

## FATIGUE IN PATIENTS WITH AUTOIMMUNE THYROID DISEASES

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## ZAMOR KOD PACIJENATA SA AUTOIMUNSKIM BOLESTIMA ŠTITASTE ŽLEZDE

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### ABSTRACT

*Fatigue is a common feature in a wide variety of chronic inflammatory and autoimmune diseases, but fatigue in autoimmune thyroid disease (AITD) has not been investigated so far. The aim of this study was to examine fatigue in patients with AITD and to analyse the correlation between fatigue and the serum concentrations of thyroid antibodies, thyroid function and depression. This cross-sectional clinical study included 62 patients with increased concentrations of thyroperoxidase antibodies (TPOAbs) as confirmation of AITD and 52 healthy individuals who were negative for thyroid antibodies; all controls were euthyroid. Thyroid antibodies, free thyroxine and thyroid-stimulating hormone were measured in the sera of all subjects. The Fatigue Severity Scale was used to measure the severity of fatigue; the level of depression was measured by the Beck Depression Inventory. Eight (12.9%) patients had evident fatigue, 7 (11.3%) patients had fatigue limit values, and 47 (75.8%) patients had no fatigue. The frequency of fatigue was highly significant and almost three times higher in the AITD patients compared to the control group, in which only 2 (3.8%) patients had evident fatigue. The majority of patients with fatigue had normal thyroid function, and only one (1.6%) patient had overt hypothyroidism. Seven (11.3%) patients had both fatigue and depression, whereas one (1.6%) patient had fatigue without depression. We did not find significant correlations between fatigue and the concentrations of thyroid antibodies, but we found statistically significant correlations between fatigue and depression in AITD patients.*

**Keywords:** antibodies, depression, fatigue, thyroid disease, thyroid function

### SAŽETAK

*Zamor je simptom koji prati mnoge hronične inflamatorne i autoimunske bolesti, međutim, učestalost zamora kod osoba sa autoimunskim bolestima štitaste žlezde (engl. autoimmune thyroid disease, AITD) do sada nije ispitivana. Cilj ovog rada je da se ispita postojanje zamora kod osoba sa AITD i da se analizira da li je težina zamora povezana sa serumskim koncentracijama anti-tireoidnih antitela, tireoidnom funkcijom i/ili depresijom. Kod svih ispitanika izmerene su serumske koncentracije anti-tireoidnih autoantitela, slobodnog tiroksina i tireostimulišućeg hormona. U eksperimentalnu grupu su uključena 62 pacijenta sa AITD i povećanom koncentracijom autoantitela specifičnih za tireoidnu peroksidazu (engl. thyroperoxidase antibodies, TPOAbs), a u kontrolnu grupu 52 eutireoidna ispitanika bez povećanih koncentracija TPOAbs. Za procenu stepena zamora korišćena je Skala težine zamora, a nivo depresije meren je primenom Beck-ove skale depresivnosti. Kod osam (12,9%) pacijenata sa AITD utvrđeno je evidentno postojanje zamora, 7 (11,3%) pacijenata sa AITD imalo je granične vrednosti, dok kod 47 (75,8%) pacijenata sa AITD nije utvrđeno postojanje zamora. Zamor je skoro tri puta učestaliji kod pacijenata sa AITD u odnosu na kontrolnu grupu, u kojoj je zamor utvrđen kod 2 (3,8%) ispitanika. Kod većine pacijenata sa zamorom tireoidna funkcija je bila normalna, a samo jedan pacijent (1,6%) imao je tešku hipotireozu. Kod sedam (11,3%) pacijenata sa AITD zamor je bio udružen sa depresijom, a samo jedan (1,6%) pacijent imao je zamor bez depresije. Korelacija između stepena zamora i koncentracije anti-tireoidnih antitela nije pokazana, dok statistički značajna korelacija između zamora i depresije kod pacijenata sa AITD postoji.*

**Ključne reči:** antitela, depresija, zamor, bolesti štitaste žlezde, tireoidna funkcija



## INTRODUCTION

Fatigue is defined as an overwhelming sense of tiredness, a lack of energy and a feeling of exhaustion (1, 2). Fatigue is a common feature of a wide variety of diseases, including chronic inflammatory, infectious, neurological, and psychiatric diseases, and cancer (2, 3). The overall prevalence of chronic fatigue depends on the type of instrument used to measure fatigue (4). In many cases, fatigue is associated with inflammation, including both acute infectious and chronic inflammatory disorders. Fatigue is a common feature among patients with multiple sclerosis (5), rheumatoid arthritis (RA) (6), systemic lupus erythematoses (SLE) (7), primary Sjögren's syndrome (8) and autoimmune thrombocytopenia (9).

To our knowledge, this is the first study of fatigue in patients with autoimmune thyroid disease (AITD). The aim of this study is to investigate fatigue in patients with AITD and to determine whether there is a correlation between the symptoms of fatigue and the serum concentrations of thyroid antibodies (Abs) or with the thyroid function. Because depression is strongly associated with fatigue and thus may affect the measurement of fatigue as a confounding factor (2), an additional aim of this study is to examine the prevalence of depression in patients with AITD and to determine whether fatigue and depression in patients with AITD are associated.

## MATERIALS AND METHODS

### Study population

The research was conducted at the Centre of Nuclear Medicine and the Clinic of Neurology, Clinical Centre Kragujevac, in accordance with the Declaration of Helsinki (2000) of the World Medical Association. This study was approved by the Ethics Committee of the Clinical Centre Kragujevac.

The study included 62 patients who showed increased concentrations of thyroperoxidase antibodies (TPOAbs) as confirmation of AITD. After the finding of increased TPOAbs concentrations, patients were informed about the study protocol, and consent was obtained from each subject before they were included in further testing. The control group consisted of 52 healthy individuals who were negative for thyroid antibodies, and all controls were euthyroid.

### Methods

The concentrations of thyroglobulin antibodies (TgAbs) and thyroid function (free thyroxine and thyrotropin) were evaluated in all study participants. All blood samples had been obtained originally for diagnostic purposes. Blood samples (10 ml) from each subject were taken by venepuncture, and the serum was separated by centrifugation at 2000 rpm for 15 minutes. The sera were divided into

separate tubes for each analysis, stored frozen at  $-20^{\circ}\text{C}$ , then thawed and assayed.

The concentration of TPOAbs was determined by a radioligand assay (TPO-Ab-CT, *Cis-Biointernational*, France) according to the manufacturer's instructions. The lower detection limit for this assay was 8 U/ml. The measured TPOAb concentrations were analysed towards the value of 130 U/ml, whereas autoantibody concentrations higher than 130 U/mL were considered "increased".

The concentration of TgAb was determined by a competitive "one-step" radioimmunoassay (TgAb I step, *Cis-Biointernational*, France). The method was calibrated against the WHO First International Reference Preparation CRM 65/93 and had an analytical detection limit of 6.0 IU/ml. Autoantibody concentrations higher than 30 IU/mL were considered "increased".

The concentration of free thyroxine (fT4) was determined by a radioimmunoassay (*Cis-Biointernational*, France). The detection limit for this assay was 0.5 pg/ml, and the reference range was 7-18 pg/ml.

The concentration of thyrotropin (TSH) was determined by an immunoradiometric assay (IRMA TSH, Zemun, Serbia), with a detection limit of 0.056 mIU/L and reference range of 0.3-5.5 mIU/L.

The Fatigue Severity Scale (FSS) (10), which focuses on the physical symptoms of fatigue, was used to assess the severity of fatigue. FSS contains a total of 9 questions, and all subjects rated their responses on the scale from 1 to 7, where 1 represents disagreement and 7 represents complete agreement with the statement. The subjects were assigned to one of two groups on the basis of FSS scores. One group included patients with fatigue (F), which was identified by an FSS score of at least 5, and the other group included patients without fatigue (WF), which was identified by an FSS score of 4 or less. Patients with FSS scores between 4.1 and 4.9 were classified in the marginal group. Patients in the marginal group were excluded from the between-group analyses, although their scores were included in the correlational analysis of fatigue severity. Patients diagnosed with chronic systemic connective tissue diseases, anaemia, tumours, liver disease or kidney disease were excluded from the study. Patients who had taken psychoactive medication (e.g., steroids, amantadine or antidepressants) in the previous two months that might have affected fatigue were also excluded.

Depression was diagnosed using the DSM-IV criteria for depressive symptoms (American 1994), and the level of depression was measured by using the Beck Depression Inventory (BDI) (12). This scale contains 21 questions that refer to the patient's mood in the last 4 weeks. The measured dimensions include cognitive, somatic and motivational aspects of depression.

### Statistical analysis

The data were analysed using descriptive statistics, the Mann-Whitney test, Spearman correlation, the Kruskal-Wallis test and binary logistic regression. Statistical sig-

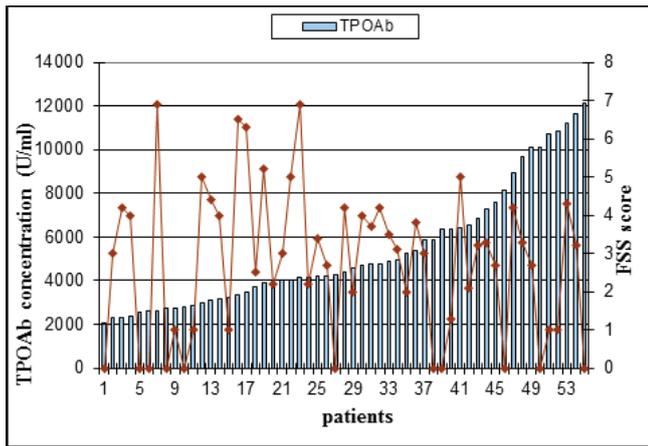


Figure 1. TPOAbs and fatigue in patients with AITD

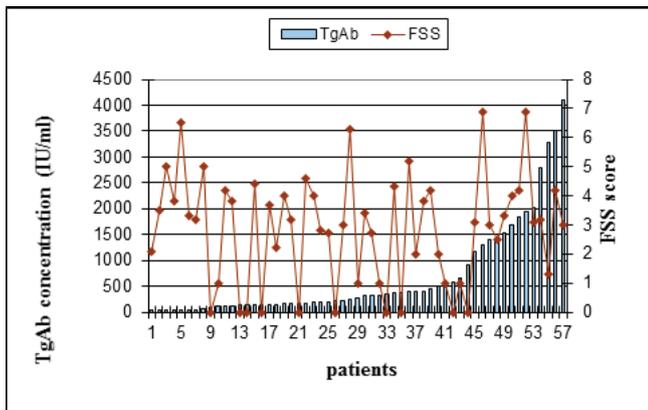


Figure 2. TgAbs and fatigue in patients with AITD

nificance was accepted when the probability (p) was less than or equal to 0.05. SPSS 10.0 and the Microsoft EXCEL programme were used for the analyses.

## RESULTS

### Fatigue and thyroid autoantibodies

The study included 62 patients (60 women, 96.8%; 2 men, 3.2%) with autoimmune thyroid disease. The mean

age was 51.6 (SD 12.45) years. The youngest patient was 22 years old, and the eldest was 75 years old. All patients had increased serum concentrations of TPO antibodies, and the average value of TPOAb was 4891 (SD 2921) U/ml (minimal concentration 280 U/ml, maximum 12125 U/ml). The control group consisted of 52 healthy subjects without TPOAbs and TgAb (46 women, 88.5%; 6 men, 11.5%). The mean age was 45 (SD 10.46) years.

From a total of 62 patients, eight (12.9%) patients had evident fatigue (FSS>5), 7 (11.3%) patients had fatigue limit values (FSS=4.1-4.9) and 47 (75.8%) patients had no fatigue (FSS≤4). The fatigue frequency was highly significant ( $p<0.01$ ), and almost three times higher in AITD patients compared to the control group, in which only 2 (3.8%) subjects had evident fatigue. The Kruskal-Wallis test showed no significant difference in the concentration of TPOAbs between patients with and without fatigue ( $p_{TPOAb}=0.733$ ). There was no significant correlation between the concentration of TPOAbs and fatigue ( $p_{FSS}=0.338$ , Spearman coefficient  $r_{FSS}= -0.124$ ). The relationship between TPOAbs and fatigue in all 62 patients is shown in Figure 1.

The majority of the patients (57/62, 91.9%) had an increased concentration of TgAb, with an average TgAb value of 679 (SD 936) IU/ml (minimal concentration 36 IU/ml, maximum 4112 IU/ml). There was no significant correlation between the concentration of TgAbs and fatigue ( $p_{FSS}= 0.773$ , Spearman coefficient  $r_{FSS}= +0.037$ ). The relationship between TgAbs and fatigue in all patients is shown in Figure 2.

### Fatigue and thyroid function

The testing revealed that 49 (79%) subjects had normal thyroid function, 5 (8.1%) patients had subclinical hypothyroidism, 3 (4.8%) patients had overt hypothyroidism, 2 (3.2%) had subclinical hyperthyroidism and 3 (4.8%) patients had overt hyperthyroidism (Table 1). Table 1 shows that the majority (7/62, 11.3%) of patients with fatigue at the time of testing had normal thyroid function, whereas only 1/62 (1.6%) patients had overt hypothyroidism. When

Table 1. Fatigue and thyroid function in patients with AITD

Thyroid function/ fatigue	Without fatigue (FSS ≤ 4)	Fatigue limit values (FSS = 4.1-4.9)	With fatigue (FSS ≥ 5)	Total
Euthyroidism	36 (58%)	6 (9.7%)	7 (11.3%)	49 (79%)
Subclinical hypothyroidism	5 (8.1%)	0	0	5 (8.1%)
Overt hypothyroidism	1 (1.6%)	1 (1.6%)	1 (1.6%)	3 (4.8%)
Subclinical hyperthyroidism	2 (3.2%)	0	0	2 (3.2%)
Overt hyperthyroidism	3 (4.8%)	0	0	3 (4.8%)
Total	47 (75.8%)	7 (11.3%)	8 (12.9%)	62 (100%)



**Table 2.** Fatigue and depression in patients with AITD

Depression/ Fatigue	Without fatigue (FSS ≤ 4)	Fatigue limit values (FSS = 4.1-4.9)	With fatigue (FSS ≥ 5)	Total
With depression	21 (33.9%)	3 (4.8%)	7 (11.3%)	31 (50%)
Without depression	26 (41.9%)	4 (6.5%)	1 (1.6%)	31 (50%)
Total	47 (75.8%)	7 (11.3%)	8 (12.9%)	62 (100%)

the relationships of fatigue and the concentration of free thyroxine were analysed, a significant correlation was revealed between the degree of fatigue and the concentration of fT4 (pFSS= 0.040, Spearman's coefficient  $r=-0.261$ ), meaning that as the concentrations of fT4 increase the fatigue level decreases. However, the linear regression revealed that the strength of connections between fT4 and FSS was rather weak ( $p=0.047$ ).

#### *Fatigue and depression*

Half of the AITD patients (31, 50%) had depression (BDI>9), where none of the subjects in the control group showed evidence of depression. Among the AITD patients, 7/62 (11.3%) had fatigue and depression, whereas only one (1.6%) had fatigue but no depression (this patient had normal thyroid function) (Table 2). There was a significant correlation between fatigue and depression among our AITD patients ( $p=0.007$ , Spearman's coefficient  $r=0.342$ ).

## DISCUSSION

This study examined the frequency of fatigue in patients with AITD and analysed whether the occurrence of fatigue among these patients was correlated with the serum concentration of thyroid antibodies or thyroid function. To our knowledge, no such study has been performed until now.

We have shown that 8 (12.9%) patients with AITD had fatigue, and this was almost three times the number of healthy control group subjects with fatigue. According to data reported in the literature, fatigue is a common problem with a prevalence that varies depending on the definition, duration, setting (13, 14), and study population. Therefore, fatigue is present in 6% of the control subjects without cancer, in comparison with more than 33% of patients with cancer (3). The frequency of fatigue among patients in primary care varies among studies; frequencies of 11.3% (4), 19% (15), or from 10% to 40% have been reported (13, 14). However, it should be noted that a portion of primary care patients have a disease that is accompanied by fatigue (e.g., systemic connective tissue diseases, anaemia, tumours, liver and kidney diseases, patients on psychoactive medication), and such patients were excluded from our study.

However, if the prevalence of fatigue in our patients with AITD is compared with data in the literature related to chronic inflammatory connective tissue diseases, then

the fatigue among our patients is less frequent than that among patients with SLE, RA or primary Sjögren's syndrome. The prevalence of fatigue is as high as 81% in patients with systemic lupus erythematosus (7), 42% in patients with RA (6), 68% in patients with Sjögren's syndrome (16) and 37% in patients with immune thrombocytopenic purpura (9). The majority of patients with multiple sclerosis (53–87%) have fatigue (17).

In our study, we have shown that the occurrence and severity of fatigue does not depend on the concentration of TPOAbs or on the concentration of TgAbs. Although multiple mechanisms are involved in the damage of the thyroid tissue in AITD, especially cellular immunity (18-20), high concentrations of thyroid antibodies in the serum of patients with AITD indicate the activity of the autoimmune process (19). Therefore, the fatigue in our patients with AITD is not correlated with disease activity. Similar results have been obtained in the majority of studies related to fatigue in autoimmune diseases. The relationship between fatigue and activity of SLE is controversial (21-23), while fatigue in RA was related to pain and functioning but not inflammation (6). Given that patients with AITD have not expressed incapacitating clinical symptoms, especially if the thyroid function is unchanged, then a similar mechanism cannot be a cause of fatigue in our patients.

Thyroid dysfunctions may be accompanied by numerous neurological (24, 25) and psychiatric disorders (26, 27), the most well-known being cognitive impairment and depression in hypothyroid patients (28, 29). Considering that the majority of subjects with fatigue in our study had normal thyroid function, we could preliminarily conclude that hypothyroidism alone cannot account for the fatigue in our study. When we tested the relationship between fatigue and the concentration of free thyroxine, we found that there was a statistically significant correlation between the degree of fatigue in our patients and the concentration of fT4; therefore, the fatigue level decreased as the concentration of fT4 increased. However, the strength of the correlation between fT4 and FSS is weak ( $p=0.047$ ). Regardless of this result, hypothyroidism is less likely an aetiology of fatigue in our AITD patients. A similar finding was reported in a recently published study of Louwerens et al. (30), in which autoimmune hypothyroid patients had significantly higher levels of fatigue compared to the patients with differentiated thyroid carcinoma, but it could not be attributed to clinical or thyroid hormone parameters.

There are numerous reports in the literature on the associated occurrence of depression and AITD (29, 31). Giv-



en that depression may affect the measurement of fatigue as a confounding factor (2), we examined the frequency of depression in patients with AITD, as well as in the healthy control group. In addition, we analysed whether the occurrence of fatigue and depression was associated. We showed that 50% of patients had depression, whereas 11.3% patients had fatigue and depression; only one (1.6%) patient had fatigue but no depression. In the control euthyroid group, none of the subjects had depression, although two subjects had evident fatigue. There was a significant correlation between fatigue and depression in our AITD patients. While a number of previously published studies found no association between fatigue and depression in patients with multiple sclerosis (32, 33), the majority of recently published studies found that depression had a significant impact on the occurrence of fatigue (34, 35). Although depression was more common than fatigue in our AITD patients, the positive correlation between the two variables indicates that the occurrence of fatigue and depression are associated. However, this does not necessarily mean that depression in our study is a confounding factor that affects the measurement of fatigue. The possibility that the fatigue and depression in AITD were caused by some other still insufficiently clarified mechanism cannot be excluded.

In conclusion, the frequency of fatigue was highly significant and almost three times higher in our AITD patients compared to the healthy subjects in the control group. The majority of patients with fatigue had normal thyroid function. We did not find significant correlations between fatigue and the concentrations of thyroid antibodies. There was a statistically significant correlation between fatigue and depression in our AITD patients.

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