EUROPEAN JOURNAL OF PHYSICAL AND REHABILITATION MEDICINE
EDIZIONI MINERVA MEDICA

Evaluation of the effect of Lake Hévíz thermal mineral water in patients with osteoarthritis of the knee: a randomized, controlled, single-blind, follow-up study

Agota KULISCH, Agota BENKO, Annamaria BERGMANN, Noemi GYARMATI, Jozsef HORVATH, Agota KRANICZ, zsuzsanna MANDO, Ágnes MATáN, András NéMETH, Erika SZAKáL, Dóra SZáNTó, László SZEKERES, Tamas BENDER

Eur J Phys Rehabil Med 2014 Mar 05 [Epub ahead of print]

EUROPEAN JOURNAL OF PHYSICAL AND REHABILITATION MEDICINE

Rivista di Medicina Fisica e Riabilitativa dopo Eventi Patologici
pISSN 1973-9087 - eISSN 1973-9095
Article type: Original Article

The online version of this article is located at http://www.minervamedica.it

Evaluation of the effect of Lake Hévíz thermal mineral water in patients with osteoarthritis of the knee: a randomized, controlled, single-blind, follow-up study

Ágota Kulisch[1], Ágota Benkő[1], Annamária Bergmann[1], Noémi Gyarmati[1], József Horváth[1], Ágota Kránicz[1], Zsuzsanna Mándó[1], Ágnes Matán[2], András Németh[3], Erika Szakál[1], Dóra Szántó[1], László Szekeres[4], Tamás Bender[5]

[1]St. Andrew Hospital for Rheumatic Diseases, Hévíz

[2]Hospital Keszthely, Rheumatology Outpatient care facility, Keszthely

[3]NK Medicor Ltd, Keszthely

[4]National Institute of Rheumatology and Physiotherapy, Budapest

[5]Polyclinic of the Hospitaller Brothers of St John of God, Budapest

Corresponding author:

Tamás Bender, M.D., Ph.D., D.Sc.

Mail address:

Budai Irgalmasrendi Kórház

H-1023 Budapest, Árpád fejedelem útja 7., Hungary

Telephone and fax: +36 1 336 0266

E-mail: bender@mail.datanet.hu, bender.tamas@irgalmas.hu

Background: Osteoarthritis is the most frequent joint disease and is a leading cause of pain and locomotor disability in elderly people. The treatment of osteoarthritis includes non-pharmacological, pharmacological, and surgical therapies. Silver level evidence has been found concerning balneotherapy in osteoarthritis.

Aim of the study: The aim of this study was to evaluate how Lake Hévíz thermal mineral water therapy influences pain, knee function, and quality of life in patients with knee osteoarthritis, compared to the control group.

Study Design: randomized, controlled, single-blind, follow-up study.

Setting: Spa Hévíz and St. Andrew Hospital for Rheumatic Diseases

Population: This study included 77 outpatients between 45 and 75 years of age with mild to moderate osteoarthritis of the knee meeting the American College of Rheumatology classification criteria.

Methods: Patients were randomized into two groups. In group I (n=38), subjects bathed in Lake Hévíz and in group II (n=39), patients were treated in a pool full of tap water. Water temperature was 34°C for both groups. Participants underwent 30-minute therapy sessions, five times a week for three weeks. Outcome measures were pain visual analogue scale scores, active flexion degree, knee circumference, stair-climb time, Western Ontario and McMaster Universities osteoarthritis index (WOMAC), and EuroQoL Group 5-Dimension Self-Report Questionnaire score (EQ-5D). Study parameters were recorded at baseline, immediately after treatment, and after 15 weeks.

Results: Comparison of the two groups revealed a statistically significant difference in pain visual analogue scale scores ($p<0.01$), active flexion degree ($p<0.01$), physical function components of WOMAC ($p<0.05$), and EQ-5D scores ($p<0.05$) even after 15 weeks.

Conclusions: Balneotherapy improved pain, function as well as the quality of life in patients with knee osteoarthritis.

Clinical Rehabilitation Impact: Balneotherapy is a potentially useful treatment modality for patients with knee osteoarthritis.

Key words: balneotherapy, knee osteoarthritis, thermal mineral water, single-blind controlled study, Lake Hévíz

Introduction

Balneotherapy uses the beneficial effects of naturally occurring mineral waters, gases, and peloids. Thermal mineral waters are mostly used for bath therapy. We call immersion when the body is dipped into water up to substernal height in a vertical position. The effects of balneotherapy are partially attributable to the aquatic environment and its basic physical characteristics (density, specific gravity, hydrostatic pressure, buoyancy, viscosity, and temperature of the water) as well as the effects of substances dissolved in the water (1). In addition to the inorganic components solved in the water, organic fractions are also present, and analysis of the organic substances has also started (2). The exact mechanism of action of this type of treatment is not known (3).

Balneotherapy is used for medical purposes predominantly in countries rich in thermal mineral water (4). In the past decades, several clinical studies, reviews, and meta-analyses have evaluated the efficacy of balneotherapy mainly in the treatment of musculoskeletal disorders (5,6,7,8,9,10,11).

Osteoarthritis is the most common musculoskeletal disorder, a slowly progressing, degenerative process leading to gradual destruction of the articular cartilage. It predominantly develops in weight-bearing joints. It can affect every aspect of a person's daily life and overall quality of life. The evidence-based therapeutic recommendations for knee osteoarthritis emphasize the importance of reducing joint pain and stiffness, preserving joint mobility, and improving physical disability and quality of life. The guidelines recommend the combination of non-pharmacological and pharmacological treatments in individually tailored therapy (12,13,14).

A Cochrane review published by Verhagen et al. in 2008 was based on the analysis of 7 randomized, controlled trials. Silver level evidence was found concerning balneotherapy in osteoarthritis. Because of the poor methodological quality and the absence of an adequate statistical analysis and data presentation, the scientific evidence is weak. The authors emphasize the need for further additional, confirmatory studies (15).

Studies involving patients with knee osteoarthritis and systematic reviews confirmed the analgesic and knee function improving effect of balneotherapy as well as its positive influence on quality of life. However, in most of the studies, bath therapy was combined with other therapies (exercise program, massage, showers, mud therapy) (16,17,18,19). Furthermore, only a limited number of previous studies covered the assessment of quality of life.

Therefore, the primary endpoint of the study was the evaluation and documenting of the pain-reducing effect of Lake Hévíz thermal mineral water on knee pain at rest or on exertion in patients with mild to moderate knee osteoarthritis as well as the assessment of the therapeutic effect compared to the control group treated with warmed tap water. The secondary endpoints included the evaluation of the effect of Lake Hévíz thermal mineral water on knee function and quality of life.

Materials and methods

This was a randomized, single-blind, controlled, parallel-group, follow-up study. The study was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonization / Good Clinical Practice standards and was approved by the Regional Research Ethics Committee (Approval No. 18/2011).

Participants

This study included male and female patients between 45 and 75 years of age with mild to moderate, bilateral primary osteoarthritis of the knee (meeting the American College of Rheumatology knee osteoarthritis classification criteria (20)) diagnosed and documented with imaging techniques (comparative knee radiograph not older than 2 years). Patients had been suffering from knee pain characteristic for osteoarthritis for at least 3 months.

After verbal agreement, the physician of the Rheumatology Outpatient Clinic of Keszthely City Hospital and the rheumatologists of our Institute invited the patients to join the study, bearing in mind the inclusion

and exclusion criteria. The enrolled patients received the treatment in an outpatient setting and they were able to continue their daily activities and work. The specialists of our Institute and the members of the Lake Hévíz Emergency Medicine Team were constantly available during the treatment for the management of side effects and problems emerging during treatment. Before enrollment, study participants were informed verbally and in writing about the purpose of the study and the study procedures. Prior to enrollment, patients read the Patient Information Sheet and signed the Informed Consent Form.

Exclusion criteria were conditions and diseases excluding warm water bath treatment (patients suffering from any severe internal, rheumatic, urogenital, or skin disorders or mental illnesses, which contraindicates bath treatment). Intra-articular corticosteroid injection within 1 month prior to the start of treatment, intra-articular hyaluronic acid therapy within 6 months prior to the initiation of treatment. Physiotherapy within 3 months prior to the start of treatment. Any change in nonsteroidal anti-inflammatory therapy or chondroprotective therapy within 1 month prior to treatment. Patients suffering from inflammatory rheumatic diseases (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, crystal arthropathies, etc.), patients with palpable fluid in the knee. Knee surgery within 6 months prior to the study; presence of metal implant in the knee joint. Patients with any previous fractures in the knee area, and/or knee injury within 6 months prior to the study. Patients with hip or spinal surgery within a year preceding the study. Patients with radiculopathy.

Study procedures

The study took place at Spa Hévíz and St. Andrew Hospital for Rheumatic Diseases (H-8380 Hévíz, Dr. Schulhof Vilmos sétány 1, Hungary), from May 2012 to August 2012.

Lake Hévíz is a biologically active, natural thermal lake is located in West Hungary. The spring of the 4.4 hectare lake, comes from a 38 m deep cave. Water-output of the lake is 410 L/sec and with this the total water volume of the lake is replaced in about every three and a half days. Its temperature never decreases under 24 degrees centigrade in winter, in summer it can reach even 37 degrees centigrade. The bed of the

lake is covered with a 6 to 8 m thick mud layer. Resulting from the eventful earth history and geological characteristics, the lake forms a hydrogeological unit together with the surrounding moorland and marshland, which has a unique, special fauna characteristic for a hot spring (21).

Patients were randomized into one of the two treatment groups. One group was treated in a covered area of Lake Hévíz and the control group was treated in a (1.2 to 1.4 m deep) pool bath filled with tap water of the same temperature as that of the thermal water. During the study, the temperature of the lake bath (34°C) was the same as that of the pool bath. Patients received Lake Hévíz or pool bath treatment for 30 minutes 5 days a week, a total of 15 times. Patients were asked not to swim during bathing.

In order to follow up the patients, they were constantly under supervision during the treatment. Patients were considered as having completed the study if they participated in more than 80% of the treatment sessions. Patients did not receive any other physiotherapy in addition to the bath therapy. Further balneo/physiotherapy treatment, intraarticular corticosteroid or hyaluronic acid therapy, arthroscopic surgery, any change in nonsteroidal anti-inflammatory therapy or chondroprotective therapy was not allowed during the study and follow-up. Participants were evaluated just before treatment (Week 0), after the end of treatment (Week 3), and during the follow-up visit (Week 15). Patients were examined by seven rheumatologists. Before the study, the study personnel standardized and practiced joint assessment two times on patients not participating in the study. Patients randomized into the control group were given the opportunity to bath in the lake for free 15 times after the follow-up visit.

Randomization and blinding

Patients were randomly assigned into two groups following simple randomization with a computer-generated sequence. The randomizer was not involved in the conduction of the study. The randomizer received the information about the patients in e-mail. The person performing the statistical analysis did not participate in the randomization process. After randomization an independent person assigned the participants to the appropriate groups.

Baseline and post-therapy assessments were performed by rheumatologists. The same patient was examined by the same physician every time. The examiners were blinded regarding the received therapy. Patients were told not to inform the study doctor about whether they received balneotherapy in Lake Hévíz or in the pool.

Evaluations

- **Visual analogue scale (VAS)** Characteristics of knee pain and condition were assessed on a 0-100 mm scale as follows:

  VAS I knee pain at rest, as rated by the patient

  VAS II knee pain on exertion, as rated by the patient

  VAS III condition of the knee, as rated by the patient

  VAS IV condition of the knee, as rated by the investigator

- **WOMAC (Western Ontario and McMaster Universities Arthritis) index**

  a self-report questionnaire was used to characterize knee joint pain, joint stiffness, and physical function. The VAS version of the index was used, with the patient assessing each question on a 0-100 mm VAS (22)

- **Angle of knee flexion on the left and right side measured by a goniometer (angle)**
- **Knee circumference (cm)**
- **Stair-climb time** in seconds to walk up 22 stairs in the pool bath building of the Hospital.
- **EQ-5D** a self-report questionnaire for the measurement of general health-related quality of life (23)

Thermal water composition

The thermal mineral water of Lake Hévíz is rich in dissolved and gas components, thereby it combines the favorable characteristics of carbonate, sulfur, calcium, magnesium, hydrogen carbonate and very light radon-containing waters.

The characteristics and composition of Lake Hévíz water are shown in Table I.

Statistical analysis

Sample size calculation was based on power analysis (α=0.05, β=0.80, effect size=0.65). Results were processed and evaluated in Microsoft Excel. For the statistical comparison of the samples, self-controlled and group-controlled methods: one-sample (paired) and two-sample t-tests were used. The analysis of the results was conducted by intention to treat. In order to avoid overestimation of the therapeutic effect, data from dropped-out patients were replaced by data of the last measurement. The level of significance was set at $p < 0.05$.

Results

Of the 77 patients included in the study, 75 completed more than 80% of the therapy sessions. Demographic and baseline clinical characteristics of patients are shown in Table II. Treatment groups were similar with regard to demographic data and baseline clinical characteristics. Two patients discontinued the treatment (1 patient in the thermal group and 1 patient in the control group). Two patients in the control group did not attend the Visit 3. Disposition of patients is presented in Figure 1.

Examination of the knee revealed an improvement in the pain parameters measured by VAS scale in both study groups. After the 3-week treatment, patients receiving thermal water therapy showed a significant therapeutic response compared to the control group, with a decrease in VAS I, VAS II, VAS III, and VAS IV scores *($p<0.01$)*. During the follow-up period, long-term significant improvement was seen in all of the VAS scales *($p<0.01$)*. All three dimensions of the WOMAC index (pain, joint stiffness, function)

showed major improvement after the treatment and during the follow-up period, than in the control group. Comparing the changes in the study groups after the treatment, all parameters of the WOMAC index showed significantly better improvement in the thermal water-treated group (pain $p<0.05$, stiffness $p<0.01$, function $p<0.01$), during the follow-up only in function score $(p<0.05)$. Knee function and movement were characterized by changes in flexion angles. Knee flexion improved in both knee in both groups. Improvement of joint function was significantly better in the thermal water-treated group than in the control group after the treatment (right side $p<0.01$, left side $p<0.05$). Similar results were obtained during the follow-up period (both sides $p<0.01$). As a response to treatment, stair-climb time decreased in both groups; patients completed the unit distance in a shorter period of time. Stair-climb time was slightly more decreased in the thermal water-treated group than in the control group when compared to baseline. The difference between the two groups was not significant. The utility index of the EQ-5D questionnaire showed permanent and significant improvement of general health-related quality of life in the thermal water-treated group compared to the control group after the treatment, and during the follow-up period $(p<0.05)$. The responders' self-rated health measured on the EQ-5D VAS scale slightly improved, but the changes were not statistically significant between the two groups. The measured values, the changes compared to baseline, and statistical data are presented in Table III.

Discussion

In this randomized, controlled, single-blind, follow-up study we evaluated the effectiveness of thermal mineral water on pain, function and quality of life in patients with knee osteoarthritis. The primary endpoint parameters indicating pain at rest and on exertion measured on a visual analogue scale and the secondary endpoint parameters such as the physical function parameter of the WOMAC index, angle of knee flexion, and index values of the EQ-5D global health-associated quality of life questionnaire showed greater improvement and were statistically significant and more durative in the thermal water-treated group compared to the control group. The difference in the above mentioned parameters were significant

between the two groups at the end of treatment and during the follow-up period. No adverse reactions were observed during treatment sessions or during the whole study period.

The results of our study demonstrated explicity the effects of thermal mineral water, in the short and long term, compared to the control group who were treated with the tap water. The decrease in pain was not only statistically but also clinically significant. In our own study the VAS scales for the reduction in pain showed a more informative response. The vast majority of studies compared the thermal mineral water treatment for outpatient care with a group not receiving such treatment (18,24,25).

Many Hungarian, Turkish, Israeli author study compares the treatment of thermal mineral water with tap water treatment. Studies were carried out on treatment with waters of different mineral content. Similar to our results in previous studies comparing the efficacy of balneotherapy applied as a 15 to 18 day course to tap water control in patients with knee osteoarthritis (26,27), a significant decrease in pain was observed. Some patients in the group treated with tap water also showed improvements which confirms the well-known analgesic effect of hot water, but the effect of short-term thermal mineral water proved to be significantly better (28). This has ratified a systematic review and meta-analysis published by Bender and associates in 2013 which analyzed the pain-reducing effect of balneotherapy. Based on their results, regardless of the composition of the mineral water, balneotherapy significantly decreased joint pain in patients with chronic low back pain and knee and hand osteoarthritis (29).

After the treatment, the WOMAC index parameters of pain, stiffness, physical function and even long-term physical function showed significant clinical improvements.

Reduction in pain and improvement in WOMAC scores were most prominent after the treatment course; and at Week 15 this effect already showed a decreasing trend.

These results differ from the results of Fioravanti and associates published in 2012, who compared the effects of balneotherapy with routine regular outpatient care and found further reduction in pain, parameters of WOMAC and Lequesne indexes at the 3-month follow-up visit (24).

In contrast, if the thermal mineral water treatment was applied intermittently twice a week for 6 weeks, no significant difference was observed between the treatment group and the tap water-treated control group in pain decrease, improvement in the Lequesne and WOMAC indexes, and improvement in the parameters of the SF-36 questionnaire (30).

Few previous studies have focused on the assessment of changes in the physical state. Our results of knee flexion, showed significant improvement after treatment compared to the control group and during follow-up as well. The stair climb speed improved in both groups, although the change in the thermal mineral water treated group was greater, but no significant difference was observed when comparing the groups.

In contrast to our results in a study by Kovacs and Bender it was showed that the stair-climb time improved significantly following 3 week balneotherapy (27).

Only a limited number of studies evaluated the effect of balneotherapy on quality of life.

In our study, EQ-5D a self-report questionnaire was evaluated, after the treatment and during the 3-month follow-up period, significant improvement was noted

In other studies, using the SF-36 questionnaire (30) and the Arthritis Impact Measurement Scales (24), a significant improvement in quality of life was seen at the end of the treatment course and during the 3-month follow-up period (24,31).

In studies where balneotherapy was combined with exercise and other treatments (18,19), even in case of severe knee osteoarthritis (25), pain decrease as well as improvement in muscle strength, walking distance, physical function, and quality of life was found to be more significant and longer term. These results were supported by a multicentre study involving a large number of patients (32).

With regard to the common side effects of continuous pharmacological, NSAID therapy, a balneotherapy course can be a useful therapeutic tool or adjunctive therapy in the treatment of knee osteoarthritis.

Our study has some limitations. First, those patients, who bathed in the covered part of the lake, were not allowed to swim, due to the deepness of the water, they had a better opportunity to move around. This might have influenced the improvement in function.

Further studies should include larger sample, maybe as a multicenter study. A larger number of patients would have increased the power of the study.

Furthermore, patients were not blinded to the received therapy. Bathing in the lake did not make the application of the double-blind method possible. In the future the double-blind method should be used with the tap water control group to ratify the effectiveness of the thermal water treatment. Group

On the other hand patients randomized into the control group were given the opportunity to bathe in the lake for free 15 times after the follow-up visit. This could have led to the results being influenced, however, this contradicts the documented improvement of the control group also.

Finally, in a future study it would be useful to design longer follow-up periods and to associate it with a study into its cost-effectiveness .

Conclusions

This randomized, tap water-controlled, single-blind study supported the efficacy of balneotherapy in the treatment of patients with mild to moderate osteoarthritis of the knee. Our results showed significant improvement in knee pain reduction, knee function, and quality of life and these changes were measurable even 12 weeks after the treatment.

This modality is another proven adjunct to the therapeutic armamentarium comprising, among others, drug treatment and physiotherapy.

Conflict of interest

The authors have declared no conflicts of interest.

Funding: The hospital provided the possibility of cost-free bathing to the patients, but the research received no other support.

References

1. Gutenbrunner C, Bender T, Cantista P and Karagulle Z. A proposal for a worldwide definition of health resort medicine, balneology, medical hydrology and climatology. Int J Biometeorol 2010; 54: 495–507.

2. Varga Cs. Volatile organics in thermal spa waters: active ingredients or environmental toxicants? Thermae & Spa Medicine March 2012 Vol. 2, N°1

3. Fioravanti A, Cantarini L, Guidelli GM and Galeazzi M. Mechanisms of action of spa therapies in rheumatic diseases: what scientific evidence is there? Rheumatol Int 2011; 1: 1-8.

4. Bender T, Karagulle Z, Balint GP, Gutenbrunner C, Balint PV and Sukenik S. Hydrotherapy, balneotherapy, and spa treatment in pain management. Rheumatol Int 2005; 25: 220–224.

5. Pittler MH, Karagulle MZ, Karagulle M and Ernst E. Spa therapy and balneotherapy for treating low back pain: meta-analysis of randomized trials. Rheumatology 2006; 45: 880–884.

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

7. Horvath K, Kulisch A, Nemeth A, Bender T. Evaluation of the effect of balneotherapy in patients with osteoarthritis of the hands: a randomized controlled single-blind follow-up study. Clin Rehabil 2012; 26: 431–441.

8. Sukenik S, Flusser D and Abu-Shakra M. The role of spa therapy in various rheumatic diseases. Rheum Dis Clin North Am 1999; 25: 883–897.

9. Kamioka H, Tsutani K, Okuizumi H, Mutoh Y, Ohta M, Handa S, Okada S, Kitayuguchi J, Kamada M, Shiozawa N, Honda T. Effectiveness of Aquatic Exercise and Balneotherapy: A Summary of Systematic Reviews Based on Randomized Controlled Trials of Water Immersion Therapies. J Epidemiol 2010; 20: 2–12.

10. Franke A, Reiner L and Resch KL. Long-term benefit of radon spa therapy in the rehabilitation of rheumatoid arthritis: a randomised, double-blinded trial. Rheumatol Int 2007; 27: 703–713.

11. Zijlstra TR, van de Laar MA, Bernelot Moens HJ, Taal E, Zakraoui L and Rasker JJ. Spa treatment for primary fibromyalgia syndrome: a combination of thalassotherapy, exercise and patient education improves symptoms and quality of life. Rheumatology 2005; 44: 539–546.

12. Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P, Gunther K, Hauselmann H, Herrero-Beaumont G, Kaklamanis P, Lohmander S, Leeb B, Lequesne M, Mazieres B, Martin-Mola E, Pavelka K, Pendleton A, Punzi L, Serni U, Swoboda B, Verbruggen G, Zimmerman-Gorska I, Dougados M; Standing Committee for International Clinical Studies Including Therapeutic Trials ESCISIT. EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis:

Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials Ann Rheum Dis. 2003; 62 : 1145-55.

13. Linda Fernandes, Kåre B Hagen, Johannes W J Bijlsma, Oyvor Andreassen, Pia Christensen, Philip G Conaghan, Michael Doherty, Rinie Geenen, Alison Hammond, Ingvild Kjeken1, L Stefan Lohmander, Hans Lund, Christian D Mallen, Tiziana Nava, Susan Oliver, Karel Pavelka, Irene Pitsillidou, José Antonio da Silva, Jenny de la Torre, Gustavo Zanoli, Theodora P M Vliet Vlieland. EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis Ann Rheum Dis doi:10.1136/annrheumdis-2012-202745

14. Hochberg M.C, Altman R.D., April K.T., Benkhalti M., Guyatt G., McGowen J., Towheed T., Welch V., Wells G., Tugwell P. American College of Rheumatology 2012 Recommendations for the Use of Nonpharmacologic and Pharmacologic Therapies in Osteoarthritis of the Hand, Hip, and Knee. Arthritis Care & ResearchVol. 64, No. 4, April 2012, pp 465–474 DOI 10.1002/acr.21596

15. Verhagen A, Bierma-Zeinstra S, Lambeck J, et al. Balneotherapy for osteoarthritis. A Cochrane Review. J Rheumatol 2008; 35: 1118–1123.

16. M. E. Falagas, E. Zarkadoulia, P. I. Rafailidis: The Therapeutic Effect of Balneotherapy: Evaluation of the Evidence from Randomised Controlled Trials Int J Clin Pract. 2009; 63 (7): 1068-1084.

17. Harzy T, Ghani N, Akasbi N, Bono W and Nejjari C.Short- and long-term therapeutic effects of thermal mineral waters in knee osteoarthritis: a systematic review of randomized controlled trials. Clin Rheumatol 2009; 28: 501–507.

18. Fioravanti A, Iacoponi F, Bellisai B, Cantarini L, Galeazzi M. Short- and long-term effects of spa therapy in knee osteoarthritis. Am J Phys Med Rehabil. 2010;89 (2):125-32.

19. Yurtkuran M, Yurtkuran M, Alp A, Nasircilar A, Bingöl U, Altan L, Sarpdere G. Balneotherapy and tap water therapy in the treatment of knee osteoarthritis. Rheumatol Int 2006; 27(1): 19-27.

20. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, Christy W, Cooke TD, Greenwald R, Hochberg M et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 1986; 29: 1039–1049.

21. Gyarmati N, Kulisch A. History and description of Hévíz spa with special emphasis on weigth bath, Press. Therm. Climat. 2008; 145: 233-242.

22. Bellamy N, Goldsmith CH, Buchanan WW, Campbell J, Duku E. Prior score availability: observations using the WOMAC osteoarthritis index. Br J Rheumatol 1991; 30: 150–151.

23. Rabin R, Charro F. EQ-5D: A measure of health status from the EuroQol Group. Annals of Medicine. 2001; 33: 337–343.

24. Fioravanti A., Giannitti C., Bellisai B., Iacoponi F., Galeazzi M.:Efficacy of balneotherapy on pain, function and quality of life in patients with osteoarthritis of the knee. Int J Biometeorol 2012; 56: 583–590.

25. Karagülle M, Karagülle MZ, Karagülle O, Dönmez A, Turan M.: A 10-day course of SPA therapy is beneficial for people with severe knee osteoarthritis. A 24-week randomised, controlled pilot study. Clin Rheumatol 2007, 12: 2063-71.

26. Szucs L, Ratko I, Lesko T, Szoor I, Genti G, Balint G. Doubleblind trial on the effectiveness of the Puspokladany thermal water on arthrosis of the knee-joints. J R Soc Health 1989; 109: 7–9.

27. Kovacs I, Bender T. The therapeutic effects of Cserkeszölö thermal water in osteoarthritis of the knee: a double blind, controlled, follow-up study. Rheumatol Int 2002; 21: 218–221.

28. Balint GP, BuchananWW, Adám A, Ratkó I, Poór L, Bálint PV, Somos E, Tefner I, Bender T. The effect of the thermal mineral water of Nagybaracska on patients with knee joint osteoarthritis—a double blind study. Clin Rheumatol 2007; 26: 890–894.

29. Bender T, Bálint G, Prohászka Z, Géher P, Tefner I.K. Evidence-based hydro- and balneotherapy in Hungary—a systematic review and meta-analysis. Int J Biometeorol 2013; DOI 10.1007/s00484-013-0667-6. Available from: http://link.springer.com/article/10.1007/s00484-013-0667-6/fulltext.html

30. Sherman G, Zeller L, Avriel A, Friger M, Harari M, Sukenik S. Intermittent balneotherapy at the Dead Sea area for patients with knee osteoarthritis. Isr Med Assoc J. 2009; 11(2): 88-93.

31. Gaal J, Varga J, Szekanecz Z, Kurkó J, Ficzere A, Bodolay E, Bender T Balneotherapy in elderly patients: effect on pain from degenerative knee and spine conditions and on quality of life. Isr Med Assoc J 2008; 10: 365–369.

32. Forestier R, Desfour H, Tessier JM, et al. Spa therapy in the treatment of knee osteoarthritis: a large randomised multicentre trial. Ann Rheum Dis 2010; 69: 660–665.

Table I. Characteristics and composition of Lake Hévíz water

Total hardness of water	198 CaO mg/L		
pH	7.14		
Water temperature	in summer: 32-35 °C, in winter: 24-26 °C		
Sodium	21.7 mg/L	Chlorine	25.0 mg/L
Potassium	6.45 mg/L	Iodine	0.02 mg/L
Magnesium	36.1 mg/L	Fluoride	1.18 mg/L
Calcium	82.1 mg/L	Hydrogen carbonate	384 mg/L
Iron	0.24 mg/L	Sulphate	63.0 mg/L
Ammonium	0.22 mg/L	H_2S	0.10 mg/L
Free CO_2	20.9 mg/L	Filtered sulfur	23.3 mg/L
Dissolved O_2	2.85 mg/L	Unfiltered sulfur	23.5 mg/L
Others	mud, radon, meta borid acid, meta silica acid, organic acid, special ecosystem		

Table II. Demographic data and other baseline clinical characteristics of the patients by treatment group

	Thermal water	**Control**	
Enrolled	**n = 38**	**n = 39**	
Male/female	**8/30**	**9/30**	
Age	**65.6** (6.4)	**65.5** (7.7)	
VASI $_{at\ rest}$	**33.6** (23.4)	**33.2** (21.8)	
VASII $_{on\ exertion}$	**55.2** (20.2)	**58.0** (20.9)	
VAS	**52.1** (20.1)	**53.5** (16.0)	

III patient's assessment			
VAS IV physician's assessment	**46.2** (15.0)	**51.2** (16.1)	
WOMAC	**Pain**	**38.5** (23.5)	**46.6** (19.9)
	Stiffness	**49.4** (26.9)	**51.2** (20.6)
	Function	**43.4** (21.7)	**44.5** (17.8)
Knee	**Flexion, right side**	**109.1** (15.5)	**111.3** (18.5)
	Flexion, left side	**112.6** (12.5)	**113.3** (17.4)
	Circumference, right side	**40.4** (3.7)	**40.9** (4.3)
	Circumference, left side	**40.3** (3.8)	**40.7** (4.5)
Stair-climb time	**20.3** (3.6)	**21.9** (5.1)	
EQ-5D	**0.6281** (0.2406)	**0.6005** (0.2035)	
EQ-5D VAS	**59.1** (16.6)	**54.7** (15.9)	

Table III. Measured values, changes from baseline, and statistical data of groups at various time points of the study

		Assessment 2 (3 weeks later)	**Assessment 3 (15 weeks later)**				
		Changes from baseline	**Group comparison**	**Changes from baseline**	**Group comparison**		
		Thermal water	**Control**	**Thermal water – Control**	**Thermal water**	**Control**	**Thermal water – Control**
		Mean 95% CI	**Mean** 95% CI		**Mean** 95% CI	**Mean** 95% CI	
VAS I	**-21.1** -27.7 to -14.6	**-3.7** -9.6 to 2.2	***p<0.01***	**-18.8** -26.0 to -11.5	**-2.8** -10.5 to 5.0	***p<0.01***	
VAS II	**-22.8** -27.1 to -18.5	**-6.8** -12.0 to -1.7	***p<0.01***	**-19.0** -25.6 to -12.4	**-2.4** -8.8 to 4.0	***p<0.01***	
VAS III	**-21.7** -27.1 to -16.3	**-8.5** -13.1 to -3.9	***p<0.01***	**-19.9** -27.1 to -12.8	**-6.2** -11.0 to -1.3	***p<0.01***	
VAS IV	**-15.1** -18.6 to -11.5	**-8.0** -11.7 to -4.3	***p<0.01***	**-16.5** -21.3 to -11.7	**-5.6** -9.8 to -1.3	***p<0.01***	
WOMAC	**Pain**	**-11.9** -16.7 to -7.1	**-5.5** -9.5 to -1.6	***p<0.05***	**-9.2** -15.2 to -3.2	**-6.8** -10.4 to -3.1	***NS***
	Stiffness	**-18.2** -24.7 to -11.7	**-3.6** -7.8 to 0.7	***p<0.01***	**-14.0** -21.9 to -6.2	**-7.1** -12.4 to -1.8	***NS***
	Function	**-15.5** -20.0 to -11.0	**-2.7** -5.7 to 0.3	***p<0.01***	**-12.0** -18.6 to -5.4	**-3.9** -7.9 to 0.1	***p<0.05***
Kn	**Flexion right side**	**15.4** 11.7 to 19.1	**6.1** 1.8 to 10.5	***p<0.01***	**14.9** 11.9 to 17.9	**5.9** 2.4 to 9.5	***p<0.01***

e e							
	Flexion left side	**11.9** 4.7 to 19.2	**3.3** 0.7 to 6.0	***p<0.05***	**14.7** 11.4 to 18.1	**2.8** -0.9 to 6.6	***p<0.01***
	Circumference right side	**-0.3** -0.7 to 0.1	**-0.1** -0.3 to 0.1	***NS***	**-0.4** -0.8 to 0.0	**-0.2** -0.7 to 0.4	***NS***
	Circumference left side	**-0.4** -0.8 to -0.1	**-0.1** -0.4 to 0.2	***NS***	**-0.6** -1.1 to -0.1	**0.2** -0.4 to 0.7	***NS***
Stair-climb time	**-3.2** -4.3 to -2.2	**-1.6** -3.0 to -0.3	***NS***	**-1.5** -3.1 to 0.1	**-1.4** -2.3 to -0.4	***NS***	
EQ-5D	**0.1606** 0.0975 to 0.2237	**0.0634** 0.0 to 0.1268	***p<0.05***	**0.1062** 0.0328 to 0.1797	**-0.0263** -0.1073 to 0.0547	***p<0.05***	
EQ-5D VAS	**6.1** -1.5 to 13.6	**2.5** -2.5 to 7.4	***NS***	**5.1** -2.1 to 12.3	**-4.4** -10.7 to 2.0	***NS***	

Figure 1. Disposition of patients