

# Fibromyalgia Syndrome and Spa Therapy

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## 1. Introduction

Fibromyalgia syndrome (FS) is a common musculo-skeletal disorder characterized by otherwise unexplained chronic widespread pain, a lowered pain threshold, high tender point counts (tenderness on examination at specific, predictable anatomic sites known as tender points), sleep disturbances, fatigue, headache, irritable bowel syndrome, morning stiffness, paraesthesias in the extremities, often psychological distress and depressed mood (Mease, 2005).

The diagnosis of FS is based on a history of widespread pain, defined as bilateral, upper and lower body, as well as spine, and the presence of excessive tenderness on applying pressure to 11 of 18 specific muscle-tendon sites (Wolfe et al., 1990). The 1990 American College of Rheumatology (ACR) classification criteria for the diagnosis of FS provide a sensitivity and specificity of nearly 85% in differentiating FS from other forms of chronic musculoskeletal pain. According to these criteria, FS can be diagnosed in about 2-3% in the United States population, with a prevalence in women of 3.4% and in men of about 0.5% (Wolfe & Cathey, 1983). The most recent data from US describes FS as the third most prevalent rheumatic disease, after low back pain and osteoarthritis (Lawrence et al., 2008).

FS has a negative impact on quality of life (QoL), working capacity, family life and social functioning. Significantly higher total healthcare costs have been reported among patients diagnosed with FS compared to the general population (Spaeth, 2009); in fact, FS patients incur high direct medical costs and significant indirect costs (e.g. disability pension, absenteeism). Effective treatment options are therefore needed for medical and economic reasons.

Because of the unknown aetiology and the unclear pathogenesis, there is no standard therapy regime for FS. In recent years, at least three sets of guidelines have been developed by different medical organizations in an attempt to standardize the treatment of this condition (American Pain Society, European League Against Rheumatism, Association of the Medical Society of Germany) (Goldenberg et al., 2004 ; Carville et al., 2008 ; Klement et al., 2008). The current recommendations suggest that the optimal treatment of FS requires a multidisciplinary approach with a combination of non-pharmacological and

pharmacological treatment modalities tailored according to pain intensity, function, associated features, such as depression, fatigue and sleep disturbances, decided through discussion with the patient. A variety of medical treatments, including antidepressants, opioids, analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), sedatives, muscle relaxants and antiepileptics have been used to treat FS (Goldenberg et al., 2004 ; Carville et al., 2008 ; Klement et al., 2008). Given the complexity and chronicity of FS and the relatively poor response to pharmacological treatments, it is not surprising that patients often resort to complementary or alternative therapies (Sarac & Gur, 2006). Non-pharmaceutical treatment modalities, including exercise, physical therapy, massage, acupuncture, osteopathic manipulation, patient education and cognitive behavioural therapy can be helpful (Goldenberg et al., 2004 ; Carville et al., 2008 ; Klement et al., 2008). Spa therapy is one of the most commonly used non-pharmacological approaches for FS in many European countries, as well as in Japan and Israel. Spa therapy comprises a broad spectrum of therapeutic options including hydrotherapy, balneotherapy, physiotherapy, mud-pack therapy and exercise (Sukenik et al., 1999; Bender et al., 2005). However, despite their long history and popularity, spa treatments are still the subject of debate and their role in modern medicine is still not clear (Verhagen et al., 2000). We summarize the currently available information on clinical effects and mechanism of action of spa therapy in FS.

## 2. Randomized clinical trials (RCTs) on spa therapy in FS

We conducted a search of the literature in April 2011. In an attempt to standardize the patient sample included, the search was conducted from 1990 (the date of publication of the ACR classification criteria for FS) to April 2011. Medline was searched using the term "randomized clinical trial", "spa therapy", "mud" and "balneotherapy" in combination with FS. RCTs written in languages other than English were excluded from the search.

We identified eight assessable articles reporting 7 RCTs on spa therapy in FS, including a total number of patients of 314 (TABLE 1). Over 90% of the participants in the studies were women. All studies were blind with an "assessor" blind to the type of treatment. In five studies mineral baths were used, in one study bathing was combined with exercise treatment, one study evaluated the effect of spa therapy and one study the effect of mud-pack treatment.

Yurtkuran et al. (Yurtkuran et al., 1996) investigated the effect of the addition of balneotherapy to relaxation exercises in 40 patients with FS. The study was conducted in a daily living environment and the treatment duration was 2 weeks. Patients taking part in the balneotherapy program bathed at 37°C for 20 min a day, 5 days per week followed by relaxation exercises. Patients in the control group received only relaxation exercises. Pain relief, as scored by Visual Analogue Scale (VAS), was achieved in both groups at the end of therapy and persisted for 6 weeks; however, significant improvements in mean Pressure Algometric Scores (PAS) during follow-up were only observed in the balneotherapy group.

Buskila et al. (Buskila et al., 2001) and Neumann et al. (Neumann et al., 2001) reported the beneficial effect of Dead Sea balneotherapy on FS-related symptoms and QoL index in patients with FS. In this study 48 patients with FS were randomly assigned to treatment and control groups of 24 subjects each. The patients in the treatment group bathed for 20 min per day in a sulphur pool at 37°C for 10 days, while the control group did not receive this

Authors	Sample size	Intervention	Outcome measures	Follow-up	Results
Yurtkuran 1996	A: 20 B: 20	A: Balneotherapy+ exercises B: Exercises only	VAS, PAS	6 weeks	Significant changes on VAS and PAS for group A at the end of treatment and at 6 weeks
Buskila 2001	A: 24 B: 24	A: Balneotherapy B: No treatment	VAS (Pain and other minor symptoms), FIQ, TPC, Dolorimeter, FDI	3 months	Significant between group improvements in pain and TPC in favour of A. Still seen after 3 months
Neumann 2001	A: 24 B: 24	A: Balneotherapy B: No treatment	SF36, AIMS, VAS (Pain and other minor symptoms),	3 months	Significant improvement in most subscales of the SF36 for both groups. The improvement in physical components of the QoL index lasted 3 months, whereas improvement in measures of psychological well-being was of shorter duration. Subjects in group A reported greater and longer-lasting improvement than subjects in the group B
Evcik 2002	A: 22 B: 20	A: Balneotherapy B: No treatment	VAS, FIQ, TPC, BDI	6 months	The group A showed statistically significant improvements in TPC, VAS, FIQ and BDI at the end of the therapy and this improvement persisted at 6 months except for BDI
Dönmez 2005	A: 16 B: 14	A :Spa therapy B: No treatment	VAS (Pain and other minor symptoms), FIQ, TPC, BDI	9 months	Significant improvements in pain, TPC and FIQ for group A. The pain and TPC results persisted for up to one month and the FIQ results for up to 6 months
Ardıç 2007	A: 12 B: 12	A: Balneotherapy B: No treatment	VAS, TPC, FIQ, BDI	3 weeks	Statistically significant improvement in VAS, BDI, TPC and FIQ was only found in group A at the end of the treatment cycle
Fioravanti 2007	A: 40 B: 40	A: Mud -packs and Baths B: No treatment	FIQ, TPC, VAS (Pain and other minor symptoms), AIMS, HAQ	16 weeks	In group A, a significant improvement in all parameters was recorded after mud-bath therapy and after 16 weeks
Özkurt 2011	A: 25 B: 25	A: Balneotherapy B: No treatment	VAS, FIQ, BDI, PGA, IGA, SF-36, TPC	3 months	Statistically significant improvement was recorded in group A for all outcome parameters at the end of the treatment cycle and after 3 months, except for BDI and IGA

Table 1. RCTs on SPA Therapy in FS (1996-2011)

treatment. All participants stayed in the Dead Sea area for 10 days and continued their regular medications for FS. Physical functioning, assessed by the Fibromyalgia Impact Questionnaire (FIQ), FS-related symptoms, assessed by VAS, Functional Disability Index (FDI), Health Assessment Questionnaire (HAQ), tenderness measurements (Tender Point Count [TPC] and dolorimetry) and QoL index (Short Form-36 [SF36] and Arthritis Impact Measurement Scales [AIMS]) were recorded at basal time, at the end of treatment and 1 month and 3 months later. Physical functioning and tenderness improved moderately in both groups. With the exception of tenderness threshold, the improvement was especially evident in the treatment group and even persisted beyond 3 months. Relief in the severity of FS-related symptoms (pain, fatigue, stiffness) and reduced frequency of symptoms (headache, sleep problems and subjective joint swelling) were reported in both groups, but lasted longer in the treatment group. Significant improvement in most subscales of the SF36 was reported for both groups. Interestingly, the improvement in physical components of the QoL index usually lasted 3 months, whereas improvement in measures of psychological well-being was of shorter duration. Subjects in the balneotherapy group reported greater and longer-lasting improvement than subjects in the control group. Improvements in the control group were explained by temporary changes in lifestyle combined with the relaxed atmosphere of the Dead Sea resort.

Evcik et al. (Evcik et al., 2002) also reported significant improvements lasting up to 6 months in patients treated with balneotherapy. In this study 42 patients with FS were randomly assigned to two groups. One group (22 patients) bathed for 20 min at 36°C once a day, five times per week for 3 consecutive weeks (total 15 sessions) and the other group (20 patients) continued their regular medications without balneotherapy. Patients were evaluated by TPC, VAS for pain, Beck's Depression Index (BDI) and FIQ at basal time, after therapy and 6 months later. The balneotherapy group showed statistically significant improvements in TPC, VAS score, FIQ and BDI values at the end of therapy; at 6 months, the improvement in all parameters except BDI persisted.

A study by Donmez et al. (Donmez et al., 2005) compared the effects of a stay at a spa centre plus balneotherapy and the effects of regular care (control), recording significant improvements in major outcome measures, such as pain, TPC and FIQ with respect to control. The pain and TPC results persisted for up to one month and the FIQ results for up to 6 months. However, they could also be attributed to the effects of the spa stay (not offered to controls, who continued their habitual medical treatment and/or daily exercises).

Ardiç et al. (Ardiç et al., 2007) investigated the clinical effects of balneotherapy in the treatment of FS, considering serum levels of certain inflammatory markers. One group of patients (n=22) bathed 20 min per day for five days per week for three consecutive weeks and the other group (n=22) (control) continued with pharmacological treatment. A statistically significant improvement in algometric score, VAS, BDI, TPC and FIQ was only found in the balneotherapy group at the end of the treatment cycle.

In a multicentric single-blind RCT study, Fioravanti et al. (Fioravanti et al., 2007) assessed the effects of a combination of mud packs and thermal baths (with two types of mineral water) on patients with primary FS who responded poorly to pharmacological therapy. They also analysed tolerance to mud packs, since no trial using this thermal treatment has been performed in FS. Eighty patients with primary FS were randomly allocated to two groups: 40 underwent a cycle of 12 mud packs and thermal baths over a period of 2 weeks,

40 were enrolled as controls and continued their regular outpatient care routine. Because many other non-specific factors may also contribute to the effects observed after spa therapy, including changes in the environment, pleasant scenery and the absence of work duties, in order to temper these factors, all patients lived near the spa, continued working and did not modify their lifestyles. Another aspect that often amplifies the effects of spa therapy is its frequent association with physio-kinesiotherapy. These treatments were excluded from the protocol if they had not yet begun and were not already established. The following parameters were evaluated at baseline, after thermal treatment and after 16 weeks: FIQ, TPC, VAS for "minor" symptoms, AIMS1 and HAQ. Controls were assessed at the same intervals. A significant improvement in all parameters was recorded after mud-pack therapy and after 16 weeks.

Figure 1 shows that the patients submitted to mud-bath therapy underwent an evident improvement of VAS score at the end of the cycle of the thermal treatment cycle (T1) and this improvement remained significant after a follow-up period of 16 weeks (T2).

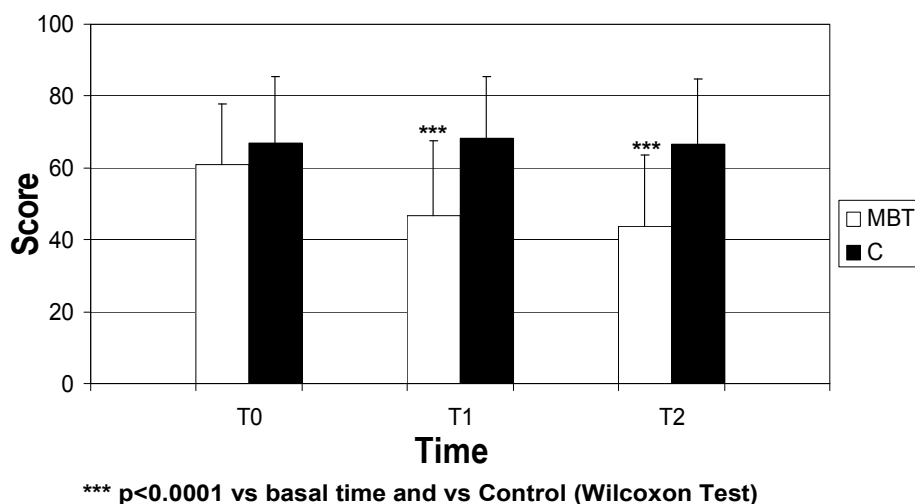


Fig. 1. VAS score (mean  $\pm$  SD) at basal time (T0), after 2 weeks (T1) and 16 weeks (T2) in mud-bath treated patients (MBT) and in controls (C). From Fioravanti et al., *Rheumatol Int* 2007

Figure 2 demonstrates that TPC significantly was reduced at the end of the spa therapy cycle and remained stable after 16 weeks in comparison to baseline only in patients treated with mud-bath therapy.

The results were similar for the two types of mineral water. Regarding tolerance mud packs, no patient reported any exacerbation of symptoms and the hot applications were well tolerated by all. No drop-outs occurred during spa therapy and all patients completed the study.

A recent RCT by Özkurt et al. (Özkurt et al., 2011) of 50 woman with FS confirmed the efficacy of balneotherapy on major outcome measures such as pain, FIQ, BDI, Patient's and

Investigator's Global Assessment (PGA and IGA) scores, and SF36. The results were maintained for up to 3 months, except for BDI and investigator's global assessment score.

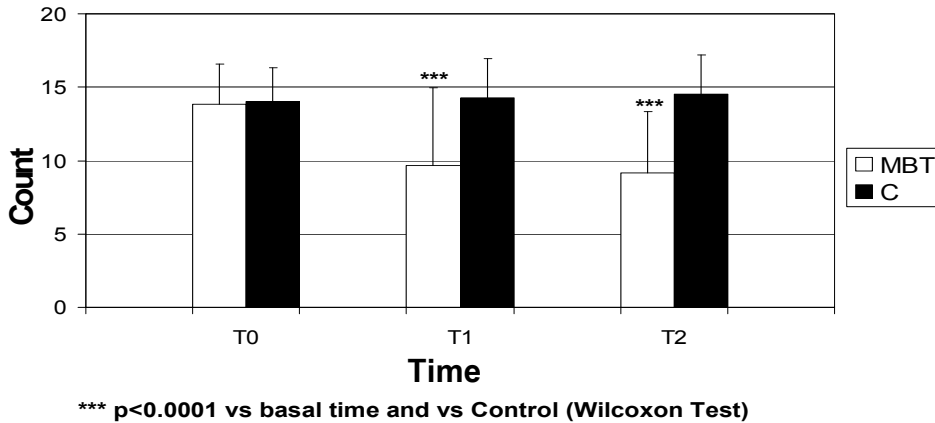


Fig. 2. Tender Point Count (mean  $\pm$  SD) at basal time (T0), after 2 weeks (T1) and 16 weeks (T2) in mud-bath treated patients (MBT) and in controls (C). From Fioravanti et al. *Rheumatol Int* 2007

These various RCTs on spa therapy for FS suggest a positive effect on pain, other FS-related symptoms and QoL (McVeigh et al., 2008; Langhorst et al., 2009). The studies assessed the medium-long-term effect and found that the clinical efficacy of spa therapy lasted for 4-6 months. Despite low tolerance of physical treatments by FS patients, spa therapy seems to be well tolerated and to have a lower percentage of side effects, which are also less severe, than those associated with pharmacological treatments.

Some aspects of the studies on spa therapy for FS are disputable and could be a source of bias, for example the lack of double-blind experimental design due to the difficulty of creating a placebo with the same characteristics as the treatment. The methodological quality of the RCTs analysed was limited for the following reasons: 1) only two studies had a sample size of at least 25 per group, the number recognized as appropriate for detecting clinically significant differences between two active treatments (Chambless & Holton, 1998); 2) no study included intention-to-treat analysis, but analysed the completers, possibly favouring the results of spa therapy, even if the drop-out rates were low; 3) most studies did not report the method of randomization used; 4) the trials did not ensure that treatment allocation was concealed (McVeigh et al., 2008; Langhorst et al., 2009).

Comparison of the studies was difficult as the baseline characteristics of the patients were heterogeneous, the interventions differed in type, intensity and duration, the methods used for assessment of efficacy varied and patients were assessed at different times after spa therapy. In particular, the heterogeneity of "spa therapy" makes it difficult to determine which form of spa therapy is most effective and no study was designed to compare different types of spa care procedures.

Although the consistency of the results suggests that spa therapy has a therapeutic effect on FS, the methodological limitations of the studies preclude any definitive conclusions.

Studies conducted according to rigorous methodological criteria in larger numbers of patients are needed to determine the potential of spa therapy for FS.

### 2.1 Mechanisms of action of spa therapy in FS

The mechanisms by which immersion in mineral or thermal water or the application of mud alleviates suffering in FS are not fully understood. The net benefit is probably the result of a combination of factors, among which mechanical, thermal and chemical effects are most prominent (Sukenic et al., 1999; Fioravanti et al., 2011). A distinction can be made between the non-specific (hydrotherapeutic in a broad sense) mechanisms of simple bathing in hot tap water, and specific (hydromineral and crenotherapeutic) mechanisms, which depend on the chemical and physical properties of the water used. While the former are well known, the latter are difficult to identify and assess. Buoyancy, immersion, resistance and temperature all play important roles. Hot stimuli may influence muscle tone and pain intensity, helping to reduce muscle spasm and to increase the pain threshold in nerve endings. According to the "gate theory", pain relief may be due to the temperature and hydrostatic pressure of water on the skin (Melzack & Wall, 1965).

Thermal stress provokes a series of neuroendocrine reactions (Kuczera & Kokot, 1996), in particular release of adrenocorticotrophic hormone (ACTH), cortisol, prolactin and growth hormone (GH), although it does not alter the circadian rhythm of these hormones. The effect of thermal stress on the hypothalamus-pituitary-adrenal axis seems to be particularly important for the antiedemigenous and anti-inflammatory effects of corticosteroids. Pituitary activation could also be particularly useful in FS, where altered reactivity of the hypothalamic-pituitary axis has been observed (Gur et al., 2004).

The increase in beta-endorphin demonstrated to occur with various spa therapy techniques has an analgesic and anti-spastic effect that is particularly important in patients with FS for whom pain is the prevalent symptom. Interestingly, it has been found that application of mature thermal mud in healthy individuals brings about a rapid increase in plasma beta-endorphin, which returns to pre-treatment levels within the period of the so-called thermal reaction (Cozzi et al., 1995). This increase in beta-endorphin is probably the key factor in the mechanism of individual tolerance to thermal mud baths. A recent study has shown a reduction in circulating levels of interleukin (IL)-1, prostaglandin E2 (PGE2) and leukotriene B4 (LTB4), important mediators of inflammation and pain, in FS patients undergoing a cycle of balneotherapy (Ardiç et al., 2007). It has been suggested that inflammatory process mediated by cytokines, proteases and inflammatory mediators located in soft body tissue may play a role in the pathogenesis of FS, in up to one third of FS patients (Salemi et al., 2003). This inflammatory process would stimulate subcutaneous nociceptors, resulting in a sensation of pain. The detection of IL-1, IL-6 and tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) in skin of one-third of FS patients and elevated plasma PGE2 levels in FS supports this hypothesis (Hedenberg-Magnusson et al., 2001). The inhibitory effect of balneotherapy on the production and/or release of IL-1, PGE2 and LTB4 could explain the mechanism of clinical benefits of spa therapy in this disorder. Mineral water may also influence the oxidant-antioxidant system (Eckmekcioglu et al., 2002; Bender et al., 2007), which could be beneficial, since oxidative stress disorders have been described in FS (Bagis et al., 2005). Finally, other aspects of the mechanisms of mud packs and balneotherapy in FS need to be considered; for example, the climatic and environmental conditions of spas and the fact that people relax away from their daily routines (Sukenic et al., 1999; Fioravanti et al., 2011).

### 3. Conclusion

In conclusion, spa therapy seems to have a role in the treatment of FS. It cannot substitute for conventional therapy but can complement to it. The improvement reported in some clinical studies lasts over time. Actually, spa therapy can represent a useful backup to pharmacologic treatment of FS or a valid alternative for patients who do not tolerate pharmacologic treatments. Future research to clarify the mechanisms of action and the effects deriving from the application of thermal treatments are imperative. Additional RCTs with high methodological quality concerning the effectiveness of spa therapy in FS are necessary in order to obtain strong evidence on the effects of spa therapy.

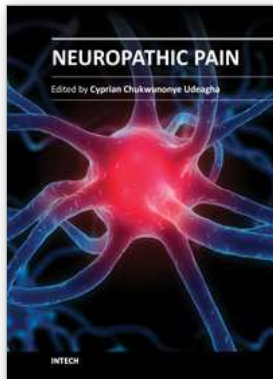
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## **Neuropathic Pain**

Edited by Dr. Cyprian Chukwunonye Udeagha

ISBN 978-953-51-0452-0

Hard cover, 140 pages

**Publisher** InTech

**Published online** 28, March, 2012

**Published in print edition** March, 2012

Neuropathic pain is known to be pain with nerve involvement. The intensity of which depends on the severity, pain threshold and the ability of suffers to cope. Neuropathic pain may need mono-therapy or combination of therapies to be resolved. Neuropathic pain may not resolve completely, therefore patient's compliance and understanding is essential in its management. Awareness and patient's education on targets may be of help during therapies for neuropathic pain. All chapters treated introduction, characteristics, diagnosis and randomized interventions to certain management of neuropathic pain. We acknowledge all those involve in the making of this book.

### **How to reference**

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Antonella Fioravanti, Nicola Giordano and Mauro Galeazzi (2012). Fibromyalgia Syndrome and Spa Therapy, Neuropathic Pain, Dr. Cyprian Chukwunonye Udeagha (Ed.), ISBN: 978-953-51-0452-0, InTech, Available from: <http://www.intechopen.com/books/neuropathic-pain/fibromyalgia-syndrome-and-spa-therapy>

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