Relationship between Thyroid Autoimmunity and Depression, Quality of Life, and Disease Symptoms in Patients with Fibromyalgia and Rheumatoid Arthritis

Fibromyalji ve Romatoid Artritli Hastalarda Tiroid Otoimmünitesinin, Depresyon, Yaşam Kalitesi ve Hastalık Semptomları ile İlişkisi

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Abstract

Objective: The aim of this study was to evaluate the presence of thyroid autoantibodies in patients with fibromyalgia (FM) and rheumatoid arthritis (RA) and to investigate the relationship of these antibodies with depression, quality of life, and disease symptoms.

Materials and Methods: Sixty-five patients with FM, 39 patients with RA, and 40 healthy controls were included in the study. Serum-free thyroxine, free triiodothyronine, thyrotropin, and anti-thyroglobulin (TgAb) and anti-thyroid peroxidase antibodies (TPOAb) were measured by immunometric assay. Sociodemographic characteristics, alcohol use, smoking status, morning stiffness, number of joints affected by pain, and presence of accompanying symptoms were recorded. All patients were questioned about the severity of pain, sleep disturbances, fatigue, and morning fatigue. The Fibromyalgia Impact Questionnaire (FIQ) was used to evaluate the quality of life and Beck Depression Inventory (BDI) was used to evaluate the presence of depression.

Results: The rates of TPOAb and TgAb positivity were 13.8% and 15.4%, 2.6% and 5.1%, and 5.0% and 5.0% in the FM, RA, and control groups, respectively; there was no significant difference between the groups. Thyroid autoimmunity was noted in 18.5%, 5.1%, and 7.5% of the patients in the FM, RA, and control groups, respectively; there was no significant difference between these groups. There were significant differences between the groups with respect to widespread pain, sleep disturbances, fatigue, and morning fatigue evaluated by VAS and the mean FIQ and BDI scores; the highest values were noted in the FM group. Significantly higher ESR, CRP and TSH levels, and proportion of postmenopausal women were noted in FM patients with thyroid autoimmunity compared to FM patients without thyroid autoimmunity. No significant difference existed between RA patients with or without thyroid autoimmunity.

Conclusion: No significant differences existed between FM patients, RA patients, and healthy controls in terms of thyroid autoimmunity. We suggest that there is no association between thyroid autoimmunity and quality of life, severity and frequency of accompanying symptoms, and presence of depression in patients with FM and RA. *(Turk J Rheumatol 2010; 25: 130-6)*

Key words: Fibromyalgia, rheumatoid arthritis, autoimmune thyroiditis

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Özet

Amaç: Bu çalışmada fibromiyalji (FM) ve romatoid artrit'li (RA) hastalarda, tiroid otoantikorlarının varlığı ve bu antikorlar ile depresyon, yaşam kalitesi ve hastalık semptomları arasındaki ilişki araştırıldı.

Yöntem ve Gereçler: Çalışmaya 65 FM'li, 39 RA'lı kadın hasta ve 40 sağlıklı kontrol alındı. Serum serbest tiroksin (sT4), serbest triiodotironin (sT3), tirotropin (TSH), antitroglobülin (Tg Ab) ve antitiroid peroksidaz (TPOAb) düzeyleri immunometrik yöntemle değerlendirildi. Aynı zamanda demografik verileri, alkol, sigara alışkanlığı, sabah tutukluğu, ağrılı eklem bölgeleri ve eşlik eden diğer semptomların varlığı kaydedildi. Tüm hastalarda ağrı, uyku bozukluğu, yorgunluk ve sabah yorgunluğunun şiddeti sorgulandı. Yaşam kalitesini değerlendirmek için Fibromiyalji Etki Sorgulama formu (FES), depresyon varlığını değerlendirmek için Beck Depresyon Ölçeği (BDÖ) kullanıldı.

Bulgular: TPOAb ve TgAb (+) olma oranı sırasıyla FM grubunda %13.8 ve %15.4, RA grubunda %2.6 ve %5.1, kontrol grubunda %5.0 ve %5.0 idi ve gruplar arasında anlamlı fark yoktu. Tiroid otoimmünitesinin (+) oluşu, FM grubunda %18.5, RA grubunda %5.1 ve kontrol grubunda %7.5 idi ve gruplar arasındaki fark anlamsızdı. VAS ile değerlendirilen yaygın ağrı, uyku bozukluğu, yorgunluk, sabah yorgunluğu ile ortalama FES ve BDÖ skoru yönünden gruplar arasında anlamlı derecede fark vardı ve en yüksek değerler FM grubuna aitti. Tiroid otoimmünitesi (+) olan FM'li hastalarda ortalama ESH, CRP, TSH düzeyi ve postmenapozal hasta oranı tiroid otoimmünitesi (-) olan FM hastalarına göre istatistiksel olarak anlamlı oranda yüksekti. Tiroid otoimmünitesi olan ve olmayan RA'lı hastalar karşılaştırıldığında iki grup arasında anlamlı fark saptanmadı.

Sonuç: Fibromyalji ve RA'lı hastalar ile sağlıklı kontroller arasında tiroid otoimmünitesi yönünden fark saptanmadı. Sonuç olarak, FM ve RA grubunda tiroid otoimmünitesi ile yaşam kalitesi, eşlik eden semptomların sıklığı ve şiddeti, depresyon varlığı arasında ilişki olmadığını söyleyebiliriz. *(Turk J Rheumatol 2010; 25: 130-6)*

Anahtar sözcükler: Fibromyalji, romatoid artrit, otoimmün tiroidit

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Introduction

Fibromyalgia (FM) is a complex clinical condition characterized by chronic widespread pain accompanied by depression, irritable bowel syndrome, dysesthesias, and other vegetative and functional disorders. Besides the presence of tenderness in at least 11 of the 18 specified tender points on examination, the diagnosis of FM includes exclusion of several pathologies, including inflammatory rheumatic diseases, diabetes, and hypo- or hyper-thyroidism, which manifest with similar symptomatology (1). Clinical manifestations of FM and symptoms associated with thyroid dysfunction closely resemble each other. Several studies have indicated that problems regarding the production and metabolism of thyroid hormones exist in a significant percentage of patients with FM. Moreover, it has been suggested some patients with FM have thyroid hormone resistance, also known as type 2 hypothyroidism, which has been purported as the major cause of FM symptoms (2). Rheumatoid arthritis (RA) is a chronic disease characterized by symmetric involvement of synovial joints, mostly the small joints of the hand and feet, accompanied by systemic findings, such as fatigue, weakness, and fever (3).

Autoimmune thyroid diseases are organ-specific autoimmune disorders characterized by autoantibodies against thyroglobulin, thyroid peroxidase, and thyrotropin receptor (4). Moreover, elevated levels of these thyroid autoantibodies have been noted in several rheumatic diseases, such as RA, systemic lupus erythematosus (SLE), and Sjögren's syndrome (SS); however, controversy exists between the results of different studies (5). Significantly high prevalence of thyroid autoantibodies has been noted in patients with chronic widespread musculoskeletal complaints (6), and an association between FM and thyroid autoimmunity has been suggested (7, 8).

The aim of this study was to evaluate the presence of thyroid autoantibodies in patients with RA and FM and investigate the relationship of these antibodies with depression, quality of life, and disease symptoms.

Materials and Methods

Sixty-five women with FM diagnosed according to American College of Rheumatology criteria (9), 39 women with RA (10), and a control group consisted of 40 age-matched healthy women were included in the study. The study was approved by the local Ethics Committee and all subjects provided written informed consent.

Following physical examination, laboratory investigations, including a complete blood count, erythrocyte sedimentation rate (ESR), routine biochemistries, and urinalysis were performed in all patients. Serum free thyroxine (sT4; N, 0.70-1.48 ng/dL), free triiodothyronine (sT3; N, 1.71-3.71 pg/mL), thyrotropin (TSH; N, 0.35-4.94 IU/mL), anti-thyroglobulin antibody (TgAb; N, 0-115 IU/mL), and antithyroid peroxidase antibody (TPOAb; N, 0-34 IU/mL) levels were measured by an immunometric assay. While abnormal levels of both TSH and sT4 were defined as clinical thyroid dysfunction, abnormal TSH levels together with normal sT4 levels were defined as subclinical thyroid dysfunction. Only euthyroid individuals were included in the study. Weight (kg) and height (m) measurements were used to calculate the body mass index (BMI, kg/m^2). Data pertaining marital status, number of children, educational status, alcohol use, and smoking status were recorded. Duration of morning stiffness (minutes), number of joints affected by pain, and presence of accompanying symptoms (fatigue, morning fatigue, morning stiffness, paresthesias, dysmenorrhea, Raynaud's phenomenon, swelling sensation, irritable bowel syndrome, sicca syndrome, urethral syndrome, shortness of breath, palpitations, temporomandibular joint dysfunction-TMJD, and headaches) were recorded.

The severity of widespread musculoskeletal pain, fatigue, and morning fatigue was evaluated by a 10 cm visual analog scale (VAS). The general status of patients was assessed using VAS by both patients and physicians. Satisfaction with sleep was assessed by asking the patient whether or not they felt rested when they woke up in the morning. Patients were asked to rate the quality of their sleep on a 10 cm VAS (0 indicating no sleep at all, and 10 indicating having slept well).

The Beck Depression Inventory (BDI) was used to assess the psychological status of patients and controls (11). The quality of life assessment was performed using the validated Turkish version of the Fibromyalgia Impact Questionnaire (FIQ), which was developed by Burkhardt et al. (12-14).

Statistical analysis was conducted using SPSS for Windows (Version 13.0; SPSS Inc., Chicago, IL, USA). Multiple group comparisons were performed by one-way analysis of variance for normally-distributed numerical variables, and by the Kruskal-Wallis test for non-normally-distributed numerical variables. Two-group comparisons were performed by an independent samples t-test for normally distributed variables, and by the Mann-Whitney U test for non-normally distributed variables. Categorical variables were compared by the chi-square, Fisher's exact test and Monte Carlo simulation. A p value <0.05 was considered statistically significant.

Results

The mean age was 43.12±11.27 years (range, 20-57 years) in patients with FM (n=65), 45.73±12.06 years (range, 25-60 years) in patients with RA (n=39), and

45.75±12.08 years (range, 29-56 years) in controls (n=40). There was no significant difference between the three groups in terms of age (p>0.05). The mean duration of disease was 4.31±5.18 years in the FM group and 12.53±9.05 years in the RA group (p<0.001). When groups were compared in terms of educational status, the number of patients with a primary school education in the RA group was higher compared to the FM group and there were more individuals with college/university education in the control group compared to the other two groups and the difference between the groups was statistically significant (p<0.001). The marital status of patients and controls was similar. None of the subjects in the patient and control groups used alcohol. The smoking rate in the FM group (24.6%) was higher than the RA (5.1%) and control groups (12.5%; p<0.05). The demographic data of the patients are presented in Table 1.

The rates of TPOAb and TgAb positivity were 13.8% and 15.4%, 2.6% and 5.1%, and 5.0% and 5.0% in the FM, RA, and control groups, respectively. There was no statistically significant difference between the groups in terms of the rates of TPOAb and TgAb positivity (p>0.05). Thyroid autoimmunity, i.e., the presence of an anti-thyroid autoantibody of at least 1 specificity, was noted in 18.5%, 5.1%, and 7.5% in the FM, RA, and control groups, respectively. There was no significant difference between the groups (p>0.05). Positivity of both thyroid autoantibodies was noted in 10.8%, 2.6%, and 2.5% in the FM, RA, and control groups, respectively. There was no significant difference between the groups (p>0.05). These results are presented in Table 2.

The mean severity of widespread pain and sleep disturbance assessed by VAS was 7.12±1.65 and 7.49±1.87, 5.79±2.50 and 4.20±2.95, and 3.07±2.89 and 0.72±1.03 in the FM, RA, and control groups, respectively. The three groups were different in terms of VAS-pain and VAS-sleep disturbance scores and the highest values were noted in the FM patient group (p<0.001). The mean severity of fatigue and morning fatigue assessed by VAS were 7.24±2.00 and 7.49±1.87, 5.74±2.24 and 4.25±2.84, and 1.70±1.69 and 0.07±1.24 in the FM, RA, and control groups, respectively. The highest VAS-

Table 1. Comparison of demographic characteristics of patients with fibromyalgia, rheumatoid arthritis and controls

	FM (n=65)	RA (n=39)	Control (n=40)	p
Age, years (mean±SD)	43.12±11.27	45.73±12.06	45.75±12.08	>0.05
Disease duration, years (mean±SD)	4.31±5.18[a]	12.53±9.05	-	**<0.001**
Postmenopausal status, n (%)	14 (21.5%)	26 (66.7%)[d]	13 (32.5%)	**<0.001**
Marital status, n (%)				
Married	56 (86.2%)	31 (79.5%)	36 (90.0%)	
Single	4 (6.2%)	1 (2.6%)	1 (2.5%)	>0.05
Widow	5 (7.7%)	7 (17.9%)	3 (7.5%)	
Educational status, n (%)				
Primary school	19 (29.2%)	36 (92.3%)	31 (77.5%)	
Secondary school	36 (55.4%)	2 (5.1%)	3 (7.5%)	**<0.001**
High school	9 (13.8%)	1 (2.6%)	2 (5.0%)	
College/university	1 (1.5%)	0 (0%)	4 (10%)[b]	
Smoking status (%)	24.6[c]	5.1	12.5	**<0.05**
Alcohol use (%)	-	-		-

[a] Significant difference between FM and RA, [b] Significant difference between controls and both FM and RA, [c] Significant difference between FM and both RA and controls, [d] Significant difference between RA and both FM and controls

Table 2. Comparison of thyroid autoantibody positivity rates in patients with fibromyalgia, rheumatoid arthritis and controls

	FM (n=65)	RA (n=39)	Control (n=40)	χ^2	p
TPOAb (+)	9 (13.8)	1 (2.6)	2 (5.0)	4.248	0.114
TgAb (+)	10 (15.4)	2 (5.1)	2 (5.0)	3.744	0.155
At least one autoantibodies (+)	12 (18.5)	2 (5.1)	3 (7.5)	4.629	0.104
Both autoantibodies (+)	7 (10.8)	1 (2.6)	1 (2.5)	3.266	0.235

TgAb: anti-thyroglobulin antibody, TPOAb: anti-thyroid peroxidase antibody
Values show n (%)

fatigue and VAS-morning fatigue scores were noted in the FM patient group and the difference between the groups was statistically significant (p<0.001). The mean FIQ score indicating quality of life was 56.69±15.33, 43.91±19.26, and 12.74±7.25 in the FM, RA, and control groups, respectively. The highest mean FIQ score was noted in the FM group and the difference between the groups was significant (p<0.001). The mean BDI score indicating the presence of depression was 22.15±11.76, 16.48±10.85, and 0.99±0.77 in the FM, RA, and control groups, respectively. The difference between the groups was significant (p<0.001). These results are presented in Table 3.

The mean ESR, CRP and TSH levels, and the proportion of postmenopausal patients were significantly higher in the FM patients with thyroid autoimmunity compared to the FM patients without thyroid autoimmunity (p<0.05, p<0.05, p<0.05, and p<0.05, respectively). There was no significant difference between these two groups in terms of other parameters (p>0.05). The comparative results are presented in Table 4. There was no significant difference between the RA patients with or without thyroid autoimmunity regarding age, duration of disease, BDI, FIQ, VAS-pain, VAS-sleep disturbance, VAS-fatigue and VAS-morning fatigue scores, as well as ESR, CRP and TSH levels (p>0.05).

The mean BDI score, ESR, CRP, and TSH levels were significantly higher in the FM patients with positive TPOAb compared to those without (p<0.05, p<0.05, p<0.05, and p<0.05, respectively). The mean ESR, CRP, and TSH levels were significantly higher in the FM patients with positive TgAb compared to those without (p<0.05, p<0.05, and p<0.05, respectively).

Discussion

Autoimmune diseases (AIDs) occur either as organ-specific or systemic diseases. The most common target organs in organ-specific AID include the thyroid, stomach, pancreas, and adrenal glands, and the antigen occurs only in the target organ. Collagen tissue diseases, such as RA, SLE, and SS, are among the systemic AIDs, in which antigens in the serum form immune complexes that accumulate within the tissues and cause tissue damage (15). Among rheumatic diseases, FM and RA are the well-known causes of chronic pain. RA is the most

Table 3. Comparison of clinical parameters in patients with fibromyalgia, rheumatoid arthritis and controls

	FM (n=65)	RA (n=39)	Control (n=40)	p
Widespread pain (VAS in cm)	7.12±1.65	5.79±2.50	3.07±2.99	<0.001
Sleep disturbance (VAS in cm)	7.49±1.87	4.20±2.95	0.72±1.03	<0.001
Morning fatigue (VAS in cm)	7.49±1.87	4.25±2.84	0.07±1.24	<0.001
Fatigue (VAS in cm)	7.24±2.00	5.74±2.24	0.71±1.24	<0.001
FIQ	56.69±15.33	43.91±19.26	12.74±7.25	<0.001
BDI	22.15±11.76	16.48±10.85	0.99±0.77	<0.001

FIQ: Fibromyalgia impact questionnaire, BDI: Beck depression inventory, VAS: Visual analog scale
Values show mean±SD

Table 4. Comparison of clinical parameters in patients with fibromyalgia with or without thyroid autoimmunity

	Thyroid autoimmunity (+) (n=12)	Thyroid autoimmunity (-) (n=53)	p
Age (years)	37.50±7.17	40.15±9.48	>0.05
Disease duration (years)	4.75±4.57	4.21±5.35	>0.05
FIQ	59.17±14.00	56.13±15.68	>0.05
BDI	26.41±12.43	21.18±11.50	>0.05
VAS-pain	7.41±1.62	7.05±1.66	>0.05
VAS-fatigue	8.16±1.46	7.03±2.05	>0.05
VAS-sleep disturbance	7.41±1.78	7.50±1.90	>0.05
VAS-morning fatigue	7.41±1.78	7.50±1.90	>0.05
ESR (mm/h)	16.33±6.19	11.92±10.54	<0.05
CRP (mg/dL)	6.18±4.06	4.37±2.55	<0.05
TSH (IU/mL)	2.06±0.92	1.53±0.98	<0.05

FIQ: Fibromyalgia Impact Questionnaire, BDI: Beck Depression Inventory, VAS: Visual analog scale, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, TSH: Thyrotropin
Values show mean±SD

frequent systemic AID, while autoimmune thyroid diseases are the most frequent organ-specific AIDs, with Hashimoto's thyroiditis being the most common (16). In general, it is thought that the frequency of the co-existence of a systemic and an organ-specific AID is quite low (15).

Elevated levels of thyroid autoantibodies have been noted in rheumatic diseases, such as RA, SLE, and SS (5). While no significant difference has been found between FM patients and healthy individuals in terms of baseline T3, T4, and TSH levels (17), higher rates of thyroid autoantibody positivity have been noted in FM patients compared to controls (7,8). Bazzichi et al. (18) compared 120 patients with FM and 30 healthy controls in terms of thyroid autoimmunity and reported a higher rate of patients who had at least one thyroid autoantibody in the FM patient group. Pamuk et al. (7) noted similar rates of thyroid autoantibody positivity in patients with FM and RA (34.4% and 29.7%, respectively), which were both significantly higher than that noted in healthy controls (18.8%). It was reported in another study that a higher rate of autoantibody positivity, especially TPOAb positivity, was observed in 28 patients newly diagnosed with RA compared to controls (19). However, Chan et al. (20) reported that a higher rate of TPOAb positivity was noted in SLE patients (23.2%) compared to the normal population, while the rate of TPOAb positivity was similar between the normal population and RA patients (10.9%). It was reported in another study that there was no significant difference between RA and osteoarthritis patients in terms of thyroid autoimmunity (16). We did not find a significant difference between the FM, RA, and control groups in terms of thyroid autoantibody levels, such as TPOAb and TgAb. This might be due to the inhibitory effects on autoantibody formation of corticosteroids used in the management of RA (21) and ethnic differences.

Widespread and chronic pain, which is the major symptom of FM, can become so intense that it may severely affect one's work life, daily activities, and quality of life (22, 23). FIQ is a questionnaire form used to evaluate quality of life, functional capacity, work status, psychological disorders, and physical symptoms in FM patients (23). In a quality of life study comparing patients with RA and FM, and controls using FIQ and SF-36, it was found that RA and FM patients had a poorer quality of life compared to controls, and mental health was found to be worse in FM patients compared to RA patients (24). In the current study, we found that widespread pain, sleep disturbances, fatigue and morning fatigue assessed by VAS were more severe while quality of life assessed by FIQ was better in the FM patient group compared to the RA patient group. However, there was no significant difference in these parameters between FM patients with or without thyroid autoimmunity. Similarly, Pamuk et al. (7) and Bazzichi et al. (18) also reported that there was no significant difference in FIQ scores of FM patients with or without thyroid autoimmunity.

It has been reported that the prevalence of lifetime psychiatric disorders is high in patients with FM, and that a previous psychiatric disorder is often present before the onset of FM (25). It has also been suggested that FM is a part of the affective disorder spectrum (26). Depression is the most frequent psychiatric disorder accompanying RA (27). Wolfe et al. (28) reported that FM patients were more depressed than RA patients. In the current study, comparison of the severity of depression in the RA, FM, and control groups using BDI revealed that the severity of depression was significantly higher in the FM group. Moreover, the mean BDI score was higher in FM patients with positive TPOAb compared to those without. While the presence of thyroid autoantibodies was associated with depression in some studies (29), no association was noted between autoimmunity and depression in other studies (7,8,18). All of our FM patients with thyroid autoimmunity were postmenopausal and there was no association between the presence of autoimmunity and the BDI score. Only TPOAb positivity was associated with the BDI score. It was reported in previous studies that the incidence of depression was increased in the postpartum and perimenopausal period in women, and that postpartum depression was associated with TPOAb (30,31). Pop et al. (29) also reported an association between depression and TPOAb, but noted that postmenopausal status did not increase the risk of depression. It should be kept in mind that the etiology of depression is multi-factorial, and in addition to the organic causes that may play role in its etiology, an individual's educational level, socioeconomic status, family history, and thus life conditions should also be considered.

Punzi et al. (32) reported in patients with autoimmune thyroiditis and widespread joint pain that TPOAb level was positively correlated with the number of joints affected by pain, pain scores, and ESR levels. It was reported in another study that there was no association between TPOAb level and FM symptom scores, TgAb was positively correlated with ESR levels, and there was no significant difference in ESR levels of FM patients with or without autoimmunity (7). In the current study, we did not found an association between autoimmunity and FM symptom scores (pain, sleep disturbances, and fatigue and morning fatigue assessed by VAS) as well as the frequency of other accompanying symptoms. However, ESR, CRP, and TSH levels were higher in FM

patients with thyroid autoimmunity than in those without, although being within the normal range.

In conclusion, we did not find a significant difference in terms of thyroid autoimmunity between FM and RA patients and healthy controls in our study. There was no association between thyroid autoimmunity and quality of life, pain and fatigue scores, the frequency of accompanying symptoms, and the presence of depression in either the FM or RA groups. On the other hand, the mean ESR, CRP, and TSH levels and the proportion of postmenopausal women were higher in FM patients with autoimmunity. We believe that further studies are needed to elucidate the relationship between thyroid autoimmunity and FM and RA, as well as the underlying pathogenic mechanism.

Conflict of Interest

No conflict of interest is declared by authors.

References

1. Kötter I, Neuscheler D, Günaydın I, Wernet D, Klein R. Is there a predisposition for the development of autoimmune diseases in patients with fibromyalgia? Retrospective analysis with long term follow-up. Rheumatol Int 2007; 27: 1031-9.
2. Garrison RL, Breeding PC. A metabolic basis for fibromyalgia and its related disorders: the possible role of resistance to thyroid hormone. Med Hypothheses 2003; 61: 182-9.
3. Hatemi G, Yazıcı H. Romatoid Artrit Kliniği. Turkiye Klinikleri J Int Med Sci 2006, 2: 12-7.
4. Weetman AP, McGregor AM. Autoimmune thyroid disease: further developments in our understanding. Endocr Rev 1994; 15: 788-830.
5. Punzi L, Beterle C. Chronic autoimmune thyroiditis and rheumatic manifestations. Joint Bone Spine 2004;71(4):275-83.
6. 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.
7. Pamuk ON, Çakir N. The frequency of thyroid antibodies in fibromyalgia patients and their relationship with symptoms. Clin Rheumatol 2007; 26: 55-9.
8. Ribeiro LS, Proietti FA. Interrelations between fibromyalgia, thyroid autoantibodies, and depression. J Rheumatol 2004; 31(10): 2036-40.
9. Wolfe F, Smythe HA, Yunus MB, Bennet RM, Bombardier C, Goldenberg DL, et al. The American college of rheumatology 1990 criteria for the classification of fibromyalgia. Arthritis Rheum 1990; 33: 160-72.
10. Arnett FC, Edworthy SM, Bloch DA , McShane DJ, Fries JF, Cooper NS et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1998; 31: 315-24.
11. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. Beck Depression Inventory. An inventory for measuring depression. Arch Gen Psychiatry 1961; 4: 561-71
12. Burckhardt CS, Clark SR, Bennett RM. The fibromyalgia impact questionnaire: development and validation. J Rheumatol 1991; 18: 728-33.
13. Offenbaecher M, Waltz M, Schoeps P. Validation of a German version of the Fibromyalgia Impact Questionnaire (FIQ-G). J Rheumatol 2000; 27: 1984-8.
14. Sarmer S, Ergin S, Yavuzer G. The validity and reliability of the Turkish version of the Fibromyalgia Impact Questionnaire. Rheumatol Int 2000; 20: 9-12.
15. Şentürk T, Yavaşoğlu İ, Coşkun A, Bolaman Z. Romatoid Artritli hastalarda tiroid otoantikor prevalansı. Adnan Menderes Üniversitesi Tıp Fakültesi Dergisi 2005; 6: 15-8.
16. Punzi L, Michelotto M, Pianon M, Bertazzolo N, Fagiolo U, Betterle C et al. Clinical, laboratory and immunogenetic aspects of arthritis associated with chronic lymphocytic thyroiditis. Clin Exp Rheumatol 1997; 15: 373-80.
17. İlias I, Mastorakos G, Mavrikakis M, Papazoglou S, Karamitsos D, Ntantis P et al. Thyroid disease associated with rheumatoid arthritis is not adequately screened with a sensitive chemiluminescence thyrotrophin assay. Acta Med Austrica 1999; 26: 26-8.
18. Neeck G, Riedel W. Thyroid function in patients with fibromyalgia syndrome. J Rheumatol 1992; 19: 1120-2.
19. Bazzichi L, Rossi A, Giuliano T, De Feo F, Giacomelli C, Consensi A, et al. Association between thyroid autoimmunity and fibromyalgic disease severity. Clin Rheumatol 2007; 26: 2115-20.
20. Del Puente A, Savastano S, Nuzzo V, Esposito A, Lupoli G. High prevalence of thyroid autoantibodies in newly diagnosed rheumatoid arthritis patients. Clin Exp Rheumatol 2003; 21: 137.
21. Chan AT, Al-Saffar Z, Bucknall RC. Thyroid disease in systemic lupus erythematosus and rheumatoid arthritis. Rheumatology (Oxford) 2001; 40: 353-4.
22. Valensi P, Perret G, Attali JR, Sebaoun J. Reduction of anti-tyroid hormone autoantibodies through plasma exchange and corticosteroid therapy. Pathol Biol Paris 1994; 42: 836-41.
23. Marques AP, Ferreira EAG, Matsutani LA, Pereira CAB, Assumpçao A. Quantifying pain threshold and quality of life of fibromyalgia patients. Clin Rheumatol 2005; 24: 266-71.
24. Pagano T, Matsutani LA, Ferreira EAG, Marques AP, Pereira CAB. Assessment of anxiety and quality of life in fibromyalgia patients. Sao Paulo Med J. 2004; 122: 252-8.
25. Birtane M, Uzunca K, Taştekin N, Tuna H. The evaluation of quality of life in fibromyalgia syndrome: a comparison with rheumatoid arthritis by using SF-36 Health Survey. Clin Rheumatol 2007; 26: 679-84.
26. Hudson JI, Hudson MS, Pliner LF, Goldenberg DL, Pope HG Jr. Fibromyalgia and Major Affective Disorder: A Controlled Phenomenology and Family History Study. Am J Psychiatry 1985; 142: 441-6.
27. Hudson JI, Goldenberg DL, Pope HG Jr, Keck PE Jr, Schlesinger L. Comorbidity of Fibromyalgia With Medical and Psychiatric Disorders. Am J Med 1992; 92: 363-7.
28. Tander B, Kivanc C, Alaylı G, Ilhanli I, Canbaz S, Cantürk F. A comparative evaluation of health related quality of life and depression in patients with fibromyalgia syndrome and rheumatoid arthritis. Rheumatol Int 2008; 28: 859-65.

29. Wolfe F, Michaud K. Severe Rheumatoid Arthritis (RA), Worse Outcomes, Comorbid Illness, and Sociodemographic Disadvantage Characterize RA Patients with Fibromyalgia. J Rheumatol 2004; 31: 695-700.
30. Pop VJ, Maartens LH, Leusink G, van Som MJ, Knottnerus AA, Ward AM et al. Are autoimmune thyroid dysfunction and depression related? J Clin Endocrinol Metab 1998; 83: 3194-7.
31. Nicol-Smith L. Causality, menopause, and depression: a critical review of the literature. BMJ 1996 Nov 16; 313: 1229-32.
32. Harris B,Othman S, Davies JA, Weppner GJ, Richards CJ, Newcombe RG et al. Association between postpartum thyroid dysfunction and thyroid antibodies and depression. BMJ 1992; 18; 305(6846): 152-6.
33. Punzi L, Sfriso P, Pianon M, Schiavon F, Ramonda R, Cozzi F at al. Clinical manifestations and outcome of polyarthralgia associated with chronic lymphocytic thyroiditis. Semin Artrhritis Rheum 2002; 32: 51-5.