

leads to an increased risk of morbidity and mortality.^{5,6} The management of this condition requires a multidisciplinary approach. Non-pharmacological measures include education programs, physical therapy, therapeutic exercises, and orthoses and walking aids.⁷

Balneotherapy or bathing in thermal or mineral waters is used as a non-invasive treatment for various rheumatic diseases.⁸ This is one of the oldest treatment modalities that is still recommended because of the therapeutic benefits of water, including reduction of edema, pain relief, and load reduction on joints affected by arthritis.⁹ Although the term balneotherapy, which comes from the Latin *balneum* (bath), has a different meaning from hydrotherapy, both terms are accepted for all forms of water treatments. Balneotherapy includes immersion baths using ordinary (tap) water, medicinal mineral waters (crenotherapies), and artificial mineral waters with addition of dissolved gases, chemicals or organic substances.¹⁰

Crenotherapy is the use of properties of mineral waters and associated gases for therapeutic purposes. It is divided into: 1) hydropinic therapy — ingestion of medicinal mineral waters in specific dosages at regular intervals and directly from sources; 2) thermal therapy — treatment administered in a spa center, consisting of showers, saunas, bubble baths, and immersion baths in bathing pools, tanks and whirlpools; 3) inhalation therapy — inhalation, fogging, mists, sprays and aerosols of mineral waters; 4) irrigations and washes — for the nose and ears; and 5) intracavitary irrigation — vaginal and intestinal.¹⁰

Mineral or thermal-water immersion baths have sedative, decongestant, myorelaxant, analgesic, regenerating, and vasodilator actions.¹⁰ Considering the trophic action of sulfur compounds on joint tissues and in reducing rheumatic symptoms, sulfurous waters may be useful in the treatment of rheumatic disease, showing the importance of crenotherapy.^{10,11}

The aim of this study was to evaluate the effectiveness of sulfurous and non-sulfurous thermal water baths in the treatment of knee osteoarthritis and their impact on pain intensity, physical function and use of pain medication.

Materials and methods

This randomized assessor-blind controlled trial was approved by the Institutional Research Ethics Com-

mittee and registered at ClinicalTrials.gov, number NCT01920360. It was performed in accordance with the ethical standards of the 1975 Declaration of Helsinki and its subsequent amendments. Written informed consent was obtained from all patients prior to their inclusion in the study. The study was conducted from February 2011 to July 2012, including data collection and interventions.

Eligibility criteria included adult patients of both genders with a mean age of 64.8 ± 8.9 years, diagnosis of osteoarthritis of the knee according to the American College of Rheumatology (ACR) classification criteria,¹² having a Kellgren/Lawrence (K/L) radiographic severity grade of 2 or 3,^{13,14} and chronic knee pain were recruited at the spa “Termas Antonio Carlos” in Poços de Caldas, Minas Gerais, Brazil.

Exclusion criteria were fibromyalgia, respiratory diseases, inflammatory autoimmune rheumatic diseases, uncontrolled thyroid diseases, other orthopedic injuries, psychiatric disorders or cognitive impairments, history of osteoporotic fractures, presence of tumors, infections, and pregnancy. Patients who could not get into the bathtub because of physical limitations were also excluded from the study.

The sample size was calculated based on a pilot study with 26 patients. Means and standard deviations (SDs) of visual analog scale (VAS) pain scores were used to determine the sample size for the present study. Setting the confidence interval at 95% ($\alpha=0.05$) and the power of the sample at 90% ($\beta=0.10$), the sample size of 126 participants (42 patients per group) would be required to detect differences between groups. Anticipating some dropouts, 140 patients were selected and randomly allocated to the study groups.

The participants were randomized into three groups: the sulfurous water (SW) group (N.=47), non-sulfurous water (NSW) group (N.=50), and control group (N.=43). The allocation sequence was generated using a computer-generated randomization chart (www.random.org) by a researcher not involved in the study. The sequence numbers were concealed in sealed, opaque envelopes. The envelopes were opened after each patient had been enrolled and initially assessed (baseline).

Patients in the SW and NSW groups received (free of charge) a 10-week treatment consisting of 30 individual thermal baths (three baths a week, each bath lasting 20 minutes) in either sulfurous water or non-sulfurous

water (tap water) respectively, at temperatures ranging from 37 °C to 39 °C;¹¹ and those in the control group received no treatment.

The baths were taken in individual 350-liter capacity bathtubs, appropriately disinfected, filled with either sulfurous or non-sulfurous hot water. The sulfurous water had a pH of 9.66 and contained hydrogen sulfide (5.0 mg/L), sulfate (66.7 mg/L), carbonate (129 mg/L), fluoride (29.02 mg/L) and sodium (230.11 mg/L). The non-sulfurous water had a pH of 9.5 and contained chloride (5.9 mg/L), chlorine (0.68 mg/L), iron (0.03 mg/L), fluoride (0.22 mg/L) and manganese (0.03 mg/L). Patients were instructed to remain motionless during the bath and drink 300 mL of filtered water before and after bathing to prevent water imbalance.

All patients also received information on the disease and self-care strategies for knee pain management, and were instructed to take only paracetamol for pain relief, if necessary, and record their intake of pain relief medication in a home diary. Results were analyzed based on the intake of paracetamol per patient during the study period. The participants did not receive any other osteoarthritis treatment.

Patients in the control group were also instructed to maintain their daily routine during the study period. After completion of the study, the same treatment protocol of thermal baths in sulfurous waters was provided free of charge to all patients in the control group, in accordance with the standards of the Brazilian National Health Council (CNS), which ensure to study participants access to the therapeutic procedures that showed to be the most effective. This justifies the high study participation rate in the control group.

Patients were asked to complete the following questionnaires: the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), consisting of 24 items divided into three subscales (pain, stiffness, and physical function), a visual analog scale (VAS) for pain intensity;¹⁹ the Lequesne's Algomfunctional Index (LAFI), which is composed of 11 items assessing pain, discomfort and functional disability;²⁰ and the 20-item Stanford Health Assessment Questionnaire (HAQ), which evaluates physical dysfunction for activities of daily living, with each item scored from zero (no functional impairment) to three (unable to perform the task).^{21, 22} The patients also provided specific information about the use of pain medication and all adverse

events were recorded. All questionnaires were administered by investigators (I.M.A. and M.C.R.) blinded to group assignment at three time points: T1 (baseline), T2 (treatment endpoint), and T3 (2-month follow-up). Participants were not blinded to treatment allocation because those in the experimental groups were able to detect the presence or absence of the characteristic odor of sulfurous waters in their baths, and the control group received no treatment.

Statistical analysis

Analysis of variance (ANOVA) was performed to assess the homogeneity of groups for quantitative variables and comparisons within groups at different time points. The parametric Tukey's *t*-test was used for multiple comparisons between groups. The confidence interval was set at 95% and the significance level at 0.05 ($P < 0.05$).

Intention-to-treat analysis was carried out maintaining the patients in the groups to which they were randomly assigned and using the last observed response for patients with missing data (last observation carried forward).

Data are expressed as mean±standard deviation (SD).

Results

A flow chart summarizing the distribution of participants during each stage of the study is shown in Figure 1. Two hundred and twenty-three patients with knee osteoarthritis were evaluated; 140 patients were included in the study, 132 (42 in the SW group; 47 in the NSW; and 43 controls) completed the treatment, and 131 (41 in the SW group; 47 in the NSW group; and 43 controls) attended the 2-month post-treatment follow-up.

The sociodemographic and clinical characteristics of the participants are listed in Table I. Most participants in all three groups were women and the mean age was 64.8±8.9 years, without significant differences in gender and age between groups. There were significant differences in Body Mass Index (BMI) between the NSW (29.7±4.6 kg/m²) and control (27.3±3.4 kg/m²) groups ($P = 0.01$), and between the SW (27.8±3.5 kg/m²) and NSW groups ($P = 0.01$). Time from onset of symptoms was 10±7.7 years in the control group, 6.6±4.5 years in the NSW group, and 6.9±5.6 years in SW group, with

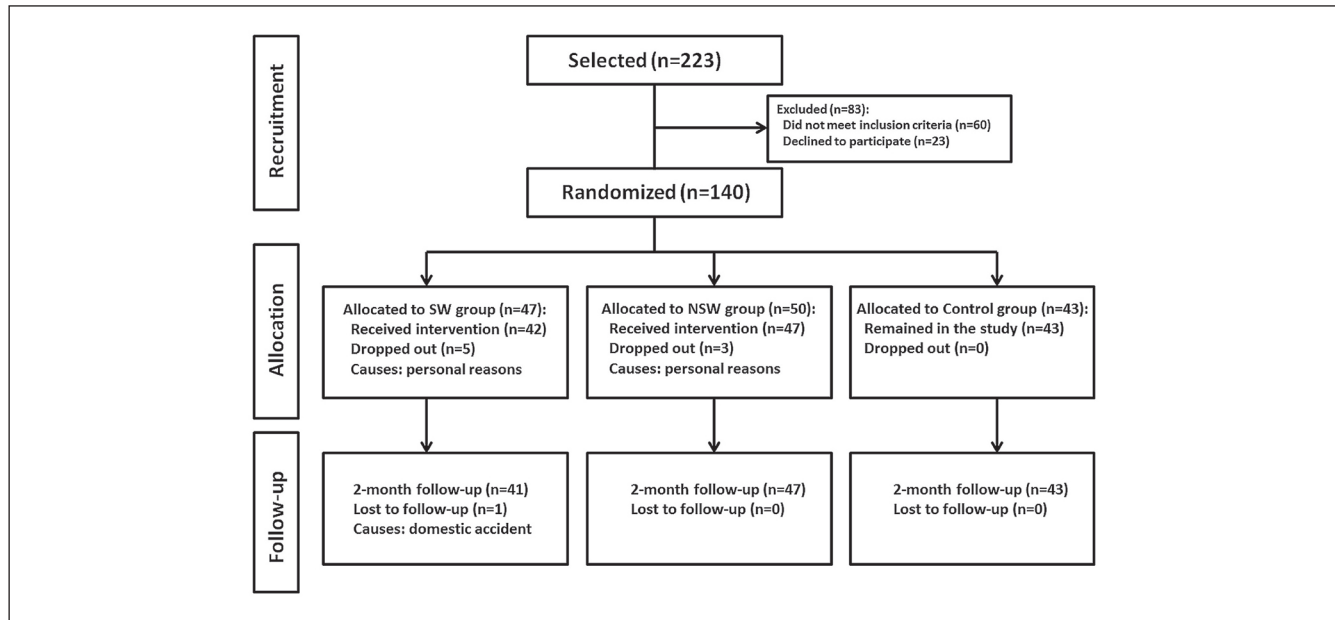


Figure 1.—Flow chart showing the distribution of participants during each stage of the study.

TABLE I.—Intergroup comparisons of patient characteristics.

| Variables | Group | | | Intergroup comparisons (P-value) | | |
|-------------------------------------|------------|------------|-------------|----------------------------------|-----------|------------|
| | C | NSW | SW | C vs. SW | C vs. NSW | SW vs. NSW |
| Women | 39 | 43 | 33 | 0.083 | 0.084 | 0.029 |
| Men | 4 | 7 | 14 | 0.029 | 0.079 | 0.029 |
| Total | 43 | 50 | 47 | | | |
| Age (years) | 65.28±7.02 | 63.69±8.89 | 65.47±10.28 | 0.553 | 0.552 | 0.553 |
| Weight (kg) | 73.4±8.86 | 76.7±12.05 | 73.7±9.2 | 0.234 | 0.243 | 0.241 |
| Height (m) | 1.63±0.03 | 1.60±0.07 | 1.62±0.06 | 0.083 | 0.083 | 0.083 |
| BMI (kg/m ²) | 27.3±3.4 | 29.7±4.6 | 27.8±3.5 | 0.082 | 0.01 | 0.01 |
| Time from onset of symptoms (years) | 10±7.7 | 6.6±4.5 | 6.9±5.6 | 0.014 | 0.014 | 0.08 |

BMI: Body Mass Index; NSW: non-sulfurous water group; SW: sulfurous water group; C: control group. Data are expressed as mean±SD.

significant differences between the control group and both the SW and NSW groups (P=0.014).

There was a significant decrease in VAS scores for pain on movement, at rest, and at night from baseline to T2 and T3 in both the SW and NSW groups (P=0.000) and between both treatment groups and the control group at T2 and T3 (P=0.000) (Table II). No significant differences between treatment groups were found in VAS scores for pain at night and at rest at the treatment endpoint (T2), but the mean VAS score for pain on movement was significant lower (less pain) in the SW group. At the 2-month-follow-up (T3), VAS scores for pain on movement, at rest, and at night were signifi-

cant lower (P=0.000) in the SW group than those of the NSW group (Table II).

Patients in both treatment groups used significantly less pain medication during the study period than controls (P=0.001). No significant difference in use of medication was observed between treatment groups at T2, but patients in the SW group reported significant less use of medication (P=0.002) than patients in the NSW group at the follow-up visit (T3) (Table III).

A significant decrease in WOMAC scores on the pain, stiffness and physical function subscales from baseline to T2 and T3 was found in both the SW and NSW groups (P=0.000), and between both treatment groups and the

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TABLE II.—*Intra- and intergroup comparisons of mean VAS pain scores.*

| Groups | Mean VAS pain scores | | | P-value |
|-------------------------|----------------------|-------------|-------------|---------|
| | T1 | T2 | T3 | |
| Pain on movement | | | | |
| Control | 8.3±0.8 (a) | 8.5±0.9 (a) | 8.4±0.8 (a) | 0.08 |
| NSW | 8.0±1.3 (a) | 4±1.6 (b) | 4.3±1.6 (b) | 0.000 |
| SW | 8.4±1.2 (a) | 2.9±2.1 (c) | 2.7±2.1 (c) | 0.000 |
| Pain at night | | | | |
| Control | 7.8±1.1 (a) | 7.9±1 (a) | 8.0±0.8 (a) | 0.07 |
| NSW | 7.5±1.5 (a) | 2.8±1.9 (c) | 3.8±1.6 (b) | 0.000 |
| SW | 7.7±1.4 (a) | 2.1±2.2 (c) | 2.1±2.1 (c) | 0.000 |
| Pain at rest | | | | |
| Control | 6.7±1.1 (a) | 6.8±1 (a) | 6.9±1.3 (a) | 0.08 |
| NSW | 5.4±2 (b) | 1.8±1.7 (d) | 2.8±1.9 (c) | 0.000 |
| SW | 6.8±1.2 (a) | 1.3±2 (d) | 1.4±2.1 (d) | 0.000 |

VAS: Visual Analog Scale; NSW: non-sulfurous water group; SW: sulfurous water group; T1: baseline; T2: treatment endpoint; T3: 2-month follow-up; subscript letters (a, b, c, and d) in parentheses = different letters in the same column indicate a significant intergroup difference in mean scores at the same time point for the different types of pain, and different letters in the same row indicate a significant intragroup difference in mean scores between time points for the different types of pain. Tukey's *t*-test at a level of significance $\alpha=0.05$ ($P<0.05$). Data are expressed as mean±SD.

TABLE IV.—*Intra- and intergroup comparisons of mean WOMAC subscale scores.*

| Groups | Time points | | | P-value |
|---|---------------|---------------|---------------|---------|
| | T1 | T2 | T3 | |
| WOMAC Pain subscale | | | | |
| Control | 60.1±6.9 (a) | 61±9.3 (a) | 59.8±9.6 (a) | 0.08 |
| NSW | 59.9±13.3 (a) | 19.3±11.5 (c) | 28.5±10.6 (b) | 0.000 |
| SW | 64.2±14 (a) | 17.3±16.3 (c) | 18.5±15.9 (c) | 0.000 |
| WOMAC Stiffness subscale | | | | |
| Control | 66±11.4 (a) | 65.4±9.8 (a) | 62.2±12.3 (a) | 0.06 |
| NSW | 65.9±14.2 (a) | 19.1±14.2 (c) | 28.7±13.3 (b) | 0.000 |
| SW | 62.9±13.2 (a) | 16.5±17.1 (c) | 18.2±16.1 (c) | 0.000 |
| WOMAC Physical Function subscale | | | | |
| Control | 54.2±9.4 (a) | 55.7±9.7 (a) | 53.6±9.3 (a) | 0.07 |
| NSW | 52.9±14.1 (a) | 18.6±10.3 (b) | 22.1±11 (b) | 0.000 |
| SW | 58.4±11.3 (a) | 16.9±15.3 (b) | 16.7±15.1 (b) | 0.000 |

WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; NSW: non-sulfurous water group; SW: sulfurous water group; T1: baseline; T2: treatment endpoint; T3: 2-month follow-up; subscript letters (a, b, c, and d) in parentheses: different letters in the same column indicate a significant intergroup difference in mean scores at the same time point for the different subscales, and different letters in the same row indicate a significant intragroup difference in mean scores between time points for the different subscales. Tukey's *t*-test at a level of significance $\alpha: 0.05$ ($P<0.05$). Data are expressed as mean±SD.

TABLE III.—*Intergroup comparisons of the mean number of times the patients in the three groups took medication for pain in the knees.*

| Time points | Use of pain relief medication | | | Intergroup comparisons (P-value) | | |
|-------------|-------------------------------|-----------|-----------|----------------------------------|-----------|------------|
| | SW | NSW | C | C vs. SW | C vs. NSW | SW vs. NSW |
| T2 | 3.27±0.57 | 3.63±0.83 | 9.86±1.50 | 0.001 | 0.001 | 0.08 |
| T3 | 3.08±0.66 | 4.55±1.01 | 8.55±0.72 | 0.002 | 0.002 | 0.003 |

SW: sulfurous water group; NSW: non-sulfurous water group; C: control group; T2: treatment endpoint; T3: 2-month follow-up. Data are expressed as mean±SD.

control group at T2 and T3 ($P=0.000$) (Table IV). The mean scores on the three WOMAC subscales were not significantly different between treatment groups at T2, but were significant lower (better outcome, $P=0.000$) in the SW group than those of the NSW group at T3 (Table IV).

A significant decrease in HAQ and LAFI scores was also found from baseline to T2 and T3 in both the SW and NSW groups ($P=0.000$) and between both treatment groups and the control group at T2 and T3 ($P=0.000$) (Table V). There were no significant differences in HAQ and LAFI scores between treatment groups at T2, but patients in the NSW group reported significant higher HAQ and LAFI scores (worse outcome; $P=0.000$) than those in the SW group at the follow-up visit (T3) (Table V). No adverse effects were observed during the study.

TABLE V.—*Intra- and intergroup comparisons of mean HAQ and LAFI scores.*

| Groups | Time points | | | P-value |
|-------------------------|--------------|--------------|--------------|---------|
| | T1 | T2 | T3 | |
| Mean HAQ scores | | | | |
| Control | 1.4±0.3 (a) | 1.4±0.3 (a) | 1.4±0.3 (a) | 0.582 |
| NSW | 1.4±0.3 (a) | 0.4±0.3 (c) | 0.6±0.4 (b) | 0.000 |
| SW | 1.4±0.3 (a) | 0.4±0.4 (c) | 0.4±0.4 (c) | 0.000 |
| Mean LAFI scores | | | | |
| Control | 14.2±2.5 (b) | 14.9±2.9 (b) | 16.8±2.6 (a) | 0.562 |
| NSW | 14.8±2.2 (b) | 7.7±3.1 (d) | 9.2±2.8 (c) | 0.020 |
| SW | 14.6±3.0 (b) | 6.8±4.1 (d) | 6.7±4.0 (d) | 0.000 |

HAQ: Stanford Health Assessment Questionnaire; LAFI: Lequesne Algofunctional Index; NSW: non-sulfurous water group; SW: sulfurous water group; T1: baseline; T2: treatment endpoint; T3: 2-month follow-up; subscript letters (a, b, c, and d) in parentheses: different letters in the same column indicate a significant intergroup difference in mean scores at the same time point, and different letters in the same row indicate a significant intragroup difference in mean scores between time points. Tukey's *t*-test at a level of significance $\alpha: 0.05$ ($P < 0.05$). Data are expressed as mean±SD.

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Discussion

Our results indicated that hot baths were effective in reducing pain and improving physical function in patients with knee osteoarthritis. Hot sulfurous water baths was the most effective treatment in reducing pain on movement at treatment endpoint and overall effects lasted longer than those of heated non-sulfurous water baths. These results are in agreement with the findings of previous studies conducted in European countries, where patients have reported significant improvement in their levels of pain and mobility after treatment in spas.¹⁹⁻²⁴

An important aspect of this study is that we had control over the conditions of the thermal waters (temperature and composition), used a true control group (patients who received no balneotherapy), and patients were randomized into treatment groups, which is consistent with the design of previous studies.²¹⁻²⁷

The WOMAC is a tool specifically designed to assess patients with hip or knee osteoarthritis.^{28, 29} Yurtkuran *et al.*⁸ conducted a study with a methodology similar to the present study, using the WOMAC to assess physical function in patients with knee osteoarthritis treated in a pool with either spa water or heated non-sulfurous water as a control. These authors found that both treatments were effective according to the three WOMAC subscales, and no significant differences in joint stiffness were observed between groups at 12 weeks post-treatment.⁸ In our study, patients treated with either sulfurous or non-sulfurous water baths reported improvement in pain, joint stiffness, and physical function (evidenced by decreased scores on all WOMAC subscales) after receiving 30 thermal baths. At the 2-month follow-up, the same general results were observed in both treatment groups; however, the results were less satisfactory for patients treated with heated non-sulfurous water bath, indicating that the positive effects of this therapy were not long-lasting. Fioravanti *et al.*²⁴ evaluated the therapeutic effects of mud baths in the treatment of patients with bilateral knee osteoarthritis. For that purpose, clinical assessments were performed 7 days before enrollment (screening visit), at the time of enrollment, 2 weeks later, and after 3, 6, 9, and 12 months after the beginning of the study. The primary efficacy outcomes were global pain score measured using a VAS and the WOMAC physical function score. Patients treated with mud baths had a significant reduc-

tion in VAS pain scores ($P < 0.001$) and WOMAC scores ($P < 0.05$) at the end of treatment and at the 3-month follow-up. The control group showed no significant differences over time.²⁴ Improvements in WOMAC scores were also reported by other similar studies on balneotherapy.^{19, 25, 30, 31}

The clinical efficacy of balneotherapy in patients with knee osteoarthritis was also assessed using the VAS for pain intensity and a significant reduction in VAS pain scores was observed at the treatment endpoint. This result is in agreement with the findings of other studies using similar treatment protocols (two thermal baths per day for 2 weeks).^{8, 20, 24, 25, 29, 31, 32}

The mechanisms by which balneotherapy relieves joint pain are yet to be well understood. It is reasonable to suppose that pain relief is associated with mechanical, thermal and chemical factors. The absorption of salts through the skin appears to be limited, but there are no definitive studies on this subject. Therefore, the therapeutic effects of balneotherapy seem to be related to the local interaction between the mineral water and surface structure of the skin.³³

The positive effects of balneotherapy on knee osteoarthritis may be attributed to specific effects of thermal waters and nonspecific effects of the hydrotherapy environment. The heat and buoyancy provided by thermal waters help reduce muscle tone, which may increase the pain threshold in nerve endings. Another explanation for the pain relief provided by balneotherapy is based on the gate control theory of pain. The body surface is stimulated by the heat and pressure exerted by the water in a thermal pool and these stimuli contribute to pain relief. Peripheral vasodilation occurs during immersion in thermal or mineral waters due to the effects of water temperature and chemical components present in these waters. Observations of the effects of thermal baths on beta-endorphin levels are controversial. It has been reported that beta-endorphin levels increase during a thermal and mineral bath.³⁴ On the other hand, it has also been reported that a three-week course of balneotherapy had no effect on plasma beta-endorphin levels in patients with osteoarthritis.³⁵

The mechanisms of pain relief associated with immersion in thermal mineral waters in rheumatic diseases are not fully understood.³⁶ It is probably the result of a combination of factors, including mechanical, thermal and chemical effects.³⁰ Thermal therapy may

have beneficial effects on muscle tone, joint mobility and pain intensity. Immersion in water to neck level at 35°C results in a cascade of reactions, such as increased diuresis, natriuresis, and cardiac output.³⁷ Prostaglandin E2 (PGE2) and leukotriene B4 (LTB4) are important mediators of inflammation and pain. Studies have reported a decrease in circulating levels of prostaglandin E2 (PGE2) and leukotriene B4 (LTB4) in patients with osteoarthritis or fibromyalgia treated with mud baths or balneotherapy.^{38, 39} In addition, patients with osteoarthritis treated with a cycle of spa therapy showed a non-significant trend toward increased plasma leptin concentrations and a significant decrease in adiponectin levels at the end of the mud-bath therapy cycle. These adipocytokines play an important role in the pathophysiology of osteoarthritis. There is some evidence that adiponectin may have pro-inflammatory effects in skeletal joints and be involved in cartilage degradation.⁴⁰⁻⁴³

The therapeutic effects of immersion baths is enhanced due to the physical-chemical composition, mineralization and possible absorption of compounds dissolved in medicinal mineral waters.³⁷ Sulfur compounds, which are the main active agents in sulfurous waters, have desensitizing and vasodilator actions and are present in the cartilage structure (e.g., chondroitin sulfuric acid).⁴⁴

The HAQ and LAFI scores, reflecting the level of functional status of the participants in this study, showed that the effects of hot sulfurous baths were more pronounced than those of the heated non-sulfurous water bath at the 2-month follow-up. This is in agreement with the findings of other studies with similar designs.^{23, 45} The increase in blood flow is a well-known physiological response to the heat associated with balneotherapy. The extra-blood flow to inflamed tissues removes noxious substances, promotes tissue repair due to an increased oxygen supply, removes free radicals, and has counter-irritant effects that relieve pain. Thermal stimulation provides temporary relief of pain by inhibiting sensory nerve endings. Pain returns after the treatment, but muscle relaxation prolongs the duration of the analgesic effect. Heat and buoyancy of the thermal bath can also increase mobility and induce sedation, having an effect on muscle tone and pain. In addition, thermal waters increase the flexibility of soft tissues and may lead to a reduction in pain and spasms, increased collagen elasticity, and improvement in func-

tional status.⁸ Some authors have proposed that sulfur, which is an element found in cartilage tissues, passes through the skin during the thermal bath and, after diffusing through soft tissues and extracellular spaces, is carried by the blood, penetrates into the connective tissue and is incorporated into mucopolysaccharides, which have a protective action on the cartilage.^{11, 46, 47}

Adherence to therapy is an essential factor in the treatment of pain caused by osteoarthritis of the knee. Of the 140 participants, 132 completed the treatment, and 131 attended the 2-month post-treatment follow up. Only 9 (6.4%) patients dropped out of the study, and therefore adherence to therapy was satisfactory. All patients received detailed information concerning the disease and its treatment, and self-care education. Baths sessions were rigorously monitored in both treatment groups.

There are several clinical trials investigating the effects of balneotherapy using different number of sessions, postures, follow-up period, comparative interventions, and especially different conditions. In most studies, the small sample size and lack of a randomized design and blind review affect the interpretation of results. Some of these studies compared baseline and post-intervention measurements, but had no control group. Studies without control group and case reports provide questionable conclusions. Still, the information found in the literature identifies the use of sulfurous waters as a promising therapeutic option for a variety of musculoskeletal conditions, including osteoarthritis of the knee.

In the present study, some variables that may be related to patient improvement could not be controlled. For example, some participants had adopted a sedentary lifestyle, reducing the functional activity of muscles around the knee due to osteoarthritis symptoms; the trip to the spa resort may have had an effect on muscular activity, with consequent improvement in function. Also, osteoarthritis may lead patients to depression and a reclusive life, which in turn may exacerbate pain. Participants may have experienced improvement in these aspects after the beginning of treatment due to their contact with other patients and the attention received from therapists involved in the study. Some patients reported weight loss, which could be derived from their stay in the spa environment, noting that obesity is a risk factor for osteoarthritis²⁸ and that weight loss may lead

to symptom improvement (this comment made by patients was not assessed in the study, thus it is necessary to investigate this hypothesis in future studies).

There is a need for further double-blind randomized clinical trials with a larger number of patients from multiple centers, involving more treatment sessions, the chemical analysis of the waters and evaluation of physical factors affecting the experiment to better understand the impact of thermal waters on osteoarthritis of the knee. In addition, the effects of treatment should be evaluated not only in patients with chronic pain, but also in those with subacute and acute pain, as well as in patients with symptoms of osteoarthritis in other joints, such as the spine, hip and hands. It is also necessary to compare results with those of other treatment methods and investigate other outcomes using postural evaluation and imaging techniques.

We acknowledge that the participants were not blinded to treatment allocation because those in the experimental groups were able to detect the presence or absence of the characteristic odor of sulfurous waters in their baths, and the control group received no treatment, which is a limitation of the study. Also, it is not clear in this study whether the positive therapeutic effect resulted from the chemical or thermal characteristics of the waters. Our results showed that both interventions were effective in reducing pain in patients with osteoarthritis of the knee, improving their functional status. Both treatment groups had similar results after 30 treatment sessions; however, the benefits of treatment were better maintained in patients treated with hot sulfurous water at 2 months post-intervention. Thus, one may infer that the two interventions can be used to treat osteoarthritis and that hot waters have a significant therapeutic effect, but hot sulfurous waters are more effective than heated non-sulfurous waters. It is also important to note that therapy with hot sulfurous water has a low cost and easy access to the general population in cities with spa resorts, making it a highly relevant adjuvant therapy in the conservative treatment of osteoarthritis.

Conclusions

Both the thermal sulfurous and non-sulfurous water bath therapies were effective in relieving pain, improving physical function and reducing the need for pain medication in patients with knee osteoarthritis. Patients

in the treatment groups reported better results than those who received no treatment. At the 2-month follow-up, patients treated with hot sulfurous water baths reported significantly less pain and improved physical function compared with those treated with heated non-sulfurous water baths.

References

- Eşen S, Akarırmak U, Aydın FY, Unalan H. Clinical evaluation during the acute exacerbation of knee osteoarthritis: the impact of diagnostic ultrasonography. *Rheumatol Int* 2013;33:711-7.
- Lund H, Weile U, Christensen R, Rostock B, Downey A, Bartels EM, *et al.* A randomized controlled trial of aquatic and land-based exercise in patients with knee osteoarthritis. *J Rehabil Med* 2008;40:137-44.
- Lyytinen T, Liikavainio T, Bragge T, Hakkarainen M, Karjalainen PA, Arokoski JP. Postural control and thigh muscle activity in men with knee osteoarthritis. *J Electromyogr Kinesiol* 2010;20:1066-74.
- Srikanth VK, Fryer JL, Zhai G, Winzenberg TM, Hosmer D, Jones G. A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. *Osteoarthritis Cartilage* 2005;13:769-81.
- Maurer BT, Stern AG, Kinossian B, Cook KD, Schumacher HR Jr. Osteoarthritis of the knee: isokinetic quadriceps exercise versus an educational intervention. *Arch Phys Med Rehabil* 1999;80:1293-9.
- Fidelix TS, Soares BG, Trevisani VF. Diacerein for osteoarthritis. *Cochrane Database Syst Rev* 2006;1:CD005117.
- Pereira HLA, Ribeiro SLE, Ciconelli RM. Topical anti-inflammatory drugs in osteoarthritis of the knee. *Rev Bras Reumatol* 2006;46:188-93.
- Yurtkuran M, Yurtkuran M, Alp A, Nasircilar A, Bingöl U, Altan L, *et al.* Balneotherapy and tap water therapy in the treatment of knee osteoarthritis. *Rheumatol Int* 2006;27:19-27.
- Vehagen A, Bierma-Zeinstra S, Lambeck J, Cardoso JR, de Bie R, Boers M, *et al.* Balneotherapy for osteoarthritis. A cochrane review. *J Rheumatol* 2008;35:1118-23.
- Quintela MM. Thermal knowledge and therapies: a comparative view of Portugal (São Pedro do Sul hot springs) and Brazil (Caldas da Imperatriz hot springs). *Hist Cienc Saude- Manguinhos* 2004;11:239-60.
- Mourão BM. Medicina hidrológica. Moderna Terapêutica das águas minerais e estâncias de cura. Poços de Caldas: Prima; 1992.
- Flores RH, Hochberg MC. Definition and classification of osteoarthritis. In: Brandt KD, Doherty M, Lohmander LS, editors. *Osteoarthritis*. New York: Oxford; 2003. p 1-8.
- Kellgren JH, Lawrence JS. Radiological assessment of osteoarthrosis. *Ann Rheum Dis* 1957;16:494-502.
- Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, *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;29:1039-49.
- Ivanovith MF. Tradução e validação do questionário de vida específico para osteoartrose WOMAC (Western Ontario and McMaster Universities) para a língua portuguesa. [PhD Dissertation]. São Paulo: Universidade Federal de São Paulo; 2002.
- Marx FC, Oliveira LM, Bellini CG, Ribeiro MCC. Translation and cultural validation of the Lequesne's Algofunctional questionnaire for osteoarthritis of knee and hip for Portuguese language. *Rev Bras Reumatol* 2006;46:253-60.
- Ferraz MB. Tradução para o português e validação do questionário para avaliar a capacidade funcional "Stanford Health Assessment Questionnaire". [PhD Dissertation]. São Paulo: Universidade Federal de São Paulo; 1990.
- Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980;23:137-45.

19. Sukenik S, Flusser D, Codish S, Abu-Shakra M. Balneotherapy at the Dead Sea area for knee osteoarthritis. *Isr Med Assoc J* 1999;1:83-5.
20. Guillemin F, Virion JM, Escudier P, De Talancé N, Weryha G. Effect on osteoarthritis of spa therapy at Bourbonne-les-Bains. *Joint Bone Spine* 2001;68:499-503.
21. Tishler M, Rosenberg O, Levy O, Elias I, Amit-Vazina M. The effect of balneotherapy on osteoarthritis. Is an intermittent regimen effective? *Eur J Intern Med* 2004;15:93-96.
22. 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;89:125-32.
23. 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;56:583-90.
24. Fioravanti A, Bacaro G, Giannitti C, Tenti S, Cheleschi S, Gui Delli GM, *et al.* One-year follow-up of mud-bath therapy in patients with bilateral knee osteoarthritis: a randomized, single-blind controlled trial. *Int J Biometeorol* 2015;59:1333-43.
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;26:2063-71.
26. Fraioli A, Serio A, Mennuni G, Ceccarelli F, Petracchia L, Fontana M, *et al.* A study on the efficacy of treatment with mud packs and baths with Sillene mineral water (Chianciano Spa Italy) in patients suffering from knee osteoarthritis. *Rheumatol Int* 2011;31:1333-40.
27. Forestier R, Desfour H, Tessier JM, Françon A, Foote AM, Genty C, *et al.* Spa therapy in the treatment of knee osteoarthritis: a large randomised multicentre trial. *Ann Rheum Dis* 2010;69:660-5.
28. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol* 1988;15:1833-40.
29. Vasconcelos KSS, Dias JMD, Dias RC. Relationship between pain intensity and functional capacity of obese individuals with knee osteoarthritis. *Rev Bras Fisioter* 2006;10:213-8.
30. Bálint GP, Buchanan WW, Adám A, Ratkó I, Poór L, Bálint PV, *et al.* The effect of the thermal mineral water of Nagybaracska on patients with knee joint osteoarthritis--a double blind study. *Clin Rheumatol* 2007;26:890-4.
31. Forestier R. Magnitude and duration of the effects of two spa therapy courses on knee and hip osteoarthritis: an open prospective study in 51 consecutive patients. *Joint Bone Spine* 2000;67:296-304.
32. Kovács I, Bender T. The therapeutic effects of Cserkeszőlő thermal water in osteoarthritis of the knee: a double blind, controlled, follow-up study. *Rheumatol Int* 2001;21:218-21.
33. Lagarto Parra L, Bernal Soluguren I. Therapeutic use of mineral and medicinal waters and muds. *Rev Cuba Farm* 2002;36:62-8.
34. Kubota K, Kurabayashi H, Tamura K, Kawada E, Tamura J, Shirakura T. A transient rise in plasma beta-endorphin after a traditional 47 degrees C hot-spring bath in Kusatsu-spa, Japan. *Life Sci* 1992;51:1877-80.
35. Yurtkuran M, Ulus H, Irdesel J. The effect of balneotherapy on the plasma- β -endorphine (BE) level in patients with osteoarthritis. *Phys Rehab Kur Med* 1993;3:130-2.
36. 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.
37. Fioravanti A, Cantarini L, Guidelli GM, Galeazzi M. Mechanisms of action of SPA therapies in rheumatic diseases: what scientific evidence is there? *Rheumatol Int* 2011;31:1-8.
38. Bellometti S, Galzigna L. Serum levels of a prostaglandin and a leukotriene after thermal mud-pack therapy. *J Invest Med* 1998;46:140-5.
39. Ardiç F, Ozgen M, Aybek H, Rota S, Cubukçu G, Gökğöz A. Effect of balneotherapy on serum IL-1, PGE2 and LTB4 levels in fibromyalgia patients. *Rheumatol Int* 2007;27:441-6.
40. Fioravanti A, Cantarini L, Bacarelli MR, de Lalla A, Ceccatelli L, Bardi P. Effects of spa therapy on serum leptin and adiponectin levels in patients with knee osteoarthritis. *Rheumatol Int* 2011;31:879-82.
41. Dumond H, Presle N, Terlain B, Mainard D, Loeuille D, Netter P, *et al.* Evidence for a key role of leptin in osteoarthritis. *Arthritis Rheum* 2003;48:3118-29.
42. Lago R, Gomez R, Otero M, Lago F, Gallego R, Dieguez C, *et al.* A new player in cartilage homeostasis: adiponectin induces nitric oxide synthase type II and pro-inflammatory cytokines in chondrocytes. *Osteoarthritis Cartilage* 2008;16:1101-9.
43. Gomez R, Lago F, Gomez-Reino J, Dieguez C, Gualillo O. Adipokines in the skeleton: influence on cartilage function and joint degenerative diseases. *J Mol Endocrinol* 2009;43:11-8.
44. Untura Filho M. Uso terapêutico das Águas Minerais. In: Untura Filho M, editors. *Termalismo no Brasil*. São Paulo: Fumest; 1989. p. 66-9.
45. 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;11:88-93.
46. Martinez, AMR, Blanco WA, Ross RMO, Diaz AIC. Efectividad del tratamiento termal en pacientes con gonoartrosis. *Atención de enfermería*. *Rev Cuba Enferm* 2002;18:23-6.
47. Valenzuela MA. Aging "fatigue of life" spa cures. *An R Acad Nac Med (Spain)* 2003;120:355-69.

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