

Original article

Thyroid dysfunction in patients with multiple sclerosis: prevalence and associated risk factors

Daliborka Tadić^{1,2}, Sanja Grgić^{1,2}, Aleksandra Dominović Kovačević^{1,2}, Zoran Vukojević^{1,2}, Gabrijela Malešević^{1,2}, Valentina Soldat Stanković^{2,3}

¹University Clinical Center of Republic of Srpska, Clinic of Neurology, Banja Luka, Republika of Srpska, Bosnia and Herzegovina

²University of Banja Luka, Faculty of Medicine, Banja Luka, Republic of Srpska, Bosnia and Herzegovina ³University Clinical Center of Republic of Srpska, Clinic of Endocrinology, Republic of Srpska, Bosnia and Herzegovina

Primljen - Received: 17/06/2025 Prihvaćen – Accepted: 15/09/2025

Corresponding author:

Daliborka Tadić, MD, PhD Lovćenska 10, 78250 Laktaši e-mail: tadic.daliborka@gmail.com

Copyright: ©2025 Daliborka Tadić et al. This is an Open Access article distributed under the terms of the Creative Commons Attribution 4.0 International (CC BY 4.0) license.

Summary

Introduction. Thyroid dysfunction has been identified as one of the most common comorbidities in people with multiple sclerosis (PwMS). This study aimed to determine the prevalence of thyroid disease and vitamin D levels in patients with MS compared to the general population, and to assess the potential impact of thyroid status and vitamin D levels on the degree of physical disability and the prediction of multiple sclerosis.

Methods. A total of 127 participants were prospectively enrolled in the study: 59 (46.5%) were healthy controls and 68 (53.5%) were patients diagnosed with MS. Both groups were assessed for serum levels of TSH, FT4, anti-TPO antibodies, and vitamin D. In the MS group, the physical disability was additionally evaluated using the Expanded Disability Status Scale (EDSS).

Results. Overt hypothyroidism (p = 0.011) and vitamin D deficiency (p = 0.013) were significantly more frequent among MS patients. Mean FT4 levels (p = 0.025) and vitamin D levels (p = 0.018) were significantly lower in the MS group, whereas anti-TPO antibody levels were markedly higher in MS patients (p < 0.001). EDSS scores showed a negative correlation with vitamin D concentrations (p < 0.050). Multivariate analysis identified independent risk factors for MS, including the presence of severe hypovitaminosis D (p = 0.035), lower vitamin D concentrations (p = 0.003), and elevated anti-TPO levels (p = 0.042).

Conclusion. Evaluation of thyroid status, as well as vitamin D concentrations, should be considered a standard part of healthcare for PwMS.

Key words: Multiple sclerosis, thyroid gland, vitamin D

Introduction

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS), primarily characterized by demyelination followed by axonal degeneration of nerve cells. Despite significant advances in understanding the pathophysiology of MS, the etiology and heterogeneous course of the disease remain incompletely understood. It is believed that clinical, demographic, and psychosocial factors, together with individual genetic, epigenetic, and environmental influences, contribute to the onset and progression of the disease. Among these, numerous studies suggest that comorbidities can have a significant impact on the development and course of MS, contributing to a reduced quality of life for people living with the condition [1].

In people with MS (PwMS), the most commonly identified comorbidities include vascular, psychiatric, and autoimmune diseases [2]. According to a systematic review from 2015 encompassing 61 studies, the most frequent autoimmune comorbidities in patients with MS were psoriasis (0.39%–7.74%) and thyroid diseases, including hormonal dysfunction (2.08%-10%) and the presence of thyroid autoantibodies (4%-21%) [3-6]. Thyroid hormones—triiodothyronine (T3) and thyroxine (T4)—play a crucial role in regulating metabolism, immune function, and neural development. They influence immune system modulation by regulating T-cell differentiation, cytokine production, and B-cell activity [7, 8]. Regarding neuroprotection and neurorepair, preclinical studies on animal models have shown that T3 promotes the differentiation and myelination of oligodendrocytes, which is essential for repairing demyelinated neurons in MS. Thyroid hormones also enhance the activity of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), supporting neuronal survival and potentially mitigating MS-related neurodegeneration [9–11]. Hyperthyroidism (elevated thyroid hormone levels) has been linked to increased production of proinflammatory cytokines (e.g., IL-6, TNF- α), potentially worsening the clinical course of MS. In contrast, hypothyroidism (low thyroid hormone levels) may suppress immune activity, reducing inflammation but impairing remyelination mechanisms and leading to worsening neurological status [12]. Additionally,

there is well-documented evidence of the association between MS treatment and the development of thyroid dysfunction or exacerbation of pre-existing thyroid disorders, especially in patients treated with interferon beta-1b and alemtuzumab [13, 14].

During the MS diagnostic process and in evaluating its impact on quality of life, there is an acknowledged overlap between non-motor MS symptoms and thyroid diseases, including fatigue, cognitive impairment, sphincter and autonomic dysfunction, and sensory disturbances found in both conditions [15]. Thyroid hormone signaling also interacts with other mechanisms implicated in MS pathogenesis, such as the influence of vitamin D and estrogen, indicating a complex interplay of multiple factors in disease modulation [16]. Current research suggests that low vitamin D concentrations, particularly in early life, may act as both an epigenetic and environmental factor for MS onset. This is supported by epidemiological data indicating a higher prevalence of MS in regions with limited sunlight exposure and, consequently, reduced vitamin D synthesis [17, 18]. The immunomodulatory effects of vitamin D include regulation of immune cell function by reducing the production of proinflammatory cytokines (IL-17, IF-γ) and enhancing the activity of anti-inflammatory cells (T lymphocytes). Some studies suggest that vitamin D supplementation is associated with slower disease progression and fewer relapses in PwMS; however, results have been inconsistent. Therefore, vitamin D is currently recommended as an adjunct rather than a replacement for MS-specific therapy. The role of vitamin D in thyroid function is well-established, and in the context of this discussion, its influence on autoimmune thyroid disease shows a pathophysiological pattern similar to that observed in MS [19, 20].

As no prior studies have addressed this topic in Republic of Srpska, we conducted this research to determine the prevalence of thyroid dysfunction and vitamin D deficiency among MS patients in our region, compared to the general population, and to assess the potential impact of thyroid status and vitamin D concentrations on physical disability and MS progression.

Methods

This cross-sectional study included 68 patients diagnosed with multiple sclerosis (MS) based on the 2017 revised McDonald criteria [21], all treated at the Department of Demyelinating Diseases at the University Clinical Center of Republic of Srpska (UCCRS). Patients with previously diagnosed autoimmune diseases other than MS were excluded. None of the participants had received corticosteroid treatment in the month preceding the study.

The control group comprised 59 patients admitted to the same department during the same period for headache evaluation, with no prior history of neurological or autoimmune diseases. All data collection was conducted in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by the UCCRS Ethics Committee (approval number: 01-19-55-2/25). Demographic data (age and sex) were collected for both groups, while additional clinical data were obtained for the MS group, including disease course, disease duration, number of relapses, and the level of physical disability assessed using the Expanded Disability Status Scale (EDSS) [22].

During the study, all participants were monitored by a team of specialists including a neurologist, an endocrinologist, and a nuclear medicine physician. Blood samples were collected for biochemical analysis. Laboratory testing was performed in both MS and control groups. Blood samples were collected after overnight fasting, centrifuged at 3,000 rpm for 10 minutes, and stored at -80°C until analysis. Serum levels of thyroid-stimulating hormone (TSH), free thyroxine (FT4), and anti-thyroid peroxidase

antibodies (anti-TPO) were measured using an immunochemiluminescence assay (ICMA) on the Roche Integra 400+ analyzer (Roche Diagnostics). The reference ranges were as follows: TSH: 0.34-4.10 µIU/mL, FT4: 11.3-20.6 pmol/L, and anti-TPO: 0-60 IU/mL.

Thyroid dysfunction was defined according to the following criteria:

- Clinical hypothyroidism: TSH > 10 μIU/mL and FT4 < 11.3 pmol/L
- Subclinical hypothyroidism: TSH 4.1– 10 μIU/mL with normal FT4
- **Hyperthyroidism**: TSH < 0.34 μIU/mL and FT4 > 20.6 pmol/L
- Subclinical hyperthyroidism: TSH < 0.34 µIU/mL with normal FT4
- **Autoimmune thyroiditis**: anti-TPO > 60 IU/mL

Vitamin D concentrations were categorized as follows:

- **Desirable**: > 30 ng/mL
- Expected range: 6.8–44.9 ng/mL
- Severe hypovitaminosis D: < 7 ng/mL

These thresholds were based on the reference values of our institutional laboratory and aligned with the recommendations of leading endocrine societies, including the American Thyroid Association and the European Thyroid Association [23]. It is worth noting that since 1953, mandatory salt iodization has been implemented in the former Yugoslavia. This policy remains in effect in Bosnia and Herzegovina, a country considered iodine-sufficient, meaning that the population is assumed to have an adequate intake of iodine necessary for normal thyroid gland function [24].

Statistical analysis

To detect a statistically significant difference among subject groups at the p<0.05 significance level with 80% study power, the study included 127 patients. The sample size was calculated using the G*Power program with a chi-square ($\chi 2$) test. Frequencies of the groups were compared using $\chi 2$ test and independent t test or Mann-Whitney test were used to test the differences in mean values. An association between various risk factors for occurrence of MS was assessed using odds ratio (OR) with 95% confidence intervals (95% CI), using binary multivariate logistic regression analysis. The data were analyzed using the statistical software SPSS version 24 (Chicago, IL, USA). The results were expressed as mean value \pm standard deviation (SD) and p-value less than 0.05 was considered statistically significant.

Results

Out of a total of 127 participants included in the study, 59 (46.5%) comprised the healthy control group, while 68 (53.5%) were diagnosed with MS. The majority of participants were females (78%), with no significant sex distribution difference between the groups.

Participants in the MS group were significantly older compared to the control group $(43.04 \pm 9.74 \text{ years vs. } 27.84 \pm 6.64 \text{ years; } p <$ 0.001). Notably, 60.3% of individuals aged 41 to 70 years belonged to the MS group, compared to only 5.1% in the control group (p < 0.001). There was no significant difference in the prevalence of subclinical hypothyroidism or hyperthyroidism between the MS and control groups. However, overt hypothyroidism (10.3% vs. 0%; p = 0.011) and vitamin D deficiency (55.9% vs. 33.9%; p = 0.013) were significantly more prevalent among patients with MS. Mean vitamin D concentrations $(10.32 \pm 9.24 \text{ ng/mL vs. } 14.84 \pm 12.00)$ ng/mL; p = 0.018) were significantly lower in the MS group (Figure 1). Mean FT4 level were also significantly lower in the MS group $(14.02 \pm 3.38 \text{ pmol/L vs. } 15.14 \pm 1.87 \text{ pmol/L}; p$ = 0.025) whereas anti-TPO levels were markedly higher in MS patients compared to controls (201.62 ± 389.68 IU/mL vs. 89.28 ± 253.48 IU/mL; p < 0.001) (Table 1).

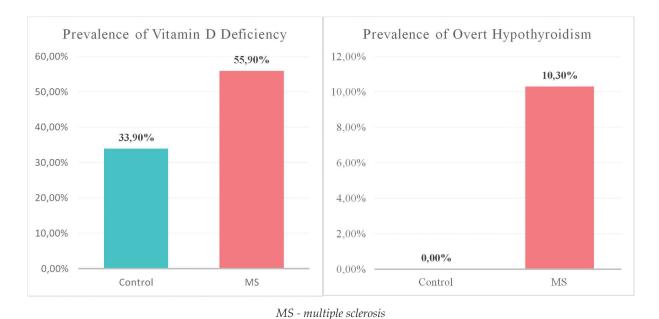


Figure 1. Prevalence of vitamin D deficiency and overt hypothyroidism in control and MS group

Table 1. Comparison of socio-demographic, clinical, and laboratory characteristics in control group and patients with MS

Variables	Control group (n = 59, 46.5%)		MS group (n = 68, 53.5%)		Total (n = 127, 100%)		p*
	n	%	n	%	n	%	
Female	46	78.0	53	77.9	99	78.0	0.997*
Age (M±SD)	27.84±6.64		43.04±9.74		35.98±11.34		< 0.001**
18 to 40 years	56	94.9	27	39.7	83	65.4	< 0.001*
41 to 70 years	3	5.1	41	60.3	44	34.6	
Subclinical hypothyroidism (yes)	9	15.3	6	8.8	15	11.8	0.263*
Overt hypothyroidism (yes)	0	0.0	7	10.3	7	5.5	0.011*
Subclinical hyperthyroidism (yes)	0	0.0	1	1.5	1	1.5	0.350*
Severe hypovitaminosis D (yes)	20	33.9	38	55.9	58	45.7	0.013*
Laboratory analyses (M±SD)							
FT4 (11.3–20.6 pmol/L)	15.14	1±1.87	14.02	2±3.38	14.54	l±2.83	0.025**
TSH (0.34–4.10 μIU/mL)	2.69	±1.20	3.41	±3.27	3.08	±2.55	0.109**
Anti-TPO (0–60 IU/mL)	89.28	£253.48	201.62	±389.68	149.43	±336.88	< 0.001#
Vitamin D (<7 ng/mL)	14.84±12.00		10.32±9.24		12.42±10.81		0.018*

MS - multiple sclerosis, FT4 - free thyroxine; TSH - thyroid-stimulating hormone, anti-TPO - Anti-thyroid peroxidase, M - mean \pm SD - standard deviation; p - statistical significance was measured by * χ 2 - chi square test, **independent t test or #Mann-Whitney U test, significant values are bolded

Mean duration of MS was 8.89±7.00 years and mean number of relapses was 3.27±2.26. Mean value of EDSS was 2.98±1.67. More than two thirds of patients with MS had relapsing-remitting type, 13.2% had secondary-progressive type, while 8.8% had primary progressive type of MS. Most of the patients were without therapy (30.9%), and the most prevalent therapy used was galtiramer acetate (16.2%), followed by ocrelizumab (14.7%) and interferon beta 1b (11.8%) (Table 2).

A moderate, statistically significant negative correlation was observed between TSH and FT4 levels (p < 0.010), while a moderate, statistically significant positive correlation was found between TSH and anti-TPO levels (p < 0.010). The EDSS showed a positive correlation with age (p < 0.050), MS duration (p <0.001), and the number of relapses (p < 0.001), whereas it was negatively correlated with vitamin D concentrations (p < 0.050). Older age was significantly associated with longer disease duration (p < 0.001) and a higher number of relapses (p < 0.001), and there was a strong

positive correlation between MS duration and the number of relapses (p < 0.001) (Table 3).

Table 2. Clinical characteristics of MS patients

Variables	MS group (n = 68, 53.5%)			
	n	%		
Duration of MS , years (M±SD)	8.89±7.00			
Number of relapses (M±SD)	3.27±2.26			
EDSS (M±SD)	2.98±1.67			
Types of MS (n=68)				
Relapsing-Remitting MS	53	77.9		
Secondary Progressive MS	9	13.2		
Primary Progressive MS	6	8.8		
Therapy				
Without therapy	21	30.9		
Glatiramer acetate	11	16.2		
Ocrelizumab	10	14.7		
Interferon beta 1 b	8	11.8		
Ofatumumab	6	8.8		
Natalizumab	3	4.4		
Siponimod	3	4.4		
Interferon beta 1a	3	4.4		
Teriflunomid	3	4.4		

MS - multiple sclerosis, EDSS - expanded disability status scale, M - $mean \pm SD$ - standard deviation

Table 3. Correlations between the amount of laboratory parameters (FT4, TSH, anti-TPO and vitamin D) with age, duration of MS, number of relapses and EDSS in MS patients

Variables	FT4	TSH	Anti-TPO	Vitamin D	Age	Duration of MS	Number of relapses	EDSS
FT4								
TSH	-0.390***							
Anti-TPO	-0.024	0.315**						
Vitamin D	-0.048	0.206	0.071					
Age	-0.036	-0.130	0.142	0.061				
Duration of MS	-0.131	-0.036	-0.060	-0.032	0.486***			
Number of relapses	-0.097	0.061	0.063	.0.143	0.334***	0.659***		
EDSS	0.187	0.032	0.055	-0.266*	0.270*	0.362***	0.461***	

MS - multiple sclerosis, FT4 - free thyroxine; TSH - thyroid-stimulating hormone, anti-TPO - Anti-thyroid peroxidase, EDSS - expanded disability status scale, Spearman's correlation test was used, significance level 0.05, r2 values are presented in the table. * - p<0.05, ** - p<0.01, *** - p<0.001 (significant p values are bolded)

Multivariate analysis showed that independent risk factors for MS were presence of hypovitaminosis D (OR = 2.268; p = 0.035), lower vitamin D concentrations (OR = 2.326; p = 0.003) and higher anti-TPO (OR = 1.375; p=0.042) meaning that presence of hypovitaminosis D and higher anti-TPO values were

independent predictor of MS occurrence in a models where univariate significant variables were included (Table 4). It is important to emphasize that some ORs had very wide confidence intervals (e.g. FT4, anti-TPO), indicating that the sample is too small to draw precise conclusions.

Table 4. Regression analysis of univariate significant variables as a predictors of MS

Regression models	Multivariate					
	В	OR	95% CI	p		
Constant	12.378	3.214	/	0.231		
Age	5.254	0.792	0.431-1.279	0.069		
Overt hypothyroidism	2.732	1.007	0.982-1.063	0.060		
Hypovitaminosis D	1.887	2.268	1.751-3.448	0.035		
FT4	-1.265	3.543	0.638-19.663	0.148		
Anti-TPO	0.092	1.375	0.106-0.673	0.042		
Vitamin D	-15.862	2.326	1.375–3.392	0.003		

FT4 - free thyroxine; anti-TPO - Anti-thyroid peroxidase, B - unstandardized regression coefficient; OR - odds ratio; 95% CI - confidence interval, p - statistical significance; significant values are bolded

Discussion

In multiple previous studies investigating the prevalence of autoimmune comorbidities in people with multiple sclerosis (PwMS), thyroid dysfunction has been consistently identified as one of the most common comorbid conditions. This finding is particularly important due to the critical role of normal thyroid gland function in myelination processes, potential neurorepair, and the impact on the quality of life of PwMS caused by overlapping symptoms of both diseases [3, 5, 7–9].

Numerous researchers have addressed this issue; however, study results have been inconsistent. Some investigations have not found thyroid dysfunction to be more prevalent in MS patients compared to controls, while others have reported an increased rate of thyroid dysfunction in PwMS [25]. Most prior research on thyroid function in PwMS has detected elevated anti-thyroid peroxidase (anti-TPO) antibody levels alongside normal hormonal status, suggesting the presence of chronic autoimmune inflammation [26]. For instance, the study by Annunziata et al. demonstrated that anti-TPO levels were significantly higher in MS patients (21.7%) compared to healthy controls (5.3%) and individuals with other neurological disorders (9.2%) [27]. A large prospective study involving 658 MS patients similarly reported increased prevalence of autoimmune thyroid disorders in PwMS relative to the general population [28]. Another study by Petek-Balči et al. found autoimmune thyroid disorders in 106 MS patients, in contrast to healthy controls, with a significant difference in thyroid antibody presence but not in hormonal status between the groups [29].

Consistent with prior findings our study shows markedly elevated anti-TPO levels in MS patients compared to controls (Table 1). However, Nilsen et al. reported no statistically significant difference in anti-TPO levels between MS patients and healthy individuals, possibly due to their choice of control subjects, who

were first-degree relatives of PwMS -thereby increasing the likelihood of autoantibodies in controls and diminishing group differences regarding autoimmunity. This may explain the contrasting results between their study and ours [30]. Mari et al. also conducted a prospective study that did not reveal significant differences in anti-TPO levels between PwMS and healthy controls [31]. An additional notable finding in our PwMS population is that elevated anti-TPO levels served as a predictive factor for MS onset, a result corroborated by other studies (Table 4) [26, 27]. Regarding hormonal dysfunction, previous research has yielded mixed results, with reported prevalence rates ranging from 1.6% to 11% [32]. In our cohort, overt hypothyroidism (10.3% vs. 0%; p = 0.011) was significantly more prevalent among MS patients (Table 1). The prevalence of subclinical or overt hypothyroidism in PwMS reported elsewhere is generally lower than in our study, such as in Karni et al. (0.8–1.5%) and Muntiesa et al. (6.45% in MS vs. 2.24% in controls) [15, 33]. Conversely, the Iranian population showed higher overt hypothyroidism prevalence (23.3% in MS vs. 9.8% in controls) [26].

Ghani et al. found no statistically significant differences in TSH and FT4 levels between MS patients and controls [34], a finding echoed by Elżbieta and Andrzej as well as Durelli et al. [35, 36]. Aylin et al. reported statistically lower TSH levels in PwMS compared to healthy controls but found no significant correlation between TSH levels and EDSS scores, consistent with our results [37]. Kisling et al. demonstrated significantly increased FT4 and decreased TSH levels in the MS group, noting similar thyroid function changes across different MS clinical forms, with no correlation to disability severity [38]. In our study, mean FT4 levels were significantly lower in PwMS, while TSH levels showed no significant difference between groups (Table 1). Studies directly linking FT4, TSH levels, and EDSS scores remain scarce [39]. Niederweiser et al. reported no significant differences in disease duration

or EDSS scores between PwMS with and without hypothyroidism [40]. Similarly, Muntiesa et al. found no relationship between thyroid dysfunction and EDSS progression during follow-up [33]. In our cohort, EDSS positively correlated with age (p < 0.050), MS duration (p < 0.001), and number of relapses (p < 0.001), but showed no correlation with thyroid function parameters (Table 3). Several studies have identified the impact of interferon beta-1b treatment on the development of autoimmune and functional thyroid disorders. There is no evidence that other MS treatments affect thyroid status, except alemtuzumab—which was not used in our population [41, 42].

Vitamin D deficiency (55.9% vs. 33.9%; p = 0.013) was significantly more prevalent among MS patients in our sample. Additionally, mean vitamin D concentrations were significantly lower in the MS group (10.32 \pm 9.24 ng/mL vs. 14.84 ± 12.00 ng/mL; p = 0.018) (Table 1). A meta-analysis of 14 studies from 2007 to 2021 reported a 54% increased risk of MS associated with vitamin D deficiency [43], a finding consistent with the majority of other studies and aligned with data from our region [44]. This study also examined potential predictive factors for MS, identifying elevated anti-TPO levels and vitamin D deficiency as significant predictors in our population, consistent with findings in other populations studied [45]. Furthermore, a statistically significant correlation was observed between vitamin D concentrations and EDSS scores, indicating that hypovitaminosis D negatively impacts the degree of physical disability in PwMS, a conclusion supported by other research [46, 47]. The generally

heterogeneous findings across studies in this field may stem from several factors, including absence of control groups, iodine deficiency in some study regions, and minimized influence of MS treatment regimens-which is also a limitation of our study [33].

This study has several limitations that should be considered. Patients with MS were older than controls, which may act as a confounder. Our study did not address effect of treatment of MS due to the small percentage of PwMS receiving this therapy relative to the total MS group.

Despite the above mentioned limitations in our study, it provides valuable hypotheses for future research. Prospective, multicenter studies with larger and more homogeneous samples and seasonal control of vitamin D are needed to more precisely define the relationships between multiple sclerosis, endocrine disorders, and the effects of various therapeutic interventions.

In conclusion, our results demonstrate significantly higher anti-TPO levels, lower FT4, and reduced vitamin D concentrations in MS patients compared to healthy controls, along with a predictive role for lower vitamin D and higher anti-TPO levels in MS onset. Considering that both functional and autoimmune thyroid status, as well as vitamin D concentrations, influence pathophysiological mechanisms involved in MS development and progression, routine evaluation of these parameters should be integrated into standard healthcare protocols for PwMS. Future prospective and multicenter studies with larger and more homogeneous samples are necessary to confirm and deepen these observations.

Funding source. The authors received no specific fund ing for this work.

Ethical approval. The Ethics Committee of the University Clinical Center of Republic of Srpska, Banja Luka, Republic of Srpska, Bosnia and Herzegovina, approved

the study (No: 01-19-55-2/25) and informed consent was obtained from all individual respondents. The research was conducted according to the Declaration of Helsinki.

Conflicts of interest. The authors declare no conflict of interest.

References:

- 1. Tadić D. Multipla skleroza i komorbiditeti. Medicinski fakultet Univerziteta u Banjoj Luci, 2020.
- 2. Culpepper WJ 2nd. The incidence and prevalence of comorbidity in multiple sclerosis. Mult Scler 2015;21(3):261–2.
- 3. Marrie RA, Reider N, Cohen J, Stuve O, Sorensen PS, Cutter G, et al. A systematic review of the incidence and prevalence of autoimmune disease in multiple sclerosis. Mult Scler 2015;21(3):282-93.
- 4. Durand B, Raff M. A cell-intrinsic timer that operates during oligodendrocyte development. Bioessays 2000;22(1):64-71.
- 5. Jendretzky KF, Lezius LM, Thiele T, Konen FF, Huss A, Heitmann L, et al. Prevalence of comorbid autoimmune diseases and antibodies in newly diagnosed multiple sclerosis patients. Neurol Res Pract 2024;6(1):55.
- 6. Franco PG, Silvestroff L, Soto EF, Pasquini JM. Thyroid hormones promote differentiation of oligodendrocyte progenitor cells and improve remyelination after cuprizone-induced demyelination. Exp Neurol 2008;212(2):458-67.
- 7. Marrie RA, Reider N, Cohen J, Stuve O, Sorensen PS, Cutter G, et al. A systematic review of the incidence and prevalence of autoimmune disease in multiple sclerosis. Mult Scler 2015;21(3):282-93.
- 8. Rogister B, Ben-Hur T, Dubois-Dalcq M. From neural stem cells to myelinating oligodendrocytes. Mol Cell Neurosci 1999;14(4-5):287-300.
- 9. Billon N, Tokumoto Y, Forrest D, Raff M. Role of hormone receptors in timing oligodendrocyte differentiation. Dev Biol 2001;235(1):110-20.
- 10. Pasquini JM, Adamo AM. Thyroid hormones and the central nervous system. Dev Neurosci 1994;16(1–2):1–8.
- 11. Sawano E, Negishi T, Aoki T, Murakami M, Tashiro T. Alterations in local thyroid hormone signaling in the hippocampus of the SAMP8 mouse at younger ages: association with delayed myelination and behavioral abnormalities. J Neurosci Res 2013;91(3):382-92.
- 12. Fancy SP, Kotter MR, Harrington EP, Huang JK, Zhao C, Rowitch H, et al. Overcoming remyelin-

- ation failure in multiple sclerosis and other myelin disorders. Exp Neurol 2010;225(1):18–23.
- 13. Demerens C, Stankoff B, Zalc B, Lubetzki C. Eliprodil stimulates CNS myelination: New prospects for multiple sclerosis? Neurology 1999;52(2):346-50.
- 14. Zhang J, Shi S, Zhang Y, Luo J, Xiao Y, Meng L, et al. Alemtuzumab versus interferon beta 1a for relapsing-remitting multiple sclerosis. Cochrane Database Syst Rev 2017;11(11):CD010968.
- 15. Gross R, Lublin F. Interferon β in multiple sclerosis. Lancet 1999;354(9177):512.
- 16. Karni A, Abramsky O. Association of MS with thyroid disorders. Neurology 1999;53(4):883–5.
- 17. Ren Y, Wang X, Wang W, Wang Z. Thyroid function and multiple sclerosis: a two-sample mendelian randomization study and mediation analysis. Sci Rep 2025;15(1):9022.
- 18. Savran Z, Baltaci SB, Aladag T, Mogulkoc R, Baltaci AK. Vitamin D and Neurodegenerative Diseases Such as Multiple Sclerosis (MS), Parkinson's Disease (PD), Alzheimer's Disease (AD), and Amyotrophic Lateral Sclerosis (ALS): A Review of Current Literature. Curr Nutr Rep 2025;14(1):77.
- 19. Al Noman A, Afrosa H, Lihu IK, Sarkar O, Nabin NR, Datta M, et al. Vitamin D and Neurological Health: Unraveling Risk Factors, Disease Progression, and Treatment Potential. CNS Neurol Disord Drug Targets 2025;24(4):245–56.
- 20. Plantone D, Primiano G, Manco C, Locci S, Servidei S, De Stefano N. Vitamin D in Neurological Diseases. Int J Mol Sci 2022;24(1):87.
- 21. Hayes CE, Nashold FE, Spach KM, Pedersen LB. The immunological functions of the vitamin D endocrine system. Cell Mol Biol (Noisy-legrand) 2003;49(2):277–300.
- 22. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2018;17(2):162-73.
- 23. Kurtzke JF. Rating neurologic instrument in multiple sclerosis: An expandede disability status scale (EDSS). Neurology 1983;33(11):1444-52.
- 24. Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JI, et al. American Association Of Clinical Endocrinologists And American

- Thyroid Association Taskforce On Hypothyroidism In Adults. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Thyroid 2012;22(12):1200-35.
- 25. Special Initiative on NCDs and Innovation (SNI), WHO Europe. Prevention and control of iodine deficiency in the WHO European Region: adapting to changes in diet and lifestyle. Copenhagen: World Health Organization, Regional Office for Europe; 2024.
- 26. Gautam S, Bhattarai A, Shah S, Thapa S, Gyawali P, Khanal P, et al. The association of multiple sclerosis with thyroid disease: A meta-analysis. Mult Scler Relat Disord 2023;80:105103.
- 27. Poursadeghfard M, Mallahzadeh A, Hamidi A, Owjfard M. Thyroid auto-antibodies in newly diagnosed multiple sclerosis patients: A cross sectional study. Health Sci Rep 2024;7(7):e2247.
- 28. Annunziata P, Lore> F, Venturini E, Morana P, Guarino E, Borghi S, et al. Early synthesis and correlation of serum anti-thyroid antibodies with critical parameters in multiple sclerosis. J Neurol Sci 1999;168(1):32-6.
- 29. Edwards LJ, Constantinescu CS. A prospective study of conditions associated with multiple sclerosis in a cohort of 658 consecutive outpatients attending a multiple sclerosis clinic. Mult Scler 2004;10(5):575-81.
- 30. Petek-Balci B, Yayla V, Ozer F. Multiple Sclerosis and Hashimoto Thyroiditis. Neurologist 2005;11(5):301-4.
- 31. Nielsen N, Frisch M, Rostgaard K, Wohlfahrt J, Hjalgrim H, Koch-Henriksen N, et al. Autoimmune diseases in patients with multiple sclerosis and their first-degree relatives: A nationwide cohort study in Denmark. Mult Scler 2008;14(6):823-9.
- 32. Marrie RA, Yu BN, Leung S, Elliott L, Warren S, Wolfson C, et al. The incidence and prevalence of thyroid disease do not differ in the multiple sclerosis and general populations. Neuroepidemiology 2012;39(2):135-42.
- 33. Monzani F, Caraccio N, Casolaro A, Lombardo F, Moscato G, Murri L, et al. Long-term interferon beta-1b therapy for MS: is routine thyroid assessment always useful? Neurology 2000;55(4):549-52.

- 34. Munteis E, Cano JF, Flores JA, Martinez-Rodriguez JE, Miret M, Roquer J. Prevalence of autoimmune thyroid disorders in a Spanish multiple sclerosis cohort. Eur J Neurol 2007;14(9):1048-52.
- 35. Abdel Ghani A, Elsharkawy K, Ghonimi N, Khyal D. Serum Levels of Thyroid Hormones in Relapsing Remitting Multiple Sclerosis. Zagazig University Medical Journal 2023;29(1):228-34.
- 36. Zych-Twardowska E, Wajgt A. BlooD concentrations of selected hormones in patients with multiple sclerosis. Med Sci Monit 2001;7(5):1005-12.
- 37. Durelli L, Oggero A, Verdun E, Isoardo GL, Barbero P, Bergamasco B, et al. Thyroid function and anti thyroid antibodies in MS patients screened for interferon treatment. A multicenter study. J Neurol Sci 2001;193(1):17-22.
- 38. Akcali A, Bal B, Erbagci B. Circulating IGF-1, IGFB-3, GH and TSH levels in multiple sclerosis and their relationship with treatment. Neurol Res 2017;39(7):606-11.
- 39. Kiessling WR, Pflughaupt KW, Haubitz I, Mertens HG. Thyroid function in multiple sclerosis. Acta Neurol Scand 1980;62(4):255-8.
- 40. Jiang Y, Yang Y, Zhang B, Peng F, Bao J, Hu X. Cerebrospinal fluid levels of iodothyronines and nerve growth factor in patients with multiple sclerosis and neuromyelitis optica. Neuro Endocrinol Lett 2009;30(1):85-90
- 41. Niederwieser G, Buchinger W, Bonelli RM, Berghold A, Reisecker F, Költringer P, et al. Prevalence of autoimmune thyroiditis and non-immune thyroid disease in multiplesclerosis. J Neurol 2003;250(6):672–5.
- 42. Erhamamcı S, Horasanlı B, Aktaş A. Assessment of the effect of interferon-beta1a therapy on thyroid and salivary gland functions in patients with multiple sclerosis using quantitative salivary gland scintigraphy. Mol Imaging Radionucl Ther 2014;23(2):43-7.
- 43. Kazakou P, Tzanetakos D, Vakrakou AG, Tzartos JS, Evangelopoulos ME, Anagnostouli M, et al. Thyroid autoimmunity following alemtuzumab treatment in multiple sclerosis patients: a prospective study. Clin Exp Med 2023;23(6):2885-94.
- 44. Balasooriya NN, Elliott TM, Neale RE, Vasquez P, Comans T, Gordon LG. The association between vitamin D deficiency and multiple sclerosis: an

- updated systematic review and meta-analysis. Mult Scler Relat Disord 2024;90:105804.
- 45. Ismailova K, Poudel P, Parlesak A, Frederiksen P, Heitmann BL. Vitamin D in early life and later risk of multiple sclerosis a systematic review, meta-analysis. PLoS One 2019;14(8):e0221645.
- 46. Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyvitamin
- D levels and risk of multiple sclerosis. JAMA 2006;296(23):2832-8.
- 47. Ascherio A, Munger KL, White R, Köchert K, Simon KC, Polman CH, et al. Vitamin D as an early predictor of multiple sclerosis activity and progression. JAMA Neurol 2014;71(3):306-14.

Disfunkcija štitne žlijezde kod pacijenata sa multiplom sklerozom: učestalost i povezani faktori rizika

Daliborka Tadić^{1,2}, Sanja Grgić^{1,2}, Aleksandra Dominović Kovačević^{1,2}, Zoran Vukojević^{1,2}, Gabrijela Malešević^{1,2}, Valentina Soldat Stanković^{2,3}

¹Univerzitetski klinički centar Republike Srpske, Klinika za neurologiju, Banja Luka, Republika Srpska, Bosna i Hercegovina

²Univerzitet u Banjoj Luci, Medicinski fakultet, Banja Luka, Republika Srpska, Bosna i Hercegovina

³Univerzitetski klinički centar Republike Srpske, Klinika za endokrinologiju, Republika Srpska, Bosna i Hercegovina

Uvod. Disfunkcija štitne žlijezde prepoznata je kao jedna od najčešćih komorbidnosti kod osoba sa multiplom sklerozom (engl. people with multiple sclerosis, PwMS). Cilj ove studije bio je da se utvrdi prevalencija oboljenja štitne žlijezde i nivoa vitamina D kod pacijenata sa MS u našem regionu u poređenju sa opštom populacijom, kao i da se procijeni potencijalni uticaj statusa štitne žlijezde i nivoa vitamina D na stepen fizičke onesposobljenosti i prognozu toka MS.

Metod. Ukupno 127 ispitanika prospektivno je uključeno u studiju: 59 (46,5%) su bile zdrave osobe iz područja sa dovoljnim unosom joda, dok je 68 (53,5%) ispitanika imalo dijagnozu MS. Kod obje grupe određivani su serumski nivoi TSH, FT4, anti-TPO antitijela i vitamina D. Kod pacijenata sa MS dodatno je procijenjen stepen fizičke onesposobljenosti pomoću Kurckeove skale proširenog statusa invaliditeta (engl. EDSS - expanded disability status scale, EDSS).

Rezultati. Nije bilo značajnih razlika u prevalenciji subkliničkog hipotireoidizma ili hipertireoidizma između MS grupe i kontrola. Međutim, klinički hipotireoidizam (10,3% naspram 0%; p = 0,011) i deficit vitamina D (55,9% naspram 33,9%; p = 0,013) bili su značajno češći kod MS pacijenata. Srednji nivoi FT4 (14,02 \pm 3,38 pmol/L naspram 15,14 \pm 1,87 pmol/L; p = 0,025) i vitamina D (10,32 \pm 9,24 ng/ mL naspram 14,84 ± 12,00 ng/mL; p = 0,018) bili su značajno niži u MS grupi, dok su nivoi anti-TPO antitijela bili znatno viši kod pacijenata sa MS u poređenju sa kontrolnom grupom (201,62 ± 389,68 IU/mL naspram 89,28 \pm 253,48 IU/mL; p < 0,001). EDSS skorovi su pokazali pozitivnu korelaciju sa godinama starosti (p < 0,050), trajanjem bolesti (p < 0,001) i brojem relapsa (p < 0,001), dok je uočena negativna korelacija sa nivoima vitamina D (p < 0,050). Multivarijantna analiza identifikovala je nezavisne faktore rizika za MS, uključujući prisustvo hipovitaminoze D (OR = 2,268; p = 0,035), niže nivoe vitamina D (OR = 2,326; p = 0,003) i povišene vrijednosti anti-TPO antitijela (OR = 1,375; p = 0,042).

Zaključak. S obzirom na uticaj i funkcionalnog i autoimunog statusa štitne žlijezde, kao i nivoa vitamina D na patofiziološke mehanizme razvoja i progresije multiple skleroze, procjena ovih parametara trebalo bi da bude standardni dio zdravstvene zaštite osoba sa MS.

Ključne riječi: multipla skleroza, štitna žlijezda, vitamin D