**INTRODUCTION** Rheumatoid arthritis (RA) is known to be associated with a higher prevalence of antithyroid antibodies and autoimmune thyroid disease, but there have been few studies regarding the correlations between the presence of these antibodies and RA activity.

**OBJECTIVES** The aim of this study was to analyze the relationship between antithyroid antibody titers and selected parameters of RA activity.

**PATIENTS AND METHODS** A total of 75 consecutive hospitalized patients with RA were enrolled into the study. Levels of antithyroid peroxidase antibodies (aTPO), antithyroglobulin antibodies (aTG), and antithyrotropin receptor antibodies (aTSH-R) were measured. The analysis of disease activity was based on the disease activity score with 28-joint count (DAS28), duration of morning stiffness, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) and hemoglobin levels.

**RESULTS** Antithyroid antibodies were present in 13.3% of the patients (n = 10), aTPO in 9.3% (n = 7), aTG in 8% (n = 6), and aTPO and aTG in 4% (n = 3); aTSH-R was not detected in any of the patients. Significant positive correlations (P <0.05) were observed between aTPO and DAS28 (r = 0.35, P = 0.002), aTG and ESR (r = 0.25, P = 0.02), and aTG and CRP (r = 0.23, P = 0.04). There were significant differences in the mean DAS28 between the aTPO-positive and aTPO-negative groups (5.35; 95% confidence interval [CI], 4.39–6.3 vs. 4.12, respectively; 95% CI, 3.81–4.43; P = 0.017) and between the aTG-positive and aTG-negative groups (5.65; 95% CI: 4.64–6.67 vs. 4.11; 95% CI: 3.81–4.41; P = 0.005; respectively).

**CONCLUSIONS** Our results suggest that RA activity may be associated with the presence of antithyroid antibodies. This finding could be useful in the clinical evaluation of RA patients.
TABLE 1 Demographic and clinical characteristics of the study group (n = 75)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>women, n (%)</td>
<td>61 (81)</td>
</tr>
<tr>
<td>age, y</td>
<td>56.8 ±11.4, 58 (50; 66)</td>
</tr>
<tr>
<td>disease duration, y</td>
<td>11.5 ±8.02, 9 (6; 16)</td>
</tr>
<tr>
<td>erosive RA, n (%)</td>
<td>69 (92)</td>
</tr>
<tr>
<td>extra-articular symptoms, n (%)</td>
<td>29 (38.7)</td>
</tr>
<tr>
<td>current therapy with prednisone, n (%)</td>
<td>56 (74.7)</td>
</tr>
<tr>
<td>current therapy with DMARDs, n (%)</td>
<td>74 (98.7)</td>
</tr>
<tr>
<td>current therapy with methotrexate, n (%)</td>
<td>38 (50.7)</td>
</tr>
<tr>
<td>history of biological treatment, n (%)</td>
<td>37 (49.3)</td>
</tr>
<tr>
<td>aTPO, IU/ml</td>
<td>66.82 ±399.91, 1.94 (1.03; 5.86)</td>
</tr>
<tr>
<td>aTG, IU/ml</td>
<td>68.44 ±262.68, 17.97 (15.48; 23.19)</td>
</tr>
<tr>
<td>IgM-RF positive, n (%)</td>
<td>57 (76)</td>
</tr>
<tr>
<td>ACAP positive, n (%)</td>
<td>64 (85.3)</td>
</tr>
<tr>
<td>ANA positive, n (%)</td>
<td>13 (17.3)</td>
</tr>
<tr>
<td>DAS28</td>
<td>4.23 ±1.3, 4.22 (3.38; 4.98)</td>
</tr>
<tr>
<td>high disease activity: DAS28 &gt;5.1, n (%)</td>
<td>14 (18.7)</td>
</tr>
<tr>
<td>CRP, mg/dl</td>
<td>16.1 ±19.91, 7.91 (1.89; 23.6)</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>32.7 ±24.4, 25 (16; 46)</td>
</tr>
<tr>
<td>hemoglobin, g/dl</td>
<td>12.5 ±41.2, 12.5 (11.8; 13.3)</td>
</tr>
<tr>
<td>MS, minutes</td>
<td>77.7 ±41.2, 60 (60; 60)</td>
</tr>
<tr>
<td>concomitant ATD, n (%)</td>
<td>8 (10.7)</td>
</tr>
<tr>
<td>concomitant SS, n (%)</td>
<td>7 (9.3)</td>
</tr>
<tr>
<td>concomitant ATD and SS, n (%)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation and median (Q1; Q3), or number (percentage).


In patients with RA, there was an increase in antithyroid antibodies in patients with RA, but there is little data about their links with disease activity parameters. The aim of the present study was to assess the relationship between antithyroid antibodies and parameters of RA activity such as disease activity score with 28-joint count (DAS28), duration of morning stiffness, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and hemoglobin levels, and other variables in patients with RA.

PATIENTS AND METHODS Patients The analysis included 75 consecutive patients with RA diagnosed according to the 1987 American Rheumatism Association criteria and hospitalized in the Department of Rheumatology and Systemic Connective Tissue Diseases, Medical University of Lublin, Poland. The need for modification of disease-modifying antirheumatic drugs (DMARDs) therapy was an indication for hospital admission. The diagnosis of ATD was based on laboratory markers, including thyroid-stimulating hormone (TSH), thyroid hormone, and antithyroid antibodies, as well as ultrasound examination and/or biopsy of the thyroid. The analyzed clinical variables included age, sex, disease duration, concomitant ATD and Sjögren’s syndrome, presence of rheumatoid factor of the immunoglobulin M class (IgM-RF), anticitrullinated peptide antibodies (ACPA), antinuclear antibodies (ANA), and history of treatment with biological agents, including fliximab, etanercept, adalimumab, and rituximab. Written informed consent was obtained from all patients according to the Declaration of Helsinki and the study was approved by the local ethics committee. Patients with additional connective tissue disease other than secondary Sjögren’s syndrome, with active infection, or with malignancy were excluded from the study.

Measurements Blood for the detection of antithyroid antibodies was drawn between 7 and 9 a.m. It was centrifuged, and serum was stored at −80°C. Serum samples were studied for aTPO, aTg, and aTSH-R using an enzyme-linked immunosorbent assay (ELISA) (Euroimmun, Lubeck, Germany). The cut-off values were 50 IU/ml, 100 IU/ml, and 2 IU/ml, respectively. The serum levels of CRP, hemoglobin, and ESR were determined in the local laboratory. IgM-RF and anticitrullinated protein antibodies were tested using ELISA, and antinuclear antibody was detected by indirect immunofluorescence with the Hep-2 cell substrate. All parameters were collected at the same time and by a single investigator.

Statistical analysis All numerical data were expressed as means ± standard deviations, median (25th percentile Q1; 75th percentile Q3), or as number and proportion. The Shapiro–Wilks test was used to analyze normally distributed variables. The differences between the subgroups of patients were compared using the Mann–Whitney test. Correlation between quantitative variables was assessed by the Spearman’s rank correlation coefficient. The χ² test was used to examine the differences in proportions. A P-value of less than 0.05 (two-sided) was considered statistically significant for all analyses. Statistical analyses were performed using the STATISTICA software version 9.0 (StatSoft Inc.). DAS28 was used as the DAS28-ESR version with 4 variables.

RESULTS The demographic and clinical characteristics of the patients are presented in Table 1. Of 75 patients, 10 (13.3%) had antithyroid antibodies: 7 (9.3%) had aTPO, 6 (8%) had aTg, 3 (4%) had both aTPO and aTg, and none had aTSH-R. Eight patients (10.7%), all women, had a previously confirmed diagnosis of ATD, including 7 subjects with Hashimoto’s thyroiditis and 1 with Graves’ disease. Significant positive correlations were observed between aTPO and DAS28 (r = 0.35 P = 0.002), aTg and ESR (r = 0.25, P = 0.02), and aTg and CRP (r = 0.23, P = 0.04). We analyzed the subgroups of patients with and without positive results of antithyroid antibodies, i.e., aTPO and aTg. Their comparative characteristics are presented in Table 2 (aTPO) and Table 3 (aTg).
The correlations between DAS28 and aTPO were observed in all study patients and when aTPO-positive and aTPO-negative subgroups were compared. The differences in DAS28 between the aTPO-positive group (5.35; 95% confidence interval [CI], 4.39–6.3) and the aTPO-negative group (4.12; 95% CI, 3.81–4.43) (FIGURE 1) and between the aTG-positive group (5.65; 95% CI, 4.64–6.67) and the aTG-negative group (4.11; 95% CI, 3.81–4.41) (FIGURE 3) were significant ($P = 0.017$ and $P = 0.005$, respectively). Moreover, aTPO-positive patients tended to be younger ($P = 0.08$) when compared with the aTPO-negative group. The distribution of DMARDs was similar in all groups. Among 8 patients with ATD, there were 7 euthyroid subjects and 1 hypothyroid one. Two patients underwent strumectomy and received thyroid hormone therapy.

**DISCUSSION** ATD is known to be associated with connective tissue diseases, especially RA, Sjögren’s syndrome, systemic lupus erythematosus, systemic sclerosis, and spondyloarthropathies. It usually occurs before RA but it is often impossible to precisely identify the onset of each of the 2 diseases. Moreover, patients with ATD without connective tissue disease had arthralgia and 26% of the patients with positive antithyroid antibodies had active hand and/or wrist synovitis, which may confound an adequate clinical evaluation of the patient. An increased prevalence of antithyroid antibodies has been documented both in patients with RA and in those with juvenile idiopathic arthritis but, to our knowledge, there have been no studies regarding the relationship of these antibodies with arthritis activity. A number of studies did not confirm any association between ATD and RA activity. Since DAS28 remains the main tool in the evaluation of RA activity, it is important to investigate whether there is any relationship between this routine score and antithyroid antibody titers. The results of our study not only show a high prevalence of antithyroid antibodies in RA patients but also provide evidence for a potential significant association between antithyroid antibody titers and the parameters of RA activity such as DAS28, ESR, and CRP. In particular, while performing an aTPO assay, the presence of a possible relationship between the aTPO titer and DAS28 might support the need for assessing these 2 indicators together in the evaluation of patients with exacerbation of RA as well as with concurrent or suspected ATD. The DAS28 seems to be less sensitive than the number of tender or swollen joints observed on physical examination. Similarly, DAS28 evaluated in combination with CRP or ESR could be more useful when potential associations with aTPO are suspected. For example, Drulovic et al. described a case of Hashimoto’s encephalopathy where during long-term follow-up, the levels of aTPO had been changing in parallel with the exacerbation and remission of the primary disease.

The relationship between the concentration of aTG and ESR was shown not only in the whole study group, but also when patients were divided into aTG-positive and aTG-negative groups, with the former having a significantly higher level of ESR.
Our results should be interpreted with caution because we have shown a weak correlation between the performed tests, especially between the mean ESR values measured in the aTPO-positive vs. aTPO-negative group ($P = 0.045$).

No significant correlations between the concentration of aTPO and DAS28 were shown in the whole group (there was some between aTPO and DAS28), but the group of aTPO-positive patients had a significantly higher DAS28 compared with the aTPO-negative group. This fact deserves attention because high activity of the disease correlated with the presence of high titers of aTPO or aTG.

We also studied the correlation between the aTPO titer and the age of patients. Despite the fact that there was no correlation between the titer of aTPO or aTG and the age of patients, when the groups with and without aTPO were compared, it occurred that the group with aTPO was statistically significantly younger than that without aTPO. The average age in the group of aTG-positive patients was lower than in the aTG-negative group. A similar relationship was shown by Kerimovic-Morina in a group of patients with various autoimmune diseases. In her study, patients with systemic sclerosis and thyroid disease were significantly younger than those without antithyroid antibodies.

Based on the above results, it can be concluded that younger patients are more likely to exhibit genetically conditioned autoimmunity. Moreover, our study indicates that there is a type of RA which manifests itself at a fairly young age and is associated with very high disease activity as well as symptoms of autoimmunity with or without ATD.

In patients with RA with high disease activity, high concentrations of antithyroid antibodies and ATD may be expected. On the other hand, such patients were often hospitalized because of the high activity of RA, and this is a limitation of our study. Moreover, we are aware of the fact that the finding of high disease activity expressed by DAS28 in patients with confirmed high aTPO titer may lead to the question of whether the previously high...
aTPO titer was actually connected with the high DAS28 or whether it had existed in the phase of low RA activity. DAS28 is a parameter which is more variable in the systematic evaluation of a patient with RA than the concentration of aTPO, which seems to be more consistent over short periods of time, provided there are no obvious factors affecting the antibody titer, such as appropriate treatment. In our study, groups with and without antithyroid antibodies did not differ significantly with respect to biological treatment.

Screening for ATD or even determination of thyroid dysfunction may be inadequate when only TSH is tested, especially in patients receiving corticosteroids. Therefore, our results may be beneficial in the evaluation of patients with RA. It is generally acknowledged that there is a relationship between aTPO and histopathological changes in the thyroid in Sjögren’s syndrome. It is well known, for example, that Hashimoto's disease and Graves' disease are 176- and 74-fold more frequent in Sjögren's syndrome than in the general population. It was found that the correlation between the concentration of aTPO and DAS28 may determine prognosis in patients with RA. This hypothesis seems to be supported by the fact that there was no statistical significant difference between the subgroups of patients with or without antithyroid antibodies when serological markers of RA such as IgM-RF and ACPA or ANA were concerned. Lazurova et al. concluded that there is no evidence for the usefulness of ANA screening in patients with ATD, regarding the coexistence of autoimmune disorders. Although antithyroid antibodies are commonly found in patients with RA and ATD, their relationship with disease activity not only in RA but also in ATD requires more in-depth studies. Huffness et al. confirmed the presence of antithyroid antibodies prior to clinical manifestation of Hashimoto’s or Graves’ disease, noting that in the group with Hashimoto’s disease, the prevalence of aTPO and aTG did not show any significant changes in the preclinical period, whereas in the group with Graves’ disease, antithyroid antibodies (aTPO, aTG, and aTSH-R) were consistently more often observed in that period.

The above study and our own results not only shed new light on the necessity of screening of RA patients for ATD but also point to the need for evaluating the current stage of ATD in a given patient. However, further studies are needed to determine whether ATD should be completely excluded and the presence of antithyroid antibodies should be considered as the expression of autoimmunity. In line with our results, Punzi et al. observed antimicrosomal antibodies in the synovial fluid of patients suffering from arthritis 1 year prior to their detection in serum and diagnosing Hashimoto’s disease. The authors suggested that this is possible when antithyroid antibodies are produced by synovial lymphocytes in the synovial membrane affected by inflammation, which may produce antithyroid antibodies more actively and promptly than peripheral lymphocytes. In their study, Przygodzka et al. showed that patients with both RA and ATD were characterized by lower disease activity, but that study was focused on the cooccurrence of ATD and thyroid dysfunction. On the contrary, Atzeni et al. concluded that antithyroid antibodies do not seem to be associated with any particular RA phenotype. Juszczewicz et al. suggested that prospective studies are required to assess the risk of the development of ATD in euthyroid patients with antithyroid antibodies and autoimmune rheumatic disease.

In conclusion, the possible association between aTPO and aTG levels and the parameters of RA activity may be useful in the global assessment of an individual with RA. Antithyroid antibodies might be associated with inflammation in RA patients. However, further studies are needed to confirm these results.

REFERENCES


Związek między aktywnością reumatoidalnego zapalenia stawów a obecnością przeciwciał przeciwtarczycowych

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SŁOWA KLUCZOWE
autoimmunologiczna choroba tarczycy, przeciwciała przeciwko tyroglobulinie, przeciwciała przeciwko tyroperoksydazie, przeciwciała przeciwtarczycowe, reumatoidalne zapalenie stawów

STRESZCZENIE

WPROWADZENIE
Reumatoidalne zapalenie stawów (RZS) jest związane z częstszym występowaniem przeciwciał przeciwtarczycowych i autoimmunologicznej choroby tarczycy, natomiast niewiele badań dotychno związku między ich obecnością a aktywnością RZS.

CELE
Celem pracy była analiza wzajemnych powiązań między mianem badanych przeciwciał przeciwtarczycowych a wybranymi parametrami aktywności RZS.

PACJENTI I METODY
Badaniem objęto 75 kolejno hospitalizowanych chorych na RZS. Oznaczono miano przeciwciał przeciwko tyroperoksydazie (aTPO), przeciwciał tyroglobulinie (aTG) i przeciwciał receptorowi dla TSH (aTSH-R). Analizę aktywności RZS przeprowadzono na podstawie obliczenia wskaźnika aktywności choroby w oparciu o badanie 28 stawów (DAS28), czasu sztywności porannej, wartości opadu Biernaczykowskiego (OB), stężenia białka C-reactywnego (C-reactive protein – CRP) i stężenia hemoglobiny we krwi.

WYNIKI
Przeciwciała przeciwtarczycowe stwierdzono u 13,3% chorych (10), aTPO u 9,3% (7), aTG u 8% (6), u żadnego pacjenta nie wykryto aTSH-R. Istotną (p <0,05) pozytywną korelację wykryto między mianem aTPO i wskaźnikiem DAS28 (r = 0,35; p = 0,002), aTG i OB (r = 0,25; p = 0,02) oraz aTG i CRP (r = 0,23; p = 0,04). Wykazano istotne różnice między średnimi wartościami DAS28 w wyodrębnionych grupach aTPO pozytywnej i aTPO negatywnej (5,35; 95% Cl: 4,39–6,3 vs. 4,12; 95% Cl: 3,81–4,43; p = 0,017), a także aTG pozytywnej i aTG negatywnej (5,65; 95% Cl: 4,64–6,67 vs. 4,11; 95% Cl: 3,81–4,41; p = 0,005).

WNIOSKI
Nasze wyniki sugerują, że miano przeciwciał przeciwtarczycowych i aktywność RZS mogą być wzajemnie powiązane. Uzyskane wyniki mogą być pomocne w ocenie klinicznej chorych na RZS.