

## Which Non-Pharmacological Treatment Is More Effective on Clinical Parameters in Patients With Fibromyalgia: Balneotherapy or Aerobic Exercise?

Emine Eda KURT, Fatmanur Aybala KOÇAK, Hatice Rana ERDEM, Figen TUNCAY, Feyzanur KELEZ

*Department of Physical Medicine and Rehabilitation, Medical Faculty of Ahi Evran University, Kırşehir, Turkey*

### ABSTRACT

**Objectives:** This study aims to determine the effects of non-pharmacological therapies, namely balneotherapy, exercise, and the combined use of balneotherapy and exercise, on total myalgic score (TMS), sleep quality, health status, and signs of depression in patients with fibromyalgia syndrome, and to compare the efficacies of these treatment programs with respect to the above parameters.

**Patients and methods:** A total of 120 female subjects (mean age 37.21±12.45 years; range 18 to 63 years) diagnosed with fibromyalgia were enrolled. The patients were randomized into three groups with 40 patients in each (group 1: balneotherapy group, group 2: balneotherapy + exercise group, and group 3: exercise group). The patients underwent the treatment program for five days a week for a total of three weeks. Clinical parameters, Fibromyalgia Impact Questionnaire, Pittsburgh Sleep Quality Index, TMS, and Beck Depression Scale were evaluated at pre-treatment and post-treatment periods, and at the third-month control visit.

**Results:** There were no differences between the groups with respect to Fibromyalgia Impact Questionnaire, Pittsburgh Sleep Quality Index, TMS and Beck Depression Scale scores on pre-treatment evaluation, while the combined use of balneotherapy + aerobic exercise was more effective on TMS ( $p<0.001$ ), health status ( $p=0.009$ ), and level of depression ( $p<0.001$ ) in post-treatment evaluation. A better state of well-being with respect to sleep quality was achieved by balneotherapy and balneotherapy + exercise groups. The third-month comparisons, on the other hand, demonstrated that the balneotherapy + exercise group had a greater state of well-being with respect to TMS ( $p<0.001$ ) and general health status ( $p<0.001$ ). Balneotherapy + exercise and exercise therapy benefited signs of depression to a better degree ( $p<0.001$ ). Balneotherapy and combined balneotherapy + exercise therapy produced more effective results in terms of sleep quality ( $p<0.001$ ). TMS regressed to near baseline levels ( $p=0.397$ ), while Fibromyalgia Impact Questionnaire levels rose to near baseline levels at the third-month control in the exercise therapy group ( $p=0.070$ ).

**Conclusion:** The combined application of balneotherapy + exercise therapy, which are two of the recommended non-pharmacological treatments, may have superior and more sustained effects than administering either therapy alone.

**Keywords:** Aerobic exercise; balneotherapy; fibromyalgia.

Fibromyalgia syndrome (FMS) is a clinical condition characterized by a constellation of multiple symptoms, such as fatigue, sleep disturbance, impaired cognitive function, and depressive episodes, in addition to chronic diffuse pain and lowered pain threshold.<sup>1</sup> While its prevalence in adult populations reportedly varies between 0.66% and 10.5%, its prevalence in the Turkish population ranges between 3% and 6%.<sup>2,3</sup> Despite the lack of clear evidence of its etiology, it is believed to originate from a disturbance in the neurobiological stress system

(hypothalamo-pituitary-adrenal axis, sympathetic nervous system, and neurotransmitters). These disturbances reduce the amino acid levels of biological amines and increase the concentrations of excitatory neurotransmitters including substance P. According to this hypothesis, fibromyalgia emerges as a result of the sensitization of the central nervous system.<sup>4</sup>

Since its etiology and pathogenesis are not clearly understood, there exists no standard therapy for FMS. The latest guidelines recommend

**Received:** December 30, 2015 **Accepted:** January 10, 2016 **Published online:** April 06, 2016

**Correspondence:** Emine Eda Kurt, MD. Ahi Evran Üniversitesi Tıp Fakültesi Fiziksel Tıp ve Rehabilitasyon Anabilim Dalı, 40100 Kırşehir, Turkey.

Tel: +90 506 - 710 86 28 e-mail: eedakurt@gmail.com

©2016 Turkish League Against Rheumatism. All rights reserved.

combined use of pharmacological and non-pharmacological treatment approaches for pain density, functional state, and related depression, fatigue, and sleep disturbance symptoms.<sup>5-8</sup>

The recommended non-pharmacological treatment approaches include spa therapies such as balneotherapy and/or mud therapy, exercise, physical therapy, massage, acupuncture, homeopathy, diet, and behavioral therapies.<sup>8-14</sup>

In this study, we aimed to determine the effects of non-pharmacological therapies, namely balneotherapy, exercise, and the combined use of balneotherapy and exercise, on total myalgic score (TMS), sleep quality, health status, and signs of depression in patients with FMS, and to compare the efficacies of these treatment programs with respect to the above parameters.

## PATIENTS AND METHODS

One hundred and twenty female patients (mean age  $37.21 \pm 12.45$  years; range 18 to 63 years) with FMS according to the American College of Rheumatology 2010 diagnostic criteria<sup>15</sup> were enrolled between January 2015 and July 2015 from among patients who admitted to Department of Physical Medicine and Rehabilitation Clinic at Ahi Evran University Medical School. The patients were randomized into three groups with 40 patients in each (group 1: balneotherapy group, group 2: balneotherapy + exercise group, and group 3: exercise group). The study included patients who had experienced no modification of pharmacological treatment over the last three months; in addition, no changes were made to the pharmacological regimens of any subject until after the follow-up visit which occurred three months after the end of therapy. Hemogram, sedimentation rate, biochemistry, urinalysis, and thyroid function tests were obtained before the start of the study, and patients with abnormal results were excluded. Furthermore, patients who had cardiac, respiratory, gastrointestinal, renal, or hematological disorders and neurological, or psychiatric disorders too severe to allow participation in balneotherapy or exercise program were excluded. Pregnancy or cancer, having advanced osteoarthritis, joint malformation, spinal disorders, or trauma within

the last three months, inflammatory rheumatic disorders, history of smoking, having had modifications related to fibromyalgia medications within the last three months or alcohol intake were also among exclusion criteria. Moreover, patients who were in a physical therapy program within the last year were also excluded. During the study period, 11 patients quit the study of their own accord or were excluded for not attending clinic appointments. Group 1 completed the study program with 37 subjects, group 2 with 36 subjects, and group 3 with 36 subjects. The study protocol was approved by the Turgut Özal University Ethics Committee. A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

The patients in groups 1 and 2 were assigned to a 20-minute balneotherapy program five days a week for a total of 15 sessions at  $42 \pm 1$  °C in Kırşehir Terme oligometallic thermal water containing a total mineralization content of 556 mg/L bicarbonate, 98.2 mg/L sulphur, 34.5 mg/L magnesium, 226 mg/L calcium, 232 mg/L chlorine, and 2.6 mg/L fluorine. Group 2 was also administered an aerobic exercise program five days a week for a total of 15 sessions, which initially started with 25 minutes and was extended to 35 minutes one week later in a gradual intensification pattern. The exercise program included muscle stretching, strengthening and relaxation exercises with few repeats to increase heart rate by 60% to 70%, particularly involving muscles of the cervical, thoracic, and lumbar regions. Group 3 was only administered an exercise program as described above.

The patients were evaluated by a single researcher at both the pre- and post-treatment (PoT) periods, and at the third-month control. Evaluations were blinded to which treatment protocol patients had been assigned. Assessment parameters were calculated as follows;

1- Functional status was calculated with the Fibromyalgia Impact Questionnaire (FIQ), which measures 10 different features, namely physical disability, feeling good, loss of work day, difficulty in working, pain, fatigue, feeling fresh, stiffness, anxiety, and depression.<sup>16,17</sup>

2- Sleep quality was calculated with the Pittsburgh Sleep Quality Index (PSQI), developed by Buysse et al.<sup>18</sup> The validity and reliability study of the scale was conducted by Ağargün et al.<sup>19</sup> PSQI is a 19-item, self-rated measure assessing sleep quality and disturbance during the past month. Each item of the test is equally scored from 0 to 3 points. The scale is composed of seven subscales assessing subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. A total PSQI score of 0 to 21 is obtained by summing the subscale scores. A total PSQI score greater than five indicates a lower sleep quality and severe disturbance in at least two, or moderate disturbance in three of the above-mentioned domains with a sensitivity of 89.6% and a specificity of 86.5%.

3- Symptoms of depression were calculated with the Beck Depression Scale (BDS). This is a scale composed of 21 questions to define levels of depression. Each question receives a point between 0 to 3 in increasing order so that the total score (0 to 63) can be calculated. The higher the total points, the more severe the depression.<sup>20,21</sup>

4- According to American College of Rheumatology diagnostic criteria, pressure pain threshold values of 18 tender points and four control points were measured in Newton/cm<sup>2</sup> with a J tech algometer (J-Tech Medical Industries,

Salt Lake City, UT) to calculate the TMS.<sup>22-24</sup> Flowchart has been depicted in Figure 1.

### Statistical analysis

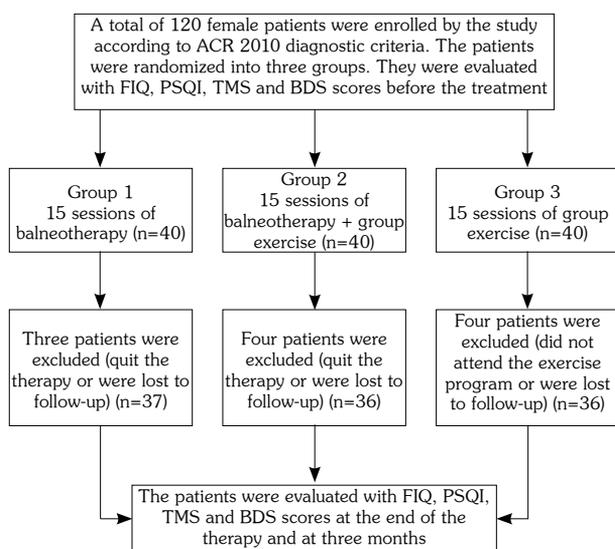
IBM SPSS version 20.0 (IBM Corporation, Armonk, NY, USA) software was used for statistical analyses. Measured data were described as the arithmetic mean  $\pm$  standard deviation, whereas categorical data were described as percentages (%). Normal distribution of measured data was examined by Kolmogorov Smirnov test. If the data were normally distributed when comparing both groups, Student's t test was employed. If the data were not normally distributed, Mann-Whitney U test was employed. Qualitative data comparisons of groups were performed using the Chi-squared test. One-way ANOVA test was used for inter-group comparison of normally distributed variables for repeated measures. A statistical level of significance was accepted at  $p < 0.05$ .

## RESULTS

The mean age of the 109 patients who completed the study was  $36.62 \pm 11.26$  (range 18 to 63 years) years. Groups were similar with respect to demographic data and baseline evaluations (Tables 1 and 2) (all  $p > 0.05$ ). However, all groups improved significantly with respect to FIQ, PSQI, TMS, and BDS scores at PoT (all  $p < 0.05$ ) and these improvements persisted in groups 1 and 2 at third-month control (all  $p < 0.05$ ) (Table 2). On the other hand, there was no significant difference between pre-treatment and third-month FIQ ( $p = 0.070$ ) and TMS ( $p = 0.397$ ) scores in group 3.

Significant differences were not observed between groups 1 and 2 with respect to FIQ ( $p = 0.0820$ ) and PSQ ( $p = 0.404$ ), and between groups 1 and 3 with respect to BDS ( $p = 0.291$ ) at PoT. Similarly, there were no significant differences between groups 1 and 2 with respect to PSQI and between groups 2 and 3 with respect to BDS at third PoT month (all  $p > 0.05$ ) (Tables 2).

Although groups 1 and 2 had better scores than group 3 in terms of FIQ, PSQI, and TMS at PoT and third-month control (all  $p < 0.05$ ), only BDS in groups 2 and 3 were better than group 1 at PoT and third-month control (all  $p < 0.05$ ) (Table 2).



**Figure 1.** A flowchart of study design. ACR: American College of Rheumatology; FIQ: Fibromyalgia Impact Questionnaire; PSQI: Pittsburgh Sleep Quality Index; TMS: Total myalgic score; BDS: Beck Depression Scale.

**Table 1.** Demographic properties of patients

	Group 1			Group 2			Group 3			p
	Balneotherapy (n=37)			Balneotherapy + exercise (n=36)			Exercise (n=36)			
	n	Mean±SD	Range	n	Mean±SD	Range	n	Mean±SD	Range	
Age (years)		38.06±10.90	18-56		35.13±11.60	18-63		41.94±12.78	20-61	0.509
Symptom duration		5.45±2.66			5.2±2.30			6.23±1.37		0.510
Educational status										0.474
Illiterate	6			5			6			
Primary-secondary	16			20			17			
High school	11			10			10			
University	4			1			3			
Working status										0.925
Working	10			9			9			
Housewife	18			20			19			
Retired	9			7			8			

SD: Standard deviation; A p value of <0.05 was considered statistically significant.

## DISCUSSION

In this study, we aimed to determine and compare the efficacy and duration of effect of aerobic exercise and balneotherapy alone or in combination, the two non-pharmacological treatment methods recommended in addition to pharmacological therapy. Although some previous studies have evaluated the efficacy and duration of effect of balneotherapy and exercise, to our knowledge, our study is the first to administer these two treatment methods in combination and compare their efficacies.

The goals of fibromyalgia treatment are to alleviate pain, increase restorative sleep, decrease depression symptoms, and improve physical function through a reduction in associated symptoms.<sup>24</sup> Recommended therapies in conjunction with medical therapy include balneotherapy and aerobic exercise. The American Pain Society and the Association of the Scientific Medical Societies in Germany gave the highest level of recommendation, "A", to aerobic exercise and a strong recommendation of "B" to balneotherapy.<sup>25,26</sup> The European League Against Rheumatism gave the highest level of

**Table 2.** Clinical findings and p values of comparisons in repeated measures and between groups

	Group 1 (n=37)		Group 2 (n=36)		Group 3 (n=36)		Group 1 vs	Group 1 vs	Group 2 vs
							group 2	group 3	group 3
	Mean±SD	p	Mean±SD	p	Mean±SD	p	p	p	p
FIQ									
PT	77.6±11.9		73.3±9.9		77.1±10.5		0.216	0.975	0.314
PoT	60.0±11.6	<0.001*	59.8±11.7	<0.001*	67.1±10.5	<0.001*	0.820	0.024	0.020
Third-month control	64.9±9.8	<0.001‡	61.0±12.8	<0.001‡	74.4±9.6	0.070‡	0.019	<0.001	<0.001
PSQI									
PT	9.05±1.7		10.05±1.7		9.7±7.6		0.098	0.830	0.163
PoT	6.05±1.2	<0.001*	6.53±1.3	<0.001*	7.6±2.1	<0.001*	0.404	<0.001	0.009
Third-month control	7.6±1.2	<0.001‡	6.72±1.1	<0.001‡	8.6±2.5	<0.001‡	0.078	<0.001	0.033
TMS									
PT	566.1±71.0		560.5±62.3		543.4±35.9		0.862	0.261	0.435
PoT	620.3±52.8	<0.001*	653.7±53.9	<0.001*	579.5±31.9	<0.001*	0.009	0.001	<0.001
Third-month control	595.5±52.4	<0.001‡	629.6±53.0	<0.001‡	550.4±37.0	0.397‡	0.008	<0.001	<0.001
BDS									
PT	20.5±3.4		20.6±4.1		21.2±4.3		0.910	0.787	0.704
PoT	17.9±2.7	<0.001*	14.9±3.9	<0.001*	16.6±3.6	<0.001*	0.001	0.291	0.020
Third-month control	18.8±2.5	0.002‡	16.5±4.2	<0.001‡	16.2±3.7	<0.001‡	0.017	0.003	0.329

FIQ: Fibromyalgia Impact Questionnaire; PT: Pre-treatment; PoT: Post-treatment; PSQI: Pittsburgh Sleep Quality Index; TMS: Total myalgic score; BDS: Beck Depression Scale; A p value of <0.05 was considered statistically significant and significant values are shown as bold. \* Comparison between pre-treatment and post-treatment. ‡ Comparison between pre-treatment and third-month control.

recommendation of “B” to aerobic exercise and a recommendation of “C” to balneotherapy.<sup>27</sup>

Neumann et al.<sup>28</sup> reported beneficial effects on FMS-related symptoms and on quality of life in FMS patients who have undergone balneotherapy. American College of Rheumatology diagnostic guideline states that balneotherapy is effective on fibromyalgia symptoms for a duration of three months.<sup>29</sup>

In a study examining the effects of balneotherapy on FIQ score, number of painful points, and Beck depression scores, Evcik et al.<sup>30</sup> found significant improvements in all three parameters after the treatment; they detected a lower FIQ score and number of painful points at sixth month follow-up compared to baseline, although Beck depression scores rose to near baseline levels.

Similarly, a study by Dönmez et al.<sup>31</sup> demonstrated that balneotherapy was effective on FIQ scores, sleep disturbance, and number of painful points compared to baseline at even the sixth month.

Our study also demonstrated a significant reduction in FIQ scores after the therapy in all three treatment programs in which balneotherapy, exercise, and both were used, with the greatest benefit seen in the group in which balneotherapy + exercise were used together. This was followed by the group that received only balneotherapy. Although these two groups showed increased FIQ scores at the third-month control, no significant difference was found between PoT scores. However, the group that only received exercise therapy had FIQ scores that rose to near baseline levels. While the three treatment programs were found effective on TMS, the combined application of balneotherapy + exercise was again the most effective treatment according to PoT evaluations. On the other hand, in group 3, in which patients were only administered the exercise program, TMS scores reduced to near baseline levels.

As for signs of depression, all three groups demonstrated significant improvement in PoT BDS scores, although the best results were achieved by the group exposed to the combined use of balneotherapy + exercise. No significant difference was observed between the balneotherapy only and exercise only groups. No significant difference was found between the third

month BDS scores and PoT scores in the exercise only group, either. Moreover, there was also no significant difference between the BDS scores of the combined balneotherapy + exercise group and the exercise only group. From these results, we may infer that balneotherapy is more effective in the early term, while exercise therapy becomes more effective over the long-term.

A study comparing the efficacy of in-water exercise and balneotherapy applied for three days a week for 12-weeks demonstrated that the effect of exercise therapy on sleep quality continued at six-months.<sup>32</sup>

In our study, an evaluation of sleep quality revealed that all three groups had significantly improved PoT scores. The best results were achieved by group 2 in which balneotherapy + exercise were applied together. The comparison of pre-treatment scores and third-month scores revealed that all groups continued a state of well-being compared to the baseline. Furthermore, no significant difference was observed between the combined balneotherapy + exercise group and the balneotherapy only group with respect to PoT and third-month scores. According to our results, the best results at third month control were achieved by balneotherapy and balneotherapy + exercise groups. We are of the opinion that the discordance between the previous reports<sup>32</sup> and our study may have originated from the short exercise duration in our study.

Martin et al.<sup>33</sup> observed improved parameters of aerobic fitness, tender points, and TMS with an exercise program of six weeks, compared to a relaxation program group, and they suggested that even better results could be obtained with longer exercise periods. Aerobic endurance exercises for 12 weeks were found to have a positive effect on the fitness and well-being of FMS patients.<sup>34</sup> Vural et al.<sup>35</sup> reported that aerobic exercise in the form of a six-week home program was effective on sleep quality, physical function, and signs of depression in patients with fibromyalgia.

In another study examining the effect of a nine-month aerobic group exercise program, it was shown that signs of depression were reduced, and physical signs and social relations were improved.<sup>36</sup>

Our study also demonstrated that balneotherapy and exercise therapy modified the signs of depression. Furthermore, according to the results

of our study, it may be suggested that exercise therapy has a more durable impact on the signs of depression.

The mechanisms responsible for the analgesic effect of exercise on fibromyalgia are not clearly understood, despite the results of several studies which consistently showed an increased pain tolerance and threshold and a lowered rate for the intensity of a given pain stimulus following exercise. It is a widely accepted hypothesis that activation of the endogenous opioid system during exercise plays a key role in the analgesic response mechanism.<sup>37</sup> An analgesic effect of exercise may also help break the vicious cycle of “pain-immobility pain” by encouraging patients to participate in the exercise programs. Exercise may also increase the well-being of patients by preventing muscular hypoxia in FMS patients.<sup>34</sup> Another positive effect of regular exercise is improved sleep quality.<sup>38</sup> Other studies related to exercise showed that, compared to other exercise types, aerobic exercise was more effective on sleep, number of painful points, pain, and signs of depression.<sup>39,40</sup>

Although the exact impact of balneotherapy on fibromyalgia is unclear, Ardiç et al.<sup>41</sup> demonstrated decreased levels of anti-inflammatory markers interleukin 1 (IL-1), prostaglandin E2, and leukotriene B4 after 15 sessions of balneotherapy in 44 patients with fibromyalgia. In addition, the beneficial effects of heat and mineral content on the human body, particularly on the musculoskeletal system, endocrinological system, and pain pathways, are well known<sup>14</sup> and include increased plasma endorphin and cortisol levels, activation of the diencephalic-pituitary-adrenal axis, and decreased plasma levels of several inflammatory mediators (IL-1, IL-6, prostaglandin E2, leukotriene B4, tumor necrosis factor- $\alpha$ ).<sup>42</sup>

Furthermore, the anti-inflammatory effects of sulphur baths have been previously demonstrated by some studies.<sup>43</sup> Sulphurous spa waters seem to exert a potent inhibitory action on the production of cytokines, especially IL-2 and interferon gamma. As these cytokines are mainly produced by CD4 lymphocytes, it may be hypothesized that memory T cells are the principal targets of sulphur-rich waters. The application of sulphurous water reduces the capacity of memory T cells to proliferate and produce cytokines, thus resulting

in an alteration of immune response.<sup>44</sup> We believe that Kırşehir thermal water has a higher anti-inflammatory action as a result of a sulphur content of 98.2 mg/L.

A limitation of this study was that the patients were not followed-up for more than three months. Therefore, we were unable to show the long-term effects of treatments. Another limitation was the small samples sizes. Thus, further studies with larger sample sizes are required.

In conclusion, our study has demonstrated that the combined treatment of balneotherapy and aerobic exercise was more effective and demonstrated longer duration of effects on clinical parameters in patients with fibromyalgia. By this treatment modality, a greater and more sustained improvement may be achieved in clinical parameters, reducing the burden of medications.

#### **Declaration of conflicting interests**

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

#### **Funding**

The authors received no financial support for the research and/or authorship of this article.

## **REFERENCES**

1. Wolfe F. Fibromyalgia wars. *J Rheumatol* 2009;36:671-8.
2. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum* 1995;38:19-28.
3. Topbas M, Cakirbay H, Gulec H, Akgol E, Ak I, Can G. The prevalence of fibromyalgia in women aged 20-64 in Turkey. *Scand J Rheumatol* 2005;34:140-4.
4. Clauw DJ, Arnold LM, McCarberg BH; FibroCollaborative. The science of fibromyalgia. *Mayo Clin Proc* 2011;86:907-11.
5. Schmidt-Wilcke T, Clauw DJ. Fibromyalgia: from pathophysiology to therapy. *Nat Rev Rheumatol* 2011;7:518-27.
6. Goldenberg DL, Burckhardt C, Crofford L. Management of fibromyalgia syndrome. *JAMA* 2004;292:2388-95.
7. Carville SF, Arendt-Nielsen L, Bliddal H, Blotman F, Branco JC, Buskila D, et al. EULAR evidence-based recommendations for the management of fibromyalgia syndrome. *Ann Rheum Dis* 2008;67:536-41.

8. Klement A, Häuser W, Brückle W, Eidmann U, Felde E, Herrmann M, et al. Principles of treatment, coordination of medical care and patient education in fibromyalgia syndrome and chronic widespread pain. *Schmerz* 2008;22:283-94. [Abstract]
9. Busch A, Schachter CL, Peloso PM, Bombardier C. Exercise for treating fibromyalgia syndrome. *Cochrane Database Syst Rev* 2002;3:CD003786
10. Nielson WR, Walker C, McCain GA. Cognitive behavioral treatment of fibromyalgia syndrome: preliminary findings. *J Rheumatol* 1992;19:98-103.
11. Berman BM, Ezzo J, Hadhazy V, Swyers JP. Is acupuncture effective in the treatment of fibromyalgia? *J Fam Prac* 1999;48:213-8.
12. Brattberg G. Connective tissue massage in the treatment of fibromyalgia. *Eur J Pain* 1999;3:235-244.
13. Sarac AJ, Gur A. Complementary and alternative medical therapies in fibromyalgia. *Curr Pharm Des* 2006;12:47-57.
14. Guidelli GM, Tenti S, De Nobili E, Fioravanti A. Fibromyalgia syndrome and spa therapy: myth or reality? *Clin Med Insights Arthritis Musculoskeletal Disord* 2012;5:19-26.
15. Häuser W, Wolfe F. Diagnosis and diagnostic tests for fibromyalgia (syndrome). *Reumatismo* 2012;64:194-205.
16. 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.
17. Burckhardt CS, Clark SR, Bennett RM. The fibromyalgia impact questionnaire: development and validation. *J Rheumatol* 1991;18:728-33.
18. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193-213.
19. Ağargün MY, Kara H, Anlar O. Pittsburgh Uyku Kalitesi indeksi'nin geçerliliği ve güvenilirliği. *Türk Psikiyatri Derg* 1996;7:107-11.
20. Hisli N. Beck Depresyon Envanteri'nin geçerliliği üzerine bir çalışma. *Psikoloji Dergisi* 1988;6:118-22.
21. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* 1961;4:561-71.
22. Fischer AA. Pressure threshold meter: its use for quantification of tender spots. *Arch Phys Med Rehabil* 1986;67:836-8.
23. Tunks E, McCain GA, Hart LE, Teasell RW, Goldsmith CH, Rollman GB, et al. The reliability of examination for tenderness in patients with myofascial pain, chronic fibromyalgia and controls. *J Rheumatol* 1995;22:944-52.
24. Bellato E, Marini E, Castoldi F, Barbasetti N, Mattei L, Bonasia DE, et al. Fibromyalgia syndrome: etiology, pathogenesis, diagnosis, and treatment. *Pain Res Treat* 2012;2012:426130.
25. Bigatti SM, Hernandez AM, Cronan TA, Rand KL. Sleep disturbances in fibromyalgia syndrome: relationship to pain and depression. *Arthritis Rheum* 2008;59:961-7.
26. Clauw DJ. Fibromyalgia: an overview. *Am J Med* 2009;122:3-13.
27. Häuser W, Thieme K, Turk DC. Guidelines on the management of fibromyalgia syndrome - a systematic review. *Eur J Pain* 2010;14:5-10.
28. Neumann L, Sukenik S, Bolotin A, Abu-Shakra M, Amir M, Flusser D, et al. The effect of balneotherapy at the Dead Sea on the quality of life of patients with fibromyalgia syndrome. *Clin Rheumatol* 2001;20:15-9.
29. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, 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.
30. Evcik D, Kizilay B, Gökçen E. The effects of balneotherapy on fibromyalgia patients. *Rheumatol Int* 2002;22:56-9.
31. Dönmez A, Karagülle MZ, Tercan N, Dinler M, İşsever H, Karagülle M, et al. SPA therapy in fibromyalgia: a randomised controlled clinic study. *Rheumatol Int* 2005;26:168-72.
32. Altan L, Bingöl U, Aykaç M, Koç Z, Yurtkuran M. Investigation of the effects of pool-based exercise on fibromyalgia syndrome. *Rheumatol Int* 2004;24:272-7.
33. Martin L, Nutting A, MacIntosh BR, Edworthy SM, Butterwick D, Cook J. An exercise program in the treatment of fibromyalgia. *J Rheumatol* 1996;23:1050-3.
34. Meiworm L, Jakob E, Walker UA, Peter HH, Keul J. Patients with fibromyalgia benefit from aerobic endurance exercise. *Clin Rheumatol* 2000;19:253-7.
35. Vural M, Berkol TD, Erdogdu Z, Pekedis K, Kuçukserat B, Aksoy C. Evaluation of the effectiveness of an aerobic exercise program and the personality characteristics of patients with fibromyalgia syndrome: a pilot study. *J Phys Ther Sci* 2014;26:1561-5.
36. Beltrán-Carrillo VJ, Tortosa-Martínez J, Jennings G, Sánchez ES. Contributions of a group-based exercise program for coping with fibromyalgia: a qualitative study giving voice to female patients. *Women Health* 2013;53:612-29.
37. Koltyn KF. Analgesia following exercise: a review. *Sports Med* 2000;29:85-98.
38. Drewes AM, Andreassen A, Schröder HD, Høgsaa B, Jennum P. Pathology of skeletal muscle in fibromyalgia: a histo-immuno-chemical and ultrastructural study. *Br J Rheumatol* 1993;32:479-83.
39. Bircan C, Karasel SA, Akgün B, El O, Alper S. Effects of muscle strengthening versus aerobic exercise program in fibromyalgia. *Rheumatol Int* 2008;28:527-32.

40. Busch AJ, Schachter CL, Overend TJ, Peloso PM, Barber KA. Exercise for fibromyalgia: a systematic review. *J Rheumatol* 2008;35:1130-44.
41. Ardiç F, Ozgen M, Aybek H, Rota S, Cubukçu D, Gökgöz A. Effects of balneotherapy on serum IL-1, PGE2 and LTB4 levels in fibromyalgia patients. *Rheumatol Int* 2007;27:441-6.
42. Fraioli A, Grassi M, Mennuni G, Geraci A, Petraccia L, Fontana M, et al. Clinical researches on the efficacy of spa therapy in fibromyalgia. A systematic review. *Ann Ist Super Sanita* 2013;49:219-29.
43. Sukenik S, Flusser D, Abu-Shakra M. The role of spa therapy in various rheumatic diseases. *Rheum Dis Clin North Am* 1999;25:883-97.
44. Ghersetich I, Lotti TM. Immunologic aspects: immunology of mineral water spas. *Clin Dermatol* 1996;14:563-6.