European Journal of Integrative Medicine 29 (2019) 100928

Contents lists available at ScienceDirect

European Journal of Integrative Medicine

journal homepage: www.elsevier.com/locate/eujim

Clinical trial

Clinical efficacy of spa therapy (balneotherapy) for chronic low back pain: A randomized single-blind trial

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ARTICLE INFO

Keywords:
Balneotherapy
Spa therapy
Physical exercise
Low back pain
Randomized controlled trial

ABSTRACT

Introduction: The effect of spa therapy, a non-pharmacological treatment for chronic low back pain (CLBP) has been evaluated by several randomized clinical trials. This randomized controlled trial was conducted to compare the effect of balneotherapy alone versus balneotherapy with physical exercise.

Methods: Participants (n = 60) with low back pain for more than 6 months and attending a musculoskeletal clinic were recruited into this study. They were randomized to either the balneotherapy group (immersion in thermo-mineral water) or to a balneotherapy + exercise group (group exercises delivered in addition to balneotherapy).

Results: Before intervention and 3 and 6 months after intervention, statistically significant decreases were observed according to a visual analog scale of pain intensity ($p < 0.05$). Improvements recorded on a health assessment questionnaire lasted up to 6 months in both groups; however, values were not statistically significant. Fingertips-to-floor distance and Schober's Index measurements showed significant decreases in the balneotherapy + exercise group after treatment and at 3 months and only after treatment in the balneotherapy alone group. The Waddell Disability Index showed better recovery for the balneotherapy group at the end of the treatment and at the 3rd month. When the two groups were compared using the Waddell evaluation, the balneotherapy group was found to be superior ($p < 0.047$).

Conclusion: Although two weeks of spa therapy was beneficial in improving pain and physical function in patients with CLBP, there was no difference between balneotherapy combined with physical exercise therapy and balneotherapy alone. However, this therapeutic approach seemed advantageous in improving mobility and flexibility in these patients.

1. Introduction

Spa therapy, or balneotherapy, is a non-pharmacological treatment commonly used for the management of painful conditions, including low back pain (LBP) [1].

Spa therapy is seen as an effective treatment approach to improve physical function and quality of life in patients with LBP. There is a long history of spa treatments and these methods have even been included in health insurance coverage in Turkey as well as European countries. Traditionally, balneotherapy consists of immersion in thermal/mineral/thermo-mineral water or the use of natural peloids (muds) and natural gases [2,3]. Balneotherapy (bathing in thermo-mineral water) is the basis of spa therapy. It has been suggested that balneotherapy provides long-term improvement with some physiotherapy interventions such as massage, manipulation, and controlled therapeutic exercises [4,5]. Despite its long history, the scientific value of balneotherapy remains controversial.

LBP is associated with pain between the lower rib margins and the buttock creases, commonly accompanied by pain in one or both legs or neurological symptoms in the lower limbs. It is a complex condition

Abbreviations: CLBP, Chronic low back pain; LBP, Low back pain; PT, Physiotherapist; BEG, Balneotherapy + Exercise Group; BG, Balneotherapy Group; ESR, Erythrocyte Sedimentation Rate; VAS, Visual Analog Scale; HAQ, Health Assessment Questionnaire; WDI, Waddell Disability Index; SI, Modified Schober Index; FFD, Finger Floor Distance

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https://doi.org/10.1016/j.eujim.2019.100928
Received 18 January 2019; Received in revised form 10 June 2019; Accepted 11 June 2019

with both pain and associated disability, including psychological, social, and biophysical factors, comorbidities, and pain-processing mechanisms [6].

LBP is an important health problem which has negative effects on health costs due to the general budgets of countries, on quality of life of affected individual, and on employers as the result of lost work days and long treatment periods. For all of these reasons, it is necessary to develop preventive approaches and apply them in the current healthcare systems. [7].

Studies suggest that therapeutic exercise is beneficial for improving impaired back function, decreasing back pain symptoms, and minimizing disability by reducing back pain [8,9].

Flexion-based therapeutic lumbar exercises provide an appropriate gap between the joint surfaces, the intervertebral foramina and facet joints, to reduce facet joint compressive forces and stretch the lumbar posterior ligamentous and myofascial tissues [10]. Stretching the hip flexors and strengthening the gluteal and abdominal muscles are the usual components of a flexion-based program. These exercises protect the spine from supporting overloads.

Chronic low back pain (CLBP) is one of the main indications for spa therapy in rheumatology. The effect of spa therapy in CLBP has been evaluated by several randomized clinical trials [11,12]. This randomized controlled trial was conducted to evaluate the effect of adding physical exercises to balneotherapy versus balneotherapy only.

2. Material and methods

2.1. Study design

A randomized controlled single-blind study was performed at İstanbul University, İstanbul Faculty of Medicine, Department of Medical Ecology and Hydroclimatology in conjunction with the Balıkesir Gönen Spa Resort.

2.2. Characterization of mineral water

The 2-week-intervention took place at the Gönen Spa Resort. Characterization of mineral water content in Gönen is provided in Table 2 [13].

2.3. Participants

A comprehensive study was performed on patients who had LBP at the İstanbul University İstanbul Faculty of Medicine, Department of Medical Ecology and Hydroclimatology Musculoskeletal Polyclinic, Istanbul, Turkey. Physicians performed a routine exam of all patients before admitting them to the study.

Patients with LBP who were admitted to the outpatient clinic were evaluated for one year. The study was planned with 60 CLBP subjects. All participants were informed about the Declaration of Helsinki and informed consent was obtained from all individual participants included in the study.

2.4. Inclusion/exclusion criteria

Patients were included in the study if they had LBP lasting more than 6 months, had no spinal inflammatory disease and had no spa treatment or any back surgery in the previous year. Patients who had at least one level of osteophytes or osteosclerosis, intervertebral osteochondrosis, spinal bone eburnation, and narrowing of facet joints were included in the study.

Patients were excluded from the study if they had acute diseases, infectious diseases, decompensated organ failure, active tumors, active ulcers, hemorrhagic diseases, presence of lumbar disc herniation, or postural back pain preventing flexion positions [14].

2.5. Intervention

A total of 60 participant patients with CLBP were randomly assigned to 2 groups in a 1:1 allocation ratio with the use of SPSS Version 11.5. At the beginning of the study, 10 subjects did not come to Balıkesir; therefore, the first intervention in the spa facility began with 50 subjects:

- Balneotherapy + exercise group (BEG) (n = 26 patients, female:male = 18:8, 64.5 ± 11.9 years of age)
- Balneotherapy group (BG) (n = 24 patients, female:male = 18:6, 60.33 ± 9.6 years of age)

BG patients received only balneotherapy. BEG patients performed physical exercises in addition to balneotherapy. All patients stayed at the Gönen Spa Hotel. The entire treatment program was carried out under the supervision of a researcher/physiotherapist (PT). A total of 24 sessions of spa treatments were administered twice a day, 6 days a week, for 2 consecutive weeks. BG participants underwent immersion in a bath filled with thermo-mineral water at 36–37 °C once a day and in a pool filled with thermo-mineral water once a day at 38 °C. Each balneotherapy session lasted 20 min after which patients rested for 20 min. Participants did not exercise in water. This model reflects the commonly used balneotherapy method in Turkey.

BEG subjects received the same balneotherapy treatment. In addition, under the supervision of the researcher/PT, they performed therapeutic lumbar flexion exercises once a day as group exercise therapy. The exercise program consisted of pelvic mobilization, strengthening of the gluteal, abdominal, and knee extensor muscles, and stretching of the hip and knee flexor muscles. Each movement was repeated 15 times.

2.6. Outcome measures

Gender, age, body mass index, and last severe back pain duration were evaluated before the start of treatment (Table 1). There was no statistically significant difference between the two groups at baseline ($p < 0.05$). All patients were evaluated at the outpatient clinic at Istanbul University, Istanbul Faculty of Medicine, Department of Medical Ecology and Hydroclimatology Musculoskeletal Polyclinic at 3 and 6 months by a PT blinded to groups.

Pain intensity visual analog scales (VAS) of 10-cm lines, Patient's Global Assessments VAS, Physician's Global Assessments VAS, 9 question Waddell Disability Index (WDI) (0–9), 20 question quality of life Health Assessment Questionnaire (HAQ) (0–3), and objective measurements based on a modified Schober's Index (SI) (cm), and fingertips-to-floor distance (FFD) (cm) were used as outcome parameters [11,14,15].

For the modified SI, patients stood upright and the PT marked the L_5 spinous process and over 10 cm. Subjects then tried to touch their feet without bending their knees and the PT re-measured the distance between the two points.

For FFD, patients bent forward without bending the knees and tried to put their fingers on the ground. The PT measured the distance

Table 1
Demographic characteristics of participants.

	BG	BEG	p	z
Population (female/male)	24 (18/6)	26 (18/8)	0,757	
Age	60,33 (± 9,6)	64,5 (± 11,9)	0,251	−1,147
BMI (kg/m2)	285 (± 4,3)	26,6 (± 4,6)	0,132	−1,505
Last severe back pain duration (month)	2,29 (± 1,08)	2,31 (± 1,01)	0,725	−0,352

* = statistically significant (p < 005.

Table 2
Characterization of mineral water in Gönen Spa Resort.

Balneological source	Ions; %20 milival to exceed:
Thermomineral water Thermal (hyperthermal water): 51-78^{0}C Mineral water : 1,5-2 g/l	Na, SO_4,HCO_3, Cl Ions; threshold: Fl 4-6 mg/l

between the 3rd finger and the ground.

2.7. Statistical analysis

SPSS version 11.5 was used for randomization. Statistical analysis was performed with mean and standard deviation according to the number of participants ($n < 30$). Nonparametric Mann-Whitney-Wilcoxon tests were used in group comparisons. All analyses were performed by the biostatistics specialist co-author.

3. Results

The study was completed with 50 patients. No complications related to treatment were reported during the study. Two BG patients did not come to the 6th- month evaluation due to personal problems; therefore, 22 BG patients and 26 BEG patients were evaluated at the 6th month. A flowchart of the study is provided in Table 3.

There was no significant difference in demographic parameters (Table 1) or baseline values (Table 4) between the two groups ($p < 0.05$).

Patients in both groups demonstrated clinical improvement at the end of the spa treatment period. This improvement in all parameters continued to the 6th-month evaluation. In all measurements, statistically significant decreases were observed in the physician's global assessment VAS, patient's global assessment VAS, and pain intensity VAS ($p < 0.05$). The clinical data of the two groups are presented in Tables 5A and 5B. Group comparisons are presented in Table 6.

Significant improvements were observed in all parameters after spa therapy except for in the WDI ($p < 0.05$) in the BEG patients and modified SI ($p < 0.05$) in both groups. BG subjects showed better recovery according to the WDI at the end of treatment and at the 3rd month after treatment ($p = 0.002$). In the two group comparison, the BG was found to be superior in the WDI evaluation ($p < 0.047$).

The HAQ showed a marked improvement in both groups after treatment and at 3 months. The improvement in HAQ lasted up to 6 months in both groups but these values were not statistically significant.

FFD measurements showed a significant decrease in BEG patients after treatment and at 3 months and only after treatment in BG patients. The SI measurement was also found to be significant in the 6th-month BEG results; however, there was no difference between the groups.

4. Discussion

The use of water in addition to non-steroidal anti-inflammatory drugs and exercises to reduce pain in CLBP patients is widely recommended in most European countries [16]. Turkey has rich underground resources in terms of spas and spa treatment as suggested by physicians in the country.

Balneotherapy aims to reduce pain as well as improve function for activities of daily living. The efficacy of this treatment is based on the hydrodynamic and physical properties of water. Water immersion increases cardiac output, muscle blood flow, and oxygen availability. It also affects pain perception and helps to stimulate skin sensory nerve endings; thus, an increase in the pain threshold occurs [16]. In addition, it has been shown that balneotherapy activates serotonin transport levels [17]. Our study showed that subjects benefited from balneotherapy. The common result seen in this study was that spa treatment reduced pain and the decrease in pain VAS scores continued in both groups for 6 months.

The use of spa therapy for CLBP was evaluated many years ago by comparing or combining spa therapy with various therapeutic methods in spa centers [18–22]. These studies have shown that balneotherapy is effective in treating LBP. A systematic review of the literature concluded that spa therapy has positive effects on osteoarthritis [23]. Our results were in accordance with these studies.

In another trial, 102 patients with osteoarthritis or back pain had therapy in Bourbonne-les-Bains, France for 3 weeks. Consistent with our study results, outcomes of that study show that quality of life was

Table 3
Flowchart of the study.

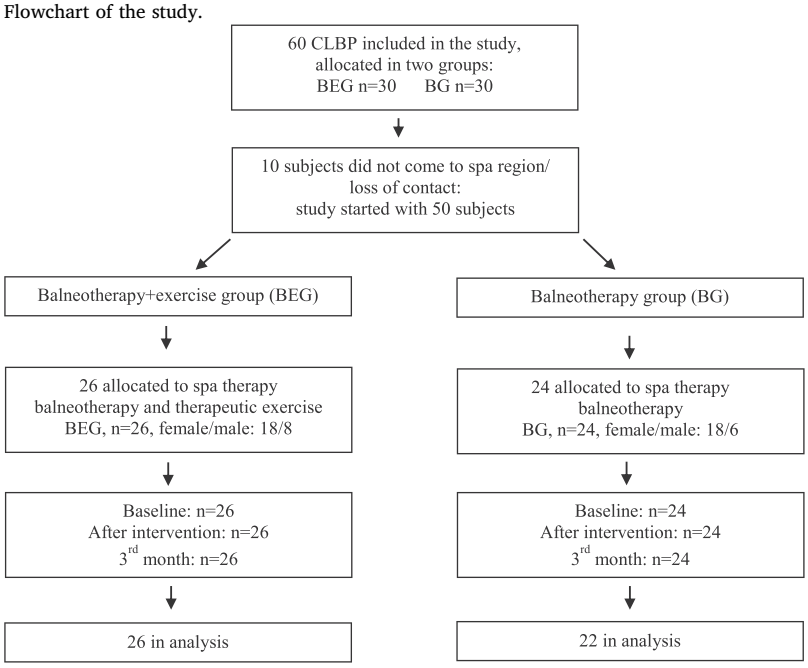

Table 4
Comparison of the baseline outcome measures between two groups.

	BG	BEG	p-Asymp. Sig.(2-tailed)
Patients global assessment-VAS (0–100 cm)	60,75 ± 16,18	65,62 ± 19,73	0,409
Phys global assessment-VAS (0-100 cm)	61,13 ± 12,37	64,23 ± 16,67	0,472
Pain assessment-VAS (0–100 cm)	62,33 ± 15,97	70,12 ± 17,32	0,113
HAQ (0-3)	0,83 ± 0,44	0,98 ± 0,47	0,189
WDI (0–9)	6,25 ± 2,71	6,81 ± 2,12	0,636
FFD (cm)	8,46 ± 8,06	15,60 ± 14,70	0,090
SI (cm)	14,54 ± 1,25	14 ± 1,17	0,102

Mann Whitney-U Test, * = statistically significant (p < 005).

Table 5A
Changes of outcome measures in BEG.

BEG	Patients glob VAS	Phys glob VAS	Pain VAS	HAQ	WDI	FFD	SI
Before therapy(a)	65,62 ± 19,73	64,23 ± 16,67	70,12 ± 17,32	0,98 ± 0,47	6,81 ± 2,12	15,60 ± 14,70	14 ± 1,17
After therapy(b)	36,42 ± 23,80	31,46 ± 21,64	4427 ± 27,14	0,82 ± 0,60	6,15 ± 2,71	8,69 ± 9,60	14,15 ± 0,95
3.month (c)	44,27 ± 18,85	33,08 ± 17,80	39,92 ± 21,04	0,77 ± 0,42	5,58 ± 2,67	9,92 ± 9,60	14,48 ± 1,01
6. month (d)	44,58 ± 18,87	39,31 ± 18,82	44,5 ± 22,91	0,86 ± 0,52	6,46 ± 2,47	12,73 ± 13,60	14,44 ± 1,11
p- (a-b) Asymp.Sig.(2-tailed)	< 0.001*	< 0.001*	< 0.001*	0045*	0,471	0,005*	0,376
p- (a-c) Asymp.Sig.(2-tailed)	0.002*	< 0.001*	< 0.001*	0.001*	0.039*	0.007*	0,070
p- (a-d) Asymp.Sig.(2tailed)	0.001*	< 0.001*	< 0.001*	0,166	0,825	0,376	0,049*

Wilcoxon Signed Ranks Test, * = statistically significant (p < 005).

Table 5B
Changes of outcome measures in BG.

BEG	Patients glob VAS	Phys glob VAS	Pain VAS	HAQ	WDI	FFD	SI
Before therapy (a)	60,17 ± 16,18	61,13 ± 12,37	62,33 ± 15,97	0,83 ± 0,44	6,25 ± 2,71	8,46 ± 8,06	14,54 ± 1,25
After therapy (b)	33,29 ± 18,83	28,08 ± 21,97	36,83 ± 21,30	0,58 ± 0,46	4,46 ± 2,99	5,58 ± 7,40	14,92 ± 1,27
3.month (c)	38,83 ± 20,81	27,13 ± 17,87	40,92 ± 23,65	0,6 ± 0,43	4,33 ± 2,87	6,37 ± 8,03	14,79 ± 1,14
6. month (d)	43,68 ± 22,09	33,23 ± 20,93	41,32 ± 25,39	0,67 ± 0,47	5,14 ± 2,62	8,27 ± 8,76	15 ± 1,36
p- (a-b) Asymp.Sig.(2-tailed)	< 0.001*	< 0.001*	< 0.001*	0.008*	0.002*	0,043*	0,065
p- (a-c) Asymp.Sig.(2-tailed)	0.001*	< 0.001*	0.002*	0,024*	0002*	0,338	0,154
p- (a-d) Asymp.Sig.(2tailed)	0.046*	0.001*	0.024*	0,269	0,174	0,911	0,323

Wilcoxon Signed Ranks Test, * = statistically significant (p < 005).

Table 6
Comparison of the changes between two groups.

Balneotherapy	Before therapy (a) p- (baseline-a) Asymp.Sig.(2-tailed)	After therapy (b) p- (baseline-b) Asymp.Sig.(2-tailed)	3.month (c) p- (baseline-c) Asymp.Sig.(2-tailed)	6. month (d) p- (baseline-d) Asymp.Sig.(2tailed)
Patients glob VAS	0,409	0,712	0,892	0,362
Phys glob VAS	0,472	0,954	0,528	0,764
Pain VAS	0,113	0,985	0,341	0,425
HAQ	0,189	0,472	0,808	0,967
WDI	0,636	0,047*	0,286	0,324
FFD	0,090	0,340	0,340	0,481
SI	0,102	0,438	0,374	0,628

Mann Whitney-U Test, * = statistically significant (p < 005).

improved by spa therapy [24]. In our study, it was observed that quality of life improved up to 3 months. Demirel et al. randomly divided 54 patients into two groups: balneotherapy combined with exercise and a control group with only exercise therapy. The exercise program was similar to that followed in our study. Both interventions significantly improved pain and quality of life and increased spine mobility, but only spa therapy increased aerobic exercise capacity. However, no significant difference was found between the two groups [25].

In our study, the BEG showed significant improvement in FFD until the 3rd month. SI was only significant at the 6th- month evaluation. In the BG, FFD was only significant at the end of the treatment. There was no significant difference in spinal mobility between the two groups.

In a double-blind randomized study conducted in Hungary, LBP patients were treated with thermo-mineral water and tap water. SI measurement resulted in favor of the thermo-mineral water group [26].

In our study, the reason why there was no superiority between the groups on spinal mobility may be due to the fact that both groups were treated with thermo-mineral water.

It is reported that balneotherapy was superior in the long term over tap water therapy in relieving pain and improving physical function. Balneotherapy combined with mud pack therapy, or potentially therapeutic exercise, or education was effective in the management of LBP and superior or equally effective to the control treatments in the short and long term [12].

Guillemin et al. showed that spa therapy is effective in CLBP over the short (26 days) and long term (9 months). Pain VAS, daily duration of pain, FFD, SI, WDI, and use of medicine showed significant improvements after 26 days from baseline. All improvements lasted up to 9 months except WDI [19]. In our trial, WDI results were found to be significant in the 3rd month in the BEG. However, in the BG both at the

end of the treatment and at the 3rd month, the significant improvement continued. While WDI values were more favorable in the BG in our study, we can say that spa treatment applied in LBP patients is effective on the WDI scale. In addition, once a day, 15 repeated exercises did not appear to have beneficial effects on LBP.

Thus, with the treatment protocol applied in this study, it is thought that balneotherapy together with physical exercise is not better for CLBP than balneotherapy alone.

The efficacy of balneotherapy might be related to other biochemical mechanisms. A hot bath decreases stress-related hormone levels, thereby exerting a direct analgesic action for relieving stress conditions [27].

The present study has some limitations. First, the small sample size could have reduced the statistical power of the study. Second, we did not evaluate analgesic use by patients. We felt that the reason for the use of analgesics could not be determined definitively, so it could create bias in the results of the study. Third, the exercise behavior of patients was not evaluated. Staying in the spa center is a strength, to check the daily rhythm of patients is a limitation. We did not check if the patients continued physical exercises outside of the spa.

5. Conclusion

It was concluded that two weeks of spa therapy is beneficial for reducing pain and increasing physical function in patients with CLBP. Spa therapy combining balneotherapy and exercise therapy seems advantageous in improving mobility and flexibility in patients with CLBP but we saw a non-statistically significant trend toward improvement over the 3rd and 6th months. Overall, the study results seem to suggest that balneotherapy combined with physical exercise therapy is not superior to balneotherapy alone for CLBP. On this basis, further studies might be designed to control exercise behavior using web-based programs or phone reminders. Establishing flexibility in the intervention, and calculation of the required number of patients to be included for statistical significance are also necessary to effectively evaluate the beneficial effects of these treatments.

Ethical approval

The study was approved by İstanbul University, Health Sciences Institute (24.02.2004-006164). All procedures performed in studies involving human participants were in accordance with the ethical standards of the university and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Authors

All research was performed by Takinacı Z.D., Karagülle M.Z., Karagülle M., statistical data were analyzed by İşsever H.

Conflict of interest

None of the authors have conflicts of interest or funding related to this work to declare.

References

[1] A. van Tubergen, S. van der Linden, A brief history of spa therapy, Ann. Rheum. Dis. 61 (10) (2002) 949–950.

[2] M.Z. Karagülle, M. Karagülle, Balneotherapie und kurorttherapie rheumatischer erkrankungen in der Türkei: Ein systematischer review, Forschende Komplementarmedizin und Klass. Naturheilkd 11 (1) (2004) 33–41.

[3] A. Fioravanti, M. Karagülle, T. Bender, M.Z. Karagülle, Balneotherapy in osteoarthritis: facts, fiction and gaps in knowledge, Eur. J. Integr. Med. 9 (2017) 148–150.

[4] R. Forestier, F.B. Erol-Forestier, A. Francon, Current role for spa therapy in rheumatology, Jt. Bone Spine. 84 (1) (2017) 9–13.

[5] A.P. Goode, A.E. Nelson, V.B. Kraus, J.B. Renner, J.M. Jordan, Biomarkers reflect differences in osteoarthritis phenotypes of the lumbar spine: the Johnston County osteoarthritis project, Osteoarthr. Cartil. 25 (10) (2017) 1672–1679.

[6] J. Hartvigsen, M.J. Hancock, A. Kongsted, et al., What low back pain is and why we need to pay attention, Lancet. 391 (10137) (2018) 2356–2367.

[7] K. AO, Bel ağrısı epidemiyolojisi, Turkiye Klin. J Neurosurg-Special Top. 3 (1) (2010) 1–7.

[8] G. Strauss-Blasche, C. Ekmekcioglu, G. Vacariu, et al., Contribution of individual spa therapies in the treatment of chronic pain, Clin. J. Pain 18 (5) (2002) 302–309.

[9] J. Rainville, C. Hartigan, E. Martinez, et al., Exercise as a treatment for chronic low back pain, Spine J. 4 (1) (2004) 106–115.

[10] V. Mazloum, M. Sahebozamani, A. Barati, et al., Randomized clinical trial the effects of selective pilates versus extension-based exercises on rehabilitation of low back pain, J. Bodyw. Mov. Ther. 22 (4) (2018) 999–1003.

[11] M.H. Pittler, M.Z. Karagülle, M. Karagülle, E. Ernst, Spa therapy and balneotherapy for treating low back pain: meta-analysis of randomized trials, Rheumatology 45 (7) (2006) 880–884.

[12] M. Karagülle, M.Z. Karagülle, Effectiveness of balneotherapy and spa therapy for the treatment of chronic low back pain: a review on latest evidence, Clin. Rheumatol. 34 (2) (2015) 207–214.

[13] M.B. Doğan, M.Z. Karagülle, Türkiye'deki ruhsatlı kaplıca tesisleri, in: M.Z. Karagülle, M.B. Doğan (Eds.), Kaplıca Tıbbı ve Türkiye Kaplıca Rehberi, Nobel Kitabevi, 2002, pp. 67–169.

[14] J.M. Koch, Physician prescription and monitoring of physical therapy, in: A.J. Haig, M. Colwell (Eds.), Back Pain: a Guide for the Primary Care Physician, 2005, pp. 237–249.

[15] A. Calin, S. Garrett, H. Whitelock, J. O'Hea, P. Mallorie, T. Jenkinson, A new approach to defining functional ability in ankylosing spondylitis: the development of the bath ankylosing spondylitis functional index, J. Rheumatol. 21 12 (1994) 2281–2285.

[16] B.E. Becker, Aquatic therapy: scientific foundations and clinical rehabilitation applications, PMR 1 (2009) 859–872.

[17] G.C.D. Marazziti, S. Baroni, G. Giannaccini, M. Catena Dell'Osso, A.G.M. Picchetti, M. Carlini, G. Massimetti, S. Provenzano, Thermal balneotherapy induces changes of the platelet serotonin transporter in healthy subjects, Prog. Neuro-Psychopharmacol. Biol. Psychiatry 31 (2007) 1436–1439.

[18] K. Konrad, T. Tatrai, A. Hunka, E. Vereckei, I. Korondi, Controlled trial of balneotherapy in treatment of low back pain, Ann. Rheum. Dis. 51 (6) (1992) 820–822.

[19] F. Guillemin, F. Constant, J.F. Collin, M. Boulangé, Short and long-term effect of spa therapy in chronic low back pain, Br. J. Rheumatol. 33 (2) (1994) 148–151.

[20] M. Nguyen, M. Revel, M. Dougados, Prolonged effects of 3week therapy in a spa resort on lumbar spine, knee and hip osteoarthritis: follow-up after 6 months, a randomized controlled trial, Br. J. Rheumatol. 36 (1) (1997) 77–81.

[21] M. Constant, J.F. Collin, F. Guillemin, M. Boulangé, Effectiveness of spa therapy in chronic low back pain, J. Rheumatol. 22 (7) (1995) 1315–1320.

[22] M. Yurtkuran, Z. Kahraman, K. Sivrioğlu, Y. Afşin, M. Doğan, Balneotherapy in low back pain, Eur. J. Phys. Med. Rehabil 7 (4) (1997) 120–123.

[23] R. Forestier, A. Françon, Crenobalneotherapy for limb osteoarthritis: systematic literature review and methodological analysis, Jt. Bone Spine 75 (2) (2008) 138–148.

[24] F. Guillemin, J.-M. Virion, P. Escudier, N. de Talancé, G. Weryha, Effect on osteoarthritis of spa therapy at Bourbonne-les-Bains, Jt. Bone Spine 68 (6) (2001) 499–503.

[25] R. Demirel, K. Öçok, V. Kavuncu, O. Geçici, D. Evcik, U. Dundar, Effects of balneotherapy with exercise in patients with low back pain, J Back Musculoskel Rehabil. 21 (2008) 263–272.

[26] A. Kulisch, T. Bender, A. Németh, L. Szekeres, Effect of thermal water and adjunctive electrotherapy on chronic low back pain: a double-blind, randomized, follow-up study, J. Rehabil. Med. 41 (1) (2009) 73–79.

[27] L. Rapoliene, A. Razbadauskas, J. Sąlyga, A. Martinkenas, Stress and fatigue management using balneotherapy in a short-time randomized controlled trial, *Evidence-based Complement*, Altern. Med. (2016) 1–10. Article ID 9631684.