Is thyroid autoimmunity a predisposing factor for fibromyalgia? A systematic review and meta-analysis

S. Park[1], J.-S. Kwon[2], Y.-B. Park[3,4], J.W. Park[1,5]

[1]Department of Oral Medicine and Oral Diagnosis, School of Dentistry and Dental Research Institute, Seoul National University, Seoul; [2]Department of Orofacial Pain and Oral Medicine, Yonsei Dental Hospital, Yonsei University College of Dentistry, Seoul; [3]Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul; [4]Institute for Immunology and Immunological Diseases, Yonsei University College of Medicine, Seoul; [5]Department of Oral Medicine, Seoul National University Dental Hospital, Seoul, Korea.

Seoeun Park, DDS, MSD
Jeong-Seung Kwon, DDS, PhD
Yong-Beom Park, MD, PhD
Ji Woon Park, DDS, PhD

Please address correspondence to:
Ji Woon Park,
Orofacial Pain Clinic, Department of Oral Medicine and Oral Diagnosis, School of Dentistry and Dental Research Institute, Seoul National University, 101 Yunkeun-Dong, Chongro-Ku, Seoul 03080, Korea.
E-mail: ankara01@snu.ac.kr

Received on April 25, 2021; accepted in revised form on June 21, 2021.

Clin Exp Rheumatol 2022; 40: 1210-1220.

Key words: fibromyalgia, thyroid autoimmunity, anti-thyroid peroxidase autoantibody, thyroglobulin antibody, menopause

Funding: this work was supported by the New Faculty Startup Fund from Seoul National University (no. 860-20190102) and the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (no. 2017015377).

Competing interests: none declared.

ABSTRACT

Objective. *Studies report that autoimmune thyroid disease and elevated levels of thyroid autoantibodies are associated with fibromyalgia and widespread chronic pain. The aim of this meta-analysis was to investigate the relationship between fibromyalgia and thyroid autoimmunity. Clinical symptoms and depression associated with fibromyalgia were also investigated in relation to the presence of thyroid autoantibodies.*

Methods. *A literature search was conducted on PubMed and Embase for studies published between January, 1980 and February, 2020 on thyroid autoimmunity in fibromyalgia patients. Two reviewers independently screened and assessed the quality of the articles. Meta-analysis was performed to analyse the difference in frequency of thyroid autoantibody positivity between fibromyalgia patients and healthy controls. Clinical symptoms and depression were also analysed according to the presence of thyroid autoantibodies.*

Results. *Data from 10 original studies were included in the systematic review, and 5 case-control studies that satisfied the selection criteria were subjected to meta-analysis. Thyroid autoantibody positivity was more common in fibromyalgia patients compared to healthy controls (thyroid peroxidase antibody: OR 3.41, 95% CI 1.97–5.90; thyroglobulin antibody: OR 2.23, 95% CI 1.23–4.01). The frequency of postmenopausal status was significantly higher in fibromyalgia patients with thyroid autoantibodies (OR 1.95, 95% CI 1.23–3.08). However, the severity of disease (pain and fatigue level, fibromyalgia impact questionnaire score, and disease duration) and prevalence of depression did not show a statistically significant difference according to thyroid autoantibody positivity.*

Conclusion. *Thyroid autoimmunity should be considered in fibromyalgia patients. The percentage of women in menopause was higher in thyroid autoantibody positive fibromyalgia patients.*

Introduction

Fibromyalgia (FM) is a chronic pain disorder with characteristic widespread musculoskeletal pain and related symptoms. Commonly found symptoms along with musculoskeletal pain include headache, temporomandibular disorders, morning stiffness, sleep disturbance, fatigue, stress, and mood disorders (1). Diagnostic criteria were first established by the American College of Rheumatology (ACR) in 1990 and revised in 2010 and 2016 to overcome its original weak points (2, 3). FM was once diagnosed when pain persisted for more than 3 months, tenderness was reported at more than 11 of the 18 musculoskeletal sites palpated, and no other cause of pain could be found. This has now changed to be based on the self-reported Widespread Pain Index and a symptom severity scale, and does not exclude the diagnosis of other clinical diseases (4). The prevalence of FM varies widely from 0.66–10.5% of the general population according to the diagnostic criteria applied and it remains highly underdiagnosed and undertreated (5). However, it is generally accepted as a frequent pain disorder that affects around 2–4% of the adult population and is more prevalent in women (6). In spite of various efforts, the underlying mechanism of FM has not been fully revealed. Currently the syndrome is considered as a phenomenon of central disinhibition resulting in pain amplification that is generated by environmental and genetic factors with the role of inflammation increasingly being investigated (7, 8). Interestingly FM is commonly found in autoimmune

disease patients and the titer of certain autoantibodies are elevated in patients with FM compared to healthy controls (9). Autoimmune thyroid disease is one of the most common immune-mediated diseases characterised by the existence of autoantigens such as thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TgAb), which play a role in loss of self-tolerance (10). It has been reported that thyroid autoantibodies are increased in several rheumatic diseases including systemic lupus erythematosus and rheumatoid arthritis (11,12) and thyroid autoimmunity may be associated with other systemic autoimmune diseases (13). The frequency of thyroid autoimmunity is known to be higher in FM (14) and speculative immunological aberration has been suggested as a possible cause of FM based on such observations (15). Unfortunately, most studies are based on relatively small sample sizes that are insufficient to determine the association between thyroid autoimmunity and FM individually.

Therefore, we conducted a systematic review and meta-analysis specifically focused on the relationship between FM and its related symptoms and the presence of thyroid autoantibodies, to determine the role of thyroid autoimmunity in the pathogenesis of FM and evaluate the need of thyroid autoantibody assessment in its diagnosis.

Methods

This review followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (16).

Data sources and search strategy

An electronic literature search was conducted on PubMed and Embase for English language studies published between January, 1980 and February, 2020 with the MeSH terms "fibromyalgia or widespread pain" and "thyroid autoantibody or thyroid antibody or thyroid autoimmunity or antithyroglobulin antibody or thyroperoxidase antibody or anti-TPO". The last search was performed on February 24, 2020.

Study selection

All resulting study titles and abstracts were screened and selected by 2 independent reviewers (S.E.P. and J.W.P.). Article evaluation followed a hierarchical approach in the order of title, abstract, and full manuscript. The disagreement in choice was resolved through discussion until consensus was reached.

Eligibility criteria

Studies with human participants in the form of case-control, cohort, cross-sectional, and clinical studies were included. The specific selection criteria for the studies included in the final meta-analysis were as follows: (1) a case-control design was used; (2) diagnosis of FM was based on 1990 or 2010 ACR criteria; (3) the relationship between FM and thyroid autoimmunity was investigated through evaluation of TPOAb and/or TgAb levels. There was no restriction concerning age and gender of the subjects from each study.

Publications with only abstracts, case reports, letters and comments, articles written in languages other than English, inaccessible articles, articles that did not study the association between FM and thyroid autoimmunity were all excluded. Also, articles that only presented the mean without descriptive values of thyroid autoantibodies could not be included in the meta-analysis.

Data extraction

Data regarding first author, publication year, number of cases and controls, study population, participant characteristics (age, gender), clinical parameters (menopause status, pain and fatigue level, fibromyalgia impact questionnaire (FIQ) score, disease duration, presence of depression and/or anxiety), diagnostic criteria for FM, the cut-off value for defining thyroid autoantibody positivity, and number of cases and controls positive for each type of thyroid autoantibody were extracted.

Risk of bias

The 2 reviewers applied the Newcastle-Ottawa Assessment Scale, a risk of bias assessment tool recommended by the Cochrane Collaboration Study in evaluating the quality of studies (17). Selection and comparability of cases/controls and ascertainment of exposure were evaluated accordingly. Of the total score of 9, studies between 7-9 were considered high quality, 4-6 were considered medium quality and ≤3 were considered low quality.

Statistical analysis

The relationship between thyroid autoimmunity and FM was evaluated by calculating the odds ratio (OR) and the corresponding 95% confidence interval (CI). Continuous outcomes that were based on identical measurement tools and expressed as mean and standard deviation (SD) in the original study were analysed yielding the estimated effect as the mean difference (MD) with a 95% CI. Depression indices were expressed as the standardised mean difference (SMD) with a 95% CI since depression indices were based on different scales in independent studies. Mata-analysis was performed using RevMan, v. 5.3 (Cochrane Collaboration, Copenhagen, Denmark), and both random effect model and fixed effect models were selected according to heterogeneity assessed by chi-square test and I^2 (18). Mantel-Haenszel method was used for dichotomous outcomes and the inverse variance method for continuous outcomes.

Results

Results of database search

The initial search yielded 724 articles among which 345 articles were duplicates. After reviewing the abstracts, 352 studies were excluded. Reasons for exclusion were non-English articles (n=2), publication of abstracts (n=3), inaccessible articles (n=1), and irrelevant studies (n=346). Twenty-seven studies were included in the full text review. Eight review articles were then excluded. The excluded review articles were not solely focused on FM and also the original studies had already been included in our systematic review and meta-analysis. Three papers were excluded because they studied rheumatoid arthritis, temporomandibular disorders, and arterial stiffness in FM patients. One study that was excluded was a case report of myalgia in a Graves' disease patient. Two studies were ex-

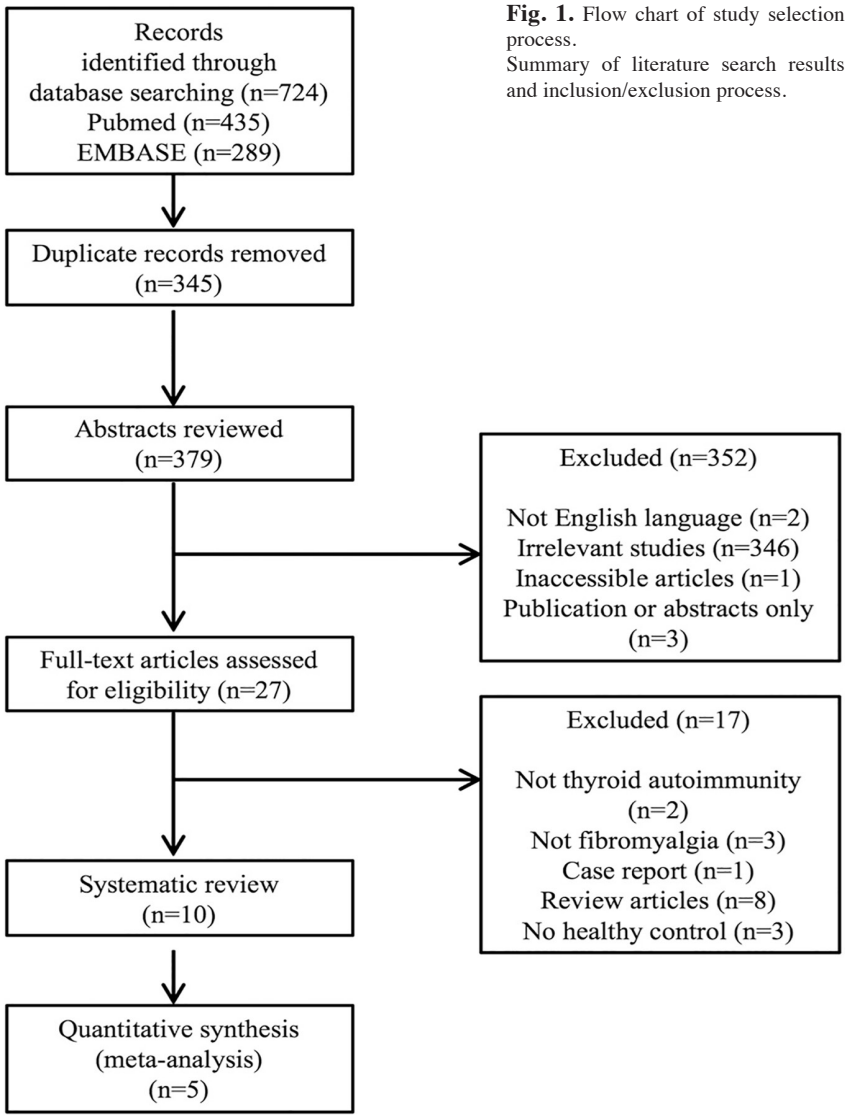

Fig. 1. Flow chart of study selection process.
Summary of literature search results and inclusion/exclusion process.

cluded because they did not report thyroid autoantibody levels and only reported antinuclear antibody data. Two studies examined rheumatic manifestations with autoimmune thyroid diseases with no healthy controls. Another article was a study of musculoskeletal manifestations in patients with thyroid disease with no healthy controls that were not diagnosed with FM. A total of 17 studies were excluded after full text review and the remaining 10 studies were included in the final systematic review (14, 19-27). Five of these studies were included in the meta-analysis (14, 20, 23-25). The detailed selection procedure is presented in Figure 1.

Characteristics of included studies

The 10 studies included 2 cross-sectional studies, 7 case-control studies and 1 retrospective study. The characteristics of each article are summarised in Table I. Six studies abided by the 1990 ACR criteria and 2 by the 2010 ACR criteria, while 2 did not specify the diagnostic criteria applied in their study. Eight studies had controls and 2 did not. Number of cases ranged from 37 to 207 patients according to the study. TPOAb and TgAb was assessed in 7 studies (14, 20-24, 26) thyroid stimulating hormone receptor antibody (TRAb) additionally in 1 study (27) and TPOAb only in 2 studies (19, 25). Risk of bias was low for the various items assessed. All 5 case-control studies included in the meta-analysis were of medium to high quality based on the Newcastle-Ottawa Assessment Scale. Detailed results of the quality assessment are shown in Table II.

Meta-analysis results

The meta-analysis included a total of 499 FM patients and 277 healthy controls.

- Thyroid autoimmunity

Serum TPOAb and TgAb levels were measured by an immunometric assay.

Table I. Quality assessment of studies included in the meta-analysis.

Studies	Selection				Comparability	Exposure			Total
	Case definition adequate	Representativeness of cases	Selection of controls	Definition of controls	Comparability on basis of design or analysis (cases and controls)	Ascertainment of exposure	Same ascertainment method (cases and controls)	Non-response rate	
Pamuk 2007 (14)	*	*	*	*	*	*	*	-	7
Bazzichi 2007 (20)	*	*	-	*	*	*	*	-	6
Başkan 2010 (23)	*	*	-	*	*	*	*	-	6
Bazzichi 2012 (24)	*	*	*	*	*	*	*	-	7
Suk 2012 (25)	*	*	-	*	*	*	*	-	6

The use of stars awarded for each criterion was based on the Ottawa-Newcastle system (17).

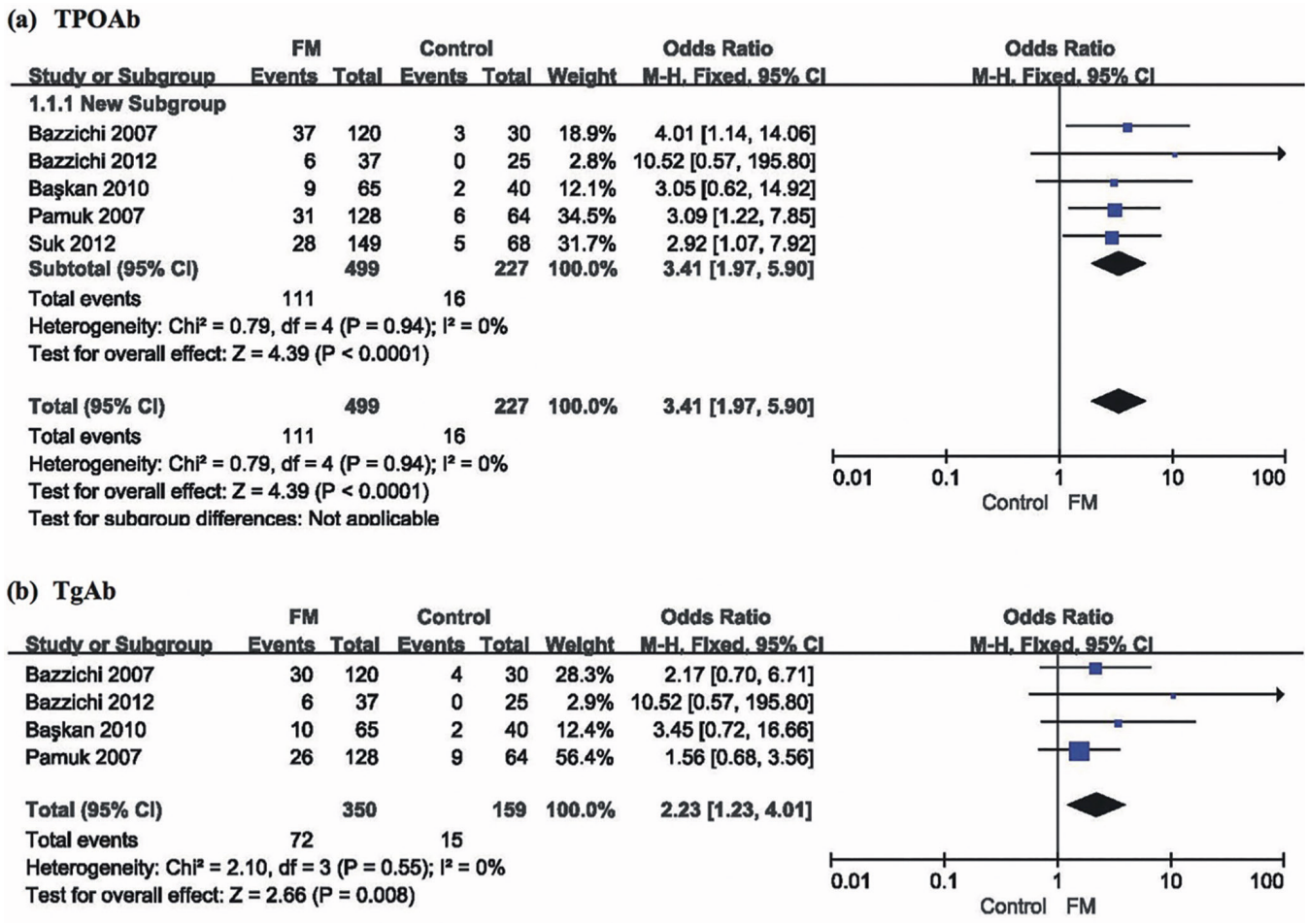

Fig. 2. Thyroid autoantibody positivity in fibromyalgia patients compared to healthy controls. The prevalence of thyroid autoantibody positivity was higher in FM patients than in healthy controls. TPOAb: thyroid peroxidase antibody; TgAb: thyroglobulin antibody.

The results of this meta-analysis indicated that thyroid autoantibody positivity was more prevalent in FM patients than in healthy controls. (TPOAb: OR 3.41; 95% CI 1.97–5.90, TgAb: OR 2.23; 95% CI 1.23–4.01). No heterogeneity was detected among the studies (I^2=0%). The forest plot is shown in Figure 2.

- Postmenopausal status

Three studies described menopausal status of FM patients. Meta-analysis showed that the proportion of postmenopausal patients was significantly higher in patients with thyroid autoantibodies. (OR 1.95, 95%; CI 1.23–3.08). No heterogeneity was detected among the studies (I^2=0%). The forest plot is shown in Figure 3.

- Pain level

Four studies described widespread pain level based on visual analogue scale (VAS) scores. The results of meta-analysis indicated that the level of pain was not correlated with the presence of thyroid autoantibodies. The pooled MD across the studies was -0.02 (95% CI -4.25–4.22). No heterogeneity was detected among the studies (I^2=0%). The forest plot is shown in Figure 3.

- Fatigue level

Two studies described fatigue score based on VAS. The results of meta-analysis showed that fatigue score was not associated with the presence of thyroid autoantibodies. This may be due to the considerable heterogeneity between the 2 studies. (I^2=82%). The forest plot is shown in Figure 3.

- Fibromyalgia impact questionnaire score

Three studies described FIQ scores. The results of meta-analysis showed that FIQ score was not significantly associated with the presence of thyroid autoantibodies. The pooled MD across the studies was 0.51 (95% CI:-3.93–4.95). No heterogeneity was detected among the studies (I^2=0%). The forest plot is shown in Figure 3.

- Disease duration

Four studies described the duration of FM. The results of meta-analysis showed that patients with thyroid autoantibodies had a longer disease duration. However, the differences were not statistically significant. The pooled MD across the studies was 1.35 (95% CI -0.14–2.84). Negligible heterogeneity was detected among the studies (I^2=23%). The forest plot is shown in Figure 3.

- Depression

Psychological problems were discussed in 3 studies. Two studies presented numerical results that could be

Table II. Characteristics of studies included in the review.

Study	Level of evidence	Region	Type of study	Study objective	FM case	Control	Thyroid antibody	Main outcome	Conclusion
Aarflot 1996 (19)	Low	Norway	Cross-sectional	Investigate relationship between thyroid antibodies and chronic widespread musculoskeletal complaints	Continuous complaints of at least three months' duration during the previous twelve months, if it involved five or more regions on the Nordic form body map by questionnaire N=152 (age: 40-42 years, F:113, M:43)	The people who answered the questionnaire not diagnosed as widespread musculoskeletal pain N=1352 (age: 40-42 years, F:658, M:694)	TPOAb (positive: ≥100)	Prevalence of TPOAb was significantly higher in persons with chronic widespread musculoskeletal complaints. ($p<0.05$) Thyroid function tests did not differ significantly between the two groups	Association between chronic widespread musculoskeletal pain complaints and thyroid antibodies may reflect a subgroup of patients in which thyroid autoimmunity is important
Ribeiro 2004 (22)	Medium	Brazil	Case-control	Detect and quantify association between FM and thyroid autoimmunity	Women over 18 years old diagnosed with FM by ACR 1990 criteria N = 146	Women over 18 years old who did not meet the ACR criteria N=74	TPOAb (positive: ≥40 IU/ml) TgAb (positive: ≥35 IU/ml)	There is an association between FM and thyroid autoimmunity OR=3.87), depression ((OR=3.94), and age (OR=1.04)	Association between FM and thyroid autoimmunity
Pamuk 2007* (14)	High	Turkey	Case-control	Determine frequency of thyroid antibodies in FM patients and investigate relationship between FM symptoms, findings accompanying FM, and thyroid autoantibodies	Euthyroid FM patients diagnosed by ACR 1990 criteria N=128 (mean age: 43.1 years, F:122, M:6)	Healthy volunteers matched for age and sex N=64 (mean age: 45.2 years, F:58, M:6)	TPOAb (positive: ≥35 IU/ml) TgAb (positive ≥40 IU/ml)	Prevalence of thyroid autoimmunity was significantly higher in FM patients than in controls (p=0.025)	Association between thyroid autoimmunity and FM Thyroid autoimmunity had no relationship with depression scores of FM patients
Bazzichi 2007* (20)	Medium	Italy	Case-control	Investigate thyroid abnormalities and autoimmunity in patients affected by FM and study their relationships with clinical data and symptoms	FM patients diagnosed by ACR 1990 criteria N=120 (mean age: 50.64 years, F:115, M:5)	Healthy people matched for sex and age N=30 (mean age: 48.6 years, F:26, M:4)	TPOAb (positive: ≥10 IU/ml) TgAb (positive: ≥50 IU/ml)	Prevalence of thyroid autoimmunity was higher in FM patients than in controls Patients with thyroid autoimmunity showed a higher percentage of dry eyes, burning pain with urination, allodynia, blurred vision and sore throat Number of postmenopausal patients was higher in the group with positive TgAb	Thyroid autoimmunity is marker of the severity of FM, especially postmenopausal patients
Başkan 2010* (23)	Medium	Turkey	Case-control	Evaluate presence of thyroid autoantibodies in patients with FM and investigate the relationship of these antibodies with depression, quality of life, and disease symptoms	Women diagnosed with FM by ACR 1990 criteria N = 65 (mean age: 43.12 years)	Healthy female matched for age N=40 (mean age: 45.75 years)	TPOAb (positive: ≥35 IU/ml) TgAb (positive: ≥116 IU/ml)	Rates of TPOAb and TgAb positivity were 13.8% and 15.4%, and 5.0% and 5.0% in the FM and control groups, respectively. There was no statistically significant difference between the groups Mean ESR, CRP, and TSH levels and the proportion of postmenopausal women were higher in FM patients with autoimmunity	No significant differences between FM patients and healthy controls in terms of thyroid autoimmunity

Bazzichi 2012* (24)	High	Italy	Case-control	Evaluate predisposition for the development of FM in patients with HT with or without SCH and in patients with SCH alone and weight of antithyroid antibody positivity and SCH on FM comorbidity	FM patients diagnosed by ACR 1990 criteria N=37 (mean age: 46.54 years, F:33, M:4)	Healthy people matched for sex age and BMI N=25 (mean age: 44.13 years, F:23, M:2)	TPOAb (positive: ≥40 IU/ml) TgAb (positive: ≥100 IU/ml)	HT patients with FM had higher and significant incidence of positive TPs, diffuse pain, atigue, paresthesiae, non-restfulf sleep, affective disorders, FIQ, VAS fatigue and VAS pain with respect to SCH patients	Significant association between thyroid autoimmunity and FM
Suk 2012* (25)	Medium	Korea	Case-control	Investigate prevalence of positive TPOAb in euthyroid FM patients, and whether TPOAb positivity is associated with clinical manifestations in euthyroid FM patients.	FM patients diagnosed by ACR 1990 criteria N=149 (mean age: 51.2 years, F:139, M:10)	Healthy people matched for age and sex N=68 (mean age: 52.2 years, F:61, M:7)	TPOAb (positive: ≥60 IU/ml)	FM patients showed higher prevalence of positive TPOAb than healthy controls (p=0.04) There was no difference of clinical and laboratory parameters in FM patients between 2 groups subdivided by the presence of TPOAb	Thyroid autoimmunity may influence the development of FM, but FM severity may not be affected by the presence of thyroid autoantibody
Ahmad 2015 (26)	Low	USA	Retrospective study	Investigate how autoimmune thyroiditis affects clinical presentation of established rheumatoid arthritis with particular reference to FM and CWP	204 RA patients for whom the presence or absence of autoimmune thyroid autoantibodies TPOAb and/or TgAb was documented		TPOAb (positive: ≥5 IU/ml) TgAb (positive: ≥10 IU/ml)	TPOAb and TgAb were positive in 29% and 24%, respectively Among the thyroid autoantibody-positive patients, 40% had a diagnosis of FM or CWP versus 17% for antibody negative patients TPOAb-positive patients were more likely to be diagnosed with FM and report the presence f CWP (OR=4.64, P<0.001) Significant relationship between TPOAb and FM or CWP in patients without diabetes (OR=4.873, P=0.001) and those without hypothyroidism (OR=4.615, P=0.001)	Association of TPOAb with FM and CWP
Haliloglu 2017 (21)	Medium	Turkey	Case-control	Identify the prevalence of FM in the HT population and evaluate associated features	FM was assessed according to 2010 criteria of the ACR in 79 patients diagnosed with HT. 49 patients were diagnosed with FM. (mean age: 38.1 years)	Healthy volunteers matched for age and sex N=35 (mean age:33.9 years)	TPOAb (positive: ≥35 IU/ml) TgAb (positive: ≥40 IU/ml)	TPOAb positivity higher in the HT plus FM group (p=0.000) Duration of disease was significantly more in patients with HT plus FM than in patents with HT without FM (p=0.000)	Concomitant FM is a common clinical problem in HT
Nishioka 2017 (27)	Medium	Japan	Cross-sectional	Explore prevalence of thyroid autoimmunity in FM patients diagnosed with 2010 ACR criteria.	Evaluation of thyroid autoimmunity by blood test in 207 FM patients		TPOAb (positive: ≥35 IU/ml) TRAb, TgAb and TPOAb in FM patients TgAb (positive: ≥40 IU/ml) TRAb (positive: ≥1.0 IU/l)	Prevalence of positivity for among patients with was 23.3%, 16.5%, and 13.2%, respectively	High prevalence of AI clinically defined FM, with TRAb being especially prominent.

* Included in the meta-analysis.

FM: fibromyalgia; F: female; M: male; ACR: American College of Rheumatology; TPOAb: thyroid peroxidase antibody; TgAb: thyroglobulin antibody; OR: odds ratio; FIQ: fibromyalgia impact questionnaire; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; TSH: thyroid stimulating hormone; SCH: subclinical hypothyroidism; BMI: body mass index; TP: tender point; VAS: visual analogue scale; CWP: chronic widespread pain; RA: rheumatoid arthritis; AITD: autoimmune thyroid diseases; HT: Hashimoto thyroiditis; TRAb: thyroid stimulation hormone receptor antibody.

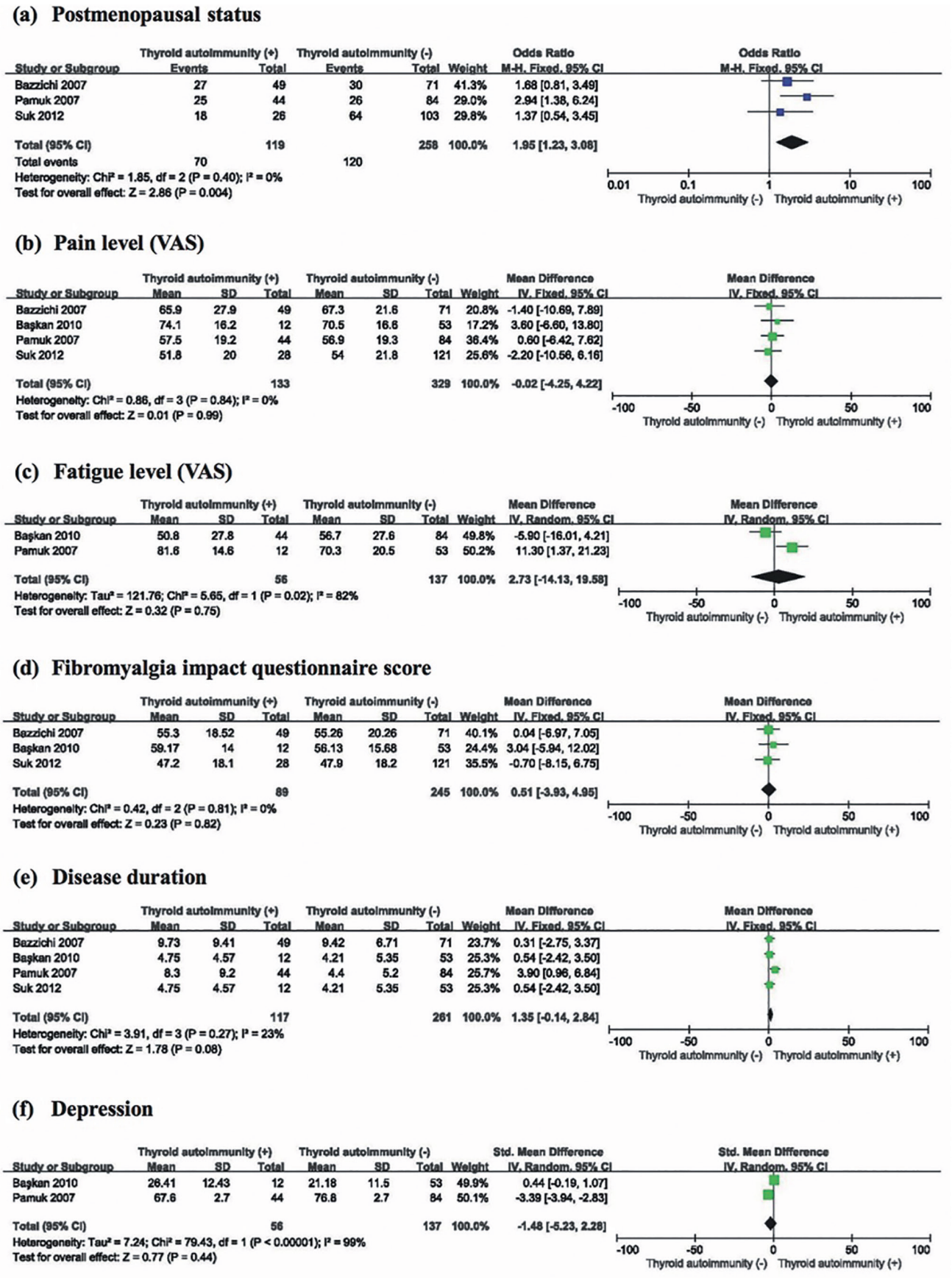

Fig. 3. Clinical symptoms and depression according to thyroid autoimmunity. The proportion of postmenopausal patients was higher in FM patients with thyroid autoimmunity than in healthy controls. VAS: visual analogue scale; FIQ: fibromyalgia impact questionnaire; FM: fibromyalgia.

included in the meta-analysis. Beck's Depression Inventory and Duke Anxiety-Depression Scale were applied, respectively. Meta-analysis results indicated that depression was not related to the presence of thyroid autoantibodies. The pooled SMD across studies was -1.48 (95% CI -5.23–2.28). This may be due to the considerable heterogeneity between the two studies. (I^2=99%). The forest plot is shown in Figure 3.

- Risk of bias

As shown in Figure 4, the funnel plot for publication bias of the reviewed articles was asymmetrical, suggesting that studies with small effect sizes and small sample sizes may not have been published. Begg's test to statistically confirm the symmetry of the plot could not be performed due to having only 5 studies in the meta-analysis.

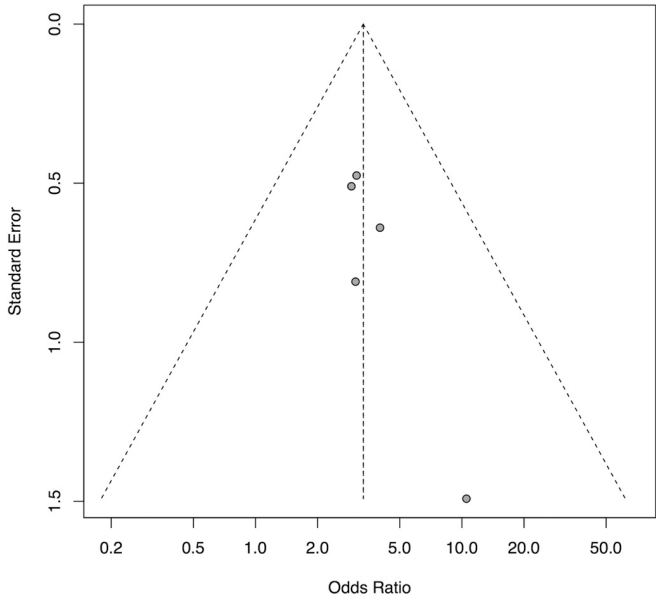

Fig. 4. Funnel plot to assess publication bias corresponding to the fixed effect model. The funnel plot shows asymmetry, suggesting the possibility of studies with small effect and small sample size being unpublished.

Discussion

The aim of this systematic review and meta-analysis was to evaluate the relationship between thyroid autoimmunity and FM and the results showed that thyroid autoantibody positivity is more prevalent in FM patients compared to healthy controls, thus suggesting the need to consider thyroid autoimmunity in the diagnosis of FM for certain cases. All forms of autoimmune thyroid diseases are associated with the formation of thyroid autoantibodies including TPOAb and TgAb. Autoimmunity in the absence clinical autoimmune disease has been diagnosed based on the presence of such autoantibodies. Recent studies on the association of thyroid autoimmune disease with various disorders include type I diabetes (28), neurological disorder (29), stress (30), and vitamin D deficiency (31). The results of such studies show that there is a significant relationship between such diseases and thyroid autoimmunity and that an increased risk for the aforementioned diseases may be considered in those that show the presence of thyroid autoantibodies. FM is another disorder that is often associated with autoimmune thyroid disease. Such assumptions were partially based on the fact that FM shares certain characteristics that are similar to those of hypothyroidism including muscle symptoms. However, previous studies are unfortunately based on different diagnostic criteria and definitions of FM and the gender and age distribution of the study groups differ widely hindering the direct comparison of results and deduction of conclusions. Therefore, there was a need to conduct a meta-analysis on the correlation between FM and thyroid autoimmunity based on all individual studies through quantitative analysis. Nine of the 10 studies we analysed showed a significant correlation between FM and the presence of thyroid autoantibodies. On the other hand, 1 study reported that there was no statistically significant difference in thyroid autoantibody levels between FM patients and healthy controls (23). The result of this meta-analysis indicated that the prevalence of thyroid autoimmunity was significantly higher in patients with FM than in healthy controls. Among thyroid autoantibodies, the presence of TPOAb imposed a higher risk for FM compared to TgAb. Generally, FM is considered as a non-inflammatory, non-autoimmune disease, but some patients display autoimmune features and FM is prevalent in autoimmune diseases. However, it is difficult to conclude that FM is an autoimmune disorder since reports on immunological markers are inconsistent. FM symptoms may be an early symptom of autoimmune diseases in certain cases since their strong correlation cannot be ignored, and thyroid autoimmune disease is among the differential diagnoses that should be considered (9). Thyroid hormone resistance that is often recognised in FM patients has been suggested as a main factor that may lead to characteristic symptoms of FM such as musculoskeletal pain and fatigue although it is difficult to comment on the role of hormone resistance based on the results of this meta-analysis (32). Pre-subclinical hypothyroidism may be suspected in euthyroid subjects with chronic autoimmune thyroiditis when muscle pain symptoms are present which may be due to the muscle damage caused by autoimmune inflammation (19, 33).

The association between various clinical parameter of FM and the level of thyroid autoantibodies was also analysed in the studies included in the meta-analysis, and some significant correlations existed. A previous study showed that the percentage of patients with postmenopausal status, headache, dry mouth, and previous psychiatric treatment history was significantly higher with thyroid autoimmune positivity compared to the negative group (14). Another study showed that dry eye, burning sensation with urination, allodynia, blurred vision, and sore throat were significantly more prevalent in the group with thyroid autoantibody positivity (20). On the other hand, 2

studies did not find a statistically significant correlation between the presence of thyroid autoantibodies and the severity of clinical parameters (23, 25). The results of this meta-analysis showed the presence of a statistically significant correlation between postmenopausal status and thyroid autoantibody positivity. For the other clinical parameters analysed including pain and fatigue level, FIQ score, disease duration, and depression, there was no association with the presence of thyroid autoantibodies. Although not statistically significant, patients with thyroid autoantibodies tended to have a longer disease duration compared to those who did not. Studies exist that report an increased level of high-sensitivity C-reactive protein (hs-CRP) in FM patients compared to healthy controls (34) and also in those with certain thyroid diseases (35). On the other hand, FM patients frequently show clinically normal hs-CRP levels, necessitating further studies to verify the role of systemic inflammation as a common factor that may contribute to the initiation and maintenance of symptoms in both diseases.

Thyroid autoimmunity is generally more common in women and this is partially explained by the action of sex hormones on the immune system. Early menarche and late menopause have been indicated as a risk factor for autoimmune thyroiditis since sex hormones may regulate the underlying mechanism of thyroid autoimmunity (36). In fact, serum thyroid autoantibodies can be detected in up to 25% of women over age 60, and autoimmune hypothyroidism is 8-9 times more common in women with this imbalance increasing with age (37). Considering the effect of age, the higher percentage of postmenopausal patients in the thyroid autoimmune positive group could be a result of different age-dependent sex hormone conditions that are known to influence the expression and distribution of various thyroid hormone receptors (38). Further investigations are needed to determine the exact pathology concerning the association of sex hormones and thyroid autoantibodies. Based on the results of this meta-analysis, examination of the thyroid should be considered especially in postmenopausal women with FM. Future studies are also necessary to determine the best method or frequency of screening for thyroid autoimmunity in FM patients since this could not be identified from the available data. Also, whether screening improves clinical outcomes in the FM population is another issue that should be addressed.

The relationship between thyroid autoimmunity and depression has been discussed in a few studies with conflicting results. Some state that no associations were found between thyroid autoantibody level and depression (39). However, 1 study found that elevated TPOAb levels were significantly associated with depression (OR 3.0, 95% CI 1.3-6.8) (40). Thus, the association between the presence of thyroid autoantibodies and depression in FM patients was evaluated in this study, and the results showed that there was no relevance between the two. However, more recent reviews and meta-analysis state that thyroid autoimmunity is associated with depressive and bipolar disorder (41-43). Regrettably, the number of studies that met the inclusion criteria for this meta-analysis were small, so additional research will be needed to further verify the relationship between thyroid autoimmunity and depression in FM patients.

The results of this study showed that the presence of thyroid autoantibodies did not have a major impact on the severity of FM symptoms itself which is reflected in the fact that there was no difference in pain and fatigue VAS scores, and FIQ scores according to thyroid autoimmunity. In a previous study on Hashimoto thyroiditis patients with or without FM, FIQ scores showed a strong positive correlation with TPOAb values (21). Another study reported that FM patients showed a higher prevalence of TRAb positivity compared to the general population. However, there was no significant difference in the prevalence of TPOAb positivity compared to controls and symptom profiles were identical for cases of FM patients with or without thyroid autoimmunity (27). Still another study supported such results stating that FM severity may not be affected by the presence of thyroid autoantibodies (25). The reason why thyroid autoimmunity does not affect FM disease severity is unclear and cannot be explained by the results of this study. Previous reports on the association between thyroid autoimmunity and FM severity are inconsistent and has been based on different symptoms and evaluation tools. Future studies based on standardised approaches are necessary to further clarify this issue.

There are some limitations of this study. Our findings are based on a relatively small number of studies and this is also the main cause of the evident publication bias. More high-quality studies are needed for accurate analyses on certain clinical parameters. The insignificance found in certain clinical differences according to thyroid autoimmunity may be due to inter-assay and laboratory variability in thyroid autoimmunity measurement methods, and differences in cut-off values for defining thyroid autoantibody positivity. In our systematic review, the cut-off value to determine thyroid autoantibody positivity could be seen to vary from 5 to 40 IU/ml for TPOAb and from 10 to 116 IU/ml for TgAb. In addition, the fact that the 1990 or the revised 2010 ACR criteria for the diagnosis of FM was selected according to different studies contributed to the heterogeneity. Future studies based on the more recently updated ACR diagnostic recommendations are necessary (4).

Autoantibodies are known to be found in healthy populations. Approximately 10% of healthy people are known to exhibit TPOAb and this value may increase to reach 30% in the elderly population (44). Furthermore, autoimmune diseases are known to be relatively common in the general population. However, clinical manifestations are non-specific, especially in the early stage of the disease, resulting in a high rate of under-diagnosis. Considering such circumstances and the significantly higher prevalence of thyroid autoantibodies found in this study, the measurement of thyroid autoantibodies may be a useful diagnostic approach in FM patients to detect and manage possible thyroid dysfunction at an early

stage to prevent further aggravation of FM symptoms. Further studies are necessary to determine a cut-off value for thyroid autoantibodies with the highest predictive value.

Despite such limitations this systematic review and meta-analysis is meaningful as it is the first attempt to investigate the association between FM and thyroid autoimmunity following the methodological criteria of systematic reviews and conduct meta-analysis with studies conforming to quality assessment scale (16, 17). More prospective cohort studies based on standardised diagnostic criteria and measurement methods should be conducted to further elucidate the true relationship between FM and thyroid autoantibodies, and such studies should include the evaluation of various FM symptoms such as pain and fatigue along with comorbidities including depression and sleep problems in relation to thyroid autoimmunity.

Conclusion

FM is associated with the increased presence of thyroid autoimmunity, especially among women with postmenopausal status. Such findings support the possible role of thyroid autoimmunity in FM pathophysiology, even though differentiating FM as an autoimmune disease may be speculative at the present time. However, a thyroid function and autoantibody test should be considered in female FM patients with postmenopausal status for its early diagnosis.

References

1. HÄUSER W, ABLIN J, FITZCHARLES MA *et al*.: Fibromyalgia. *Nat Rev Dis Primers* 2015; 1: 15022.
2. WOLFE F, SMYTHE HA, YUNUS MB *et al*.: The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum* 1990; 33: 160-72.
3. WOLFE F, CLAUW DJ, FITZCHARLES MA *et al*.: The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res* (Hoboken) 2010; 62: 600-10.
4. WOLFE F, CLAUW DJ, FITZCHARLES MA *et al*.: 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. *Semin Arthritis Rheum* 2016; 46: 319-29.
5. CAVALCANTE AB, SAUER JF, CHALOT SD *et al*.: A prevalência de fibromialgia: uma revisão de literatura. *Rev Bras Reumatol* 2006; 46: 40-8.
6. WOLFE F, ROSS K, ANDERSON J, RUSSELL J, HERBERT L: The prevalence and characteristics of Fibromyalgia in the general population. *Arthritis Rheum* 1995; 38: 19-28.
7. BUSKILA D, SARZI-PUTTINI P: Biology and therapy of fibromyalgia. Genetic aspects of fibromyalgia syndrome. *Arthritis Res Ther* 2006; 8: 218-22.
8. BAZZICHI L, GIACOMELLI C, CONSENSI A *et al*.: One year in review 2020: fibromyalgia. *Clin Exp Rheumatol* 2020; 38 (Suppl. 123): S3-8.
9. BUSKILA D, SARZI-PUTTINI P: Fibromyalgia and autoimmune diseases: the pain behind autoimmunity. *Isr Med Assoc J* 2008; 10: 77-8.
10. MCLACHLAN SM, RAPOPORT B: Breaking tolerance to thyroid antigens: changing concepts in thyroid autoimmunity. *Endocr Rev* 2014; 35: 59-105.
11. PAN XF, GU JQ, SHAN ZY: Increased risk of thyroid autoimmunity in rheumatoid arthritis: a systematic review and meta-analysis. *Endocrine* 2015; 50: 79-86.
12. FERRARI SM, ELIA G, VIRILI C, CENTANNI M, ANTONELLI A, FALLAHI P: Systemic lupus erythematosus and thyroid autoimmunity. *Front Endocrinol* (Lausanne) 2017; 8: 138.
13. FALLAHI P, ELIA G, RAGUSA F *et al*.: The aggregation between AITD with rheumatologic, or dermatologic, autoimmune diseases. *Best Pract Res Clin Endocrinol Metab* 2019; 33: 101372.
14. PAMUK ON, CAKIR N: The frequency of thyroid antibodies in fibromyalgia patients and their relationship with symptoms. *Clin Rheumatol* 2007; 26: 55-9.
15. ANDRÉS-RODRÍGUEZ L, BORRÀS X, FELIU-SOLER A *et al*.: Peripheral immune aberrations in fibromyalgia: A systematic review, meta-analysis and meta-regression. *Brain Behav Immun* 2019; 1591: 31274-7.
16. MOHER D, LIBERATI A, TETZLAFF J *et al*.: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009; 339: b2535.
17. WELLS GA, SHEA B, O'CONNELL D *et al*.: The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Internet]. 2019. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
18. CUMPSTON M, LI T, PAGE MJ *et al*.: Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst Rev* 2019; 10: ED000142.
19. AARFLOT T, BRUUSGAARD D: Association between chronic widespread musculoskeletal complaints and thyroid autoimmunity. Results from a community survey. *Scand J Prim Health Care* 1996; 14: 111-5.
20. BAZZICHI L, ROSSI A, GIULIANO T *et al*.: Association between thyroid autoimmunity and fibromyalgic disease severity. *Clin Rheumatol* 2007; 26: 2115-20.
21. HALILOGLU S, EKINCI B, UZKESER H, SEVIMLI H, CARLIOGLU A, MACIT PM: Fibromyalgia in patients with thyroid autoimmunity: prevalence and relationship with disease activity. *Clin Rheumatol* 2017; 36: 1617-21.
22. RIBEIRO LS, PROIETTI FA: Interrelations between fibromyalgia, thyroid autoantibodies, and depression. *J Rheumatol* 2004; 31: 2036-40.
23. BAŞKAN BM, SIVAS F, AKTEKIN LA *et al*.: Relationship between thyroid autoimmunity and depression, quality of life, and disease symptoms in patients with fibromyalgia and rheumatoid arthritis. *Arch Rheumatol* 2010; 25: 130-6.
24. BAZZICHI L, ROSSI A, ZIRAFA C *et al*.: Thyroid autoimmunity may represent a predisposition for the development of fibromyalgia? *Rheumatol Int* 2012; 32: 335-41.
25. SUK JH, LEE JH, KIM JM: Association between thyroid autoimmunity and fibromyalgia. *Exp Clin Endocrinol Diabetes* 2012; 120: 401-4.
26. AHMAD J, BLUMEN H, TAGOE CE: Association of antithyroid peroxidase antibody with fibromyalgia in rheumatoid arthritis. *Rheumatol Int* 2015; 35: 1415-21.
27. NISHIOKA K, UCHIDA T, USUI C *et al*.: High prevalence of anti-TSH receptor antibody in fibromyalgia syndrome. *Int J Rheum Dis* 2017; 20: 685-690.
28. SHUN CB, DONAGHUE KC, PHELAN H, TWIGG SM, CRAIG ME: Thyroid autoimmunity in Type 1 diabetes: systematic review and meta-analysis. *Diabet Med* 2014; 31: 126-35.
29. FERRACCI F, CARNEVALE A: The neurological disorder associated with thyroid autoimmunity. *J Neurol* 2006; 253: 975-84.
30. MIZOKAMI T, WU LI A, EL-KAISSI S, WALL JR: Stress and thyroid autoimmunity. *Thyroid* 2004; 14: 1047-55.
31. WANG J, LV S, CHEN G *et al*.: Meta-analysis of the association between vitamin D and autoimmune thyroid disease. *Nutrients* 2015; 7: 2485-98.
32. GARRISON RL, BREEDING PC: A metabolic basis for fibromyalgia and its related disorders: the possible role of resistance to thyroid hormone. *Med Hypotheses* 2003; 61: 182-9.
33. MÁRQUEZ A, FINOL HJ, DE BLANCO MC, ADJOUNIAN H, PULIDO-MÉNDEZ M: Skeletal muscle microvascular alterations in euthyroid and hypothyroid patients with autoimmune thyroid disease. *J Submicrosc Cytol Pathol* 2001; 33: 425-32.
34. GROVEN N, FORS EA, REITAN SK: Patients with Fibromyalgia and Chronic Fatigue Syndrome show increased hsCRP compared to healthy controls. *Brain Behav Immun* 2019; 81: 172-7.
35. STANCIU AE, SERDAREVIC N, HURDUC AE, STANCIU MM: IL-4, IL-10 and high sensitivity-CRP as potential serum biomarkers of persistent/recurrent disease in papillary thyroid carcinoma with/without Hashimoto's thyroiditis. *Scand J Clin Lab Invest* 2015; 75: 539-48.
36. FRANCESCHI C, OSTAN R, MARIOTTI S, MONTI D, VITALE G: The aging thyroid: a reappraisal within the geroscience integrated perspective. *Endocr Rev* 2019; 40: 1250-70.
37. LAURBERG P, CERQUEIRA C, OVESEN L *et al*.: Iodine intake as a determinant of thyroid

disorders in populations. *Best Pract Res Clin Endocrinol Metab* 2010; 24: 13-27.
38. SAYEM ASM, GIRIBABU N, KARIM K, SI LK, MUNIANDY S, SALLEH N: Differential expression of the receptors for thyroid hormone, thyroid stimulating hormone, vitamin D and retinoic acid and extracellular signal-regulated kinase in uterus of rats under influence of sex-steroids. *Biomed Pharmacother* 2018; 100: 132-41.
39. ENGUM A, BJØRO T, MYKLETUN A, DAHL AA: Thyroid autoimmunity, depression and anxiety; are there any connections? An epidemiological study of a large population. *J Psychosom Res* 2005; 59: 263-8.
40. POP VJ, MAARTENS LH, LEUSINK G *et al*.: Are autoimmune thyroid dysfunction and depression related? *J Clin Endocrinol Metab* 1998; 83: 3194-7.
41. JUCEVIČIŪTĖ N, ŽILAITIENĖ B, ANIULIENĖ R, VANAGIENĖ V: The link between thyroid autoimmunity, depression and bipolar disorder. *Open Med* (Wars) 2019; 14: 52-5.
41. LE DONNE M, MENTO C, SETTINERI S, ANTONELLI A, BENVENGA S: Postpartum mood disorders and thyroid autoimmunity. *Front Endocrinol* (Lausanne) 2017; 8: 91.
43. SIEGMANN EM, MÜLLER HHO, LUECKE C, PHILIPSEN A, KORNHUBER J, GRÖMER TW: Association of depression and anxiety disorders with autoimmune thyroiditis: a systematic review and meta-analysis. *JAMA Psychiatry* 2018; 75: 577-84.
44. PEDERSEN IB, KNUDSEN N, JØRGENSEN T, PERRILD H, OVESEN L, LAURBERG P: Thyroid peroxidase and thyroglobulin autoantibodies in a large survey of populations with mild and moderate iodine deficiency. *Clin Endocrinol* (Oxford) 2003; 58: 36-42.