywnością choroby

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SŁOWA KLUCZOWE

czynnik reumatoidalny klasy IgM, przeciwciała antyfosfolipidowe, przeciwciała przeciwko cyklicznemu cytrulinowanemu peptydowi, reumatoidalne zapalenie stawów

STRESZCZENIE

WPROWADZENIE Znaczenie występowania przeciwciał antyfosfolipidowych (*antiphospholipid antibodies* – aPL) u chorych na reumatoidalne zapalenie stawów (RZS) nie jest w pełni jasne.

CELE Celem naszej pracy była ocena częstości występowania wybranych aPL u chorych na RZS, ich związku z obecnością przeciwciał markerowych dla RZS oraz z aktywnością choroby.

PACJENCI I METODY Grupa badana liczyła 97 chorych na RZS, nigdy wcześniej nieleczonych lekami biologicznymi. U wszystkich chorych oznaczano w surowicy stężenia przeciwciał antykardiolipinowych (*anticardiolipin antibodies* – aCL), przeciwciał przeciwko β_2-glikoproteinie I (a-β_2-GPI), oznaczano obecność antykoagulantu toczniowego (*lupus anticoagulant* – LAC), czynnika reumatoidalnego (*rheumatoid factor* – RF) klasy IgM i przeciwciał przeciwko cyklicznemu cytrulinowanemu peptydowi (*anticyclic citrullinated peptide antibodies* – anti-CCP) oraz oceniano aktywność choroby.

WYNIKI Obecność aPL stwierdzono u 27 chorych (27,8%): aCL u 20 chorych (20,6%), a-β_2-GPI u 12 chorych (12,4%), a LAC u 1 pacjenta (1%). Dodatnie wyniki aCL w niskich i średnich mianach stwierdzono w klasie IgM u 11 pacjentów (11,3%), a w klasie IgG u 12 pacjentów (12,5%). Dodatnie wyniki a-β_2-GPI uzyskano tylko w klasie IgM. Obecność LAC była związana z aCL-IgM i a-β_2-GPI-IgM. Stwierdzono istotną zależność między obecnością anti-CCP i różnymi typami aPL. Nie znaleziono zależności między aPL a RF-IgM oraz markerami aktywności choroby.

WNIOSKI Częstość występowania aPL u chorych na RZS jest stosunkowo duża. Istnieje zależność między występowaniem aPL a obecnością anti-CCP markerowych dla RZS, brak natomiast istotnych zależności między aktywnością choroby a występowaniem aPL.

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