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ORIGINAL PAPER

Evidence for the therapeutic effect of the organic content in Szigetvár thermal water on osteoarthritis: a double-blind, randomized, controlled clinical trial

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Abstract
The therapeutic effects of mineral waters have been attributed to the inorganic components alone; however, biologically active organic components are also present. We aimed to investigate whether the healing effect of Szigetvár thermal mineral water could relate to the organic matter in patients suffering from osteoarthritis of the hips and the knees. XAD macroreticular resins were used to prepare the organic fraction. Patients received a 30-min thermal water (34 °C) treatment in a bath tub, five times a week for 3 weeks. After randomization, patients were divided into three groups: tap water, mineral water, and organic fraction group. Primary outcomes were range of movement (ROM), Western Ontario and McMaster University Osteoarthritis Index (WOMAC), and visual analog scale (VAS) for pain severity, and the Short Form 36 (SF-36) questionnaire was used. These scores and indices were measured at baseline, after the last treatment, and at the end of the 3-month follow-up period. Seventy-four patients (age 67.3 ± 4.48 years) were enrolled: tap water $n = 24$, mineral water $n = 26$, and organic fraction $n = 24$. Treatment with the redissolved organic fraction significantly improved ROM, WOMAC, and SF-36 scores compared to the tap water. Our clinical trial provided evidence for the beneficial health effects of the organic fraction of Szigetvár medicinal water.

Keywords Balneotherapy · Arthritis · Thermal water · Organic fraction · ROM · WOMAC · Double-blind

Introduction

Previous studies have shown the beneficial effects of balneotherapy in musculoskeletal (chronic low back pain, rheumatoid arthritis, etc), gynecological, and dermatological conditions (psoriasis in particular); peripheral vascular disease; fibromyalgia; and many other disorders (Ayán et al. 2017; Bender et al. 2014; Fioravanti et al. 2018; Hanzel et al. 2018; Karagülle et al. 2018; Péter et al. 2017).

Thanks to its special geothermal conditions and great natural power, Hungary is one of the leading countries worldwide using thermal water for medical purposes. Hungary is rich in thermal mineral waters as it has more than 1300 thermal wells. From the eighteenth century, chemical analyses focused mainly on the inorganic substances of natural thermal mineral waters, and therefore, these waters were categorized according to their inorganic compositions. Mineral waters are defined as waters containing more than 1000 mg of total dissolved solids (Ministry of Health Decree no. 74/1999 (XII. 25.)), and thermal waters have to reach the temperature of more than 30 °C (General Directorate of Water Management n.d.). In the second half of the twentieth century, several analytical methods were developed to analyze the organic compounds of medicinal waters (Kárpáti et al. 1999; Kompanichenkoa et al. 2016). Still, the presence of organic components was almost completely ignored both in the categorization of thermal mineral waters and their mechanism of action. We could not find any publications investigating the effects of the organic compounds of medicinal waters on diseases.

Osteoarthritis (OA), the most common musculoskeletal condition of aged population, is a chronic degenerative disease involving large weight-bearing joints resulting in

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stiffness, pain, and impaired movement. The 2010 Global Burden of Disease Study reports that the burden of musculoskeletal disorders accounts for 6.8% of DALYs worldwide (Lozano et al. 2012). OA can affect any joints, but most commonly develops in the hips, knees, and hands. Its prevalence is 18.3% in Hungary (Musculoskeletal Health in Europe: Report v5.0. European Musculoskeletal Conditions Surveillance and Information Network 2012.), higher than the worldwide estimates (9.6% of men and 18.0% of women aged over 60 years) (WHO Department of Chronic Diseases and Health Promotion n.d.), and it is increasing due to aging and related factors such as obesity. OA has a significant negative impact on patients' quality of life. The goals of OA treatment include alleviation of pain and improvement of functional status. Nonpharmacological therapies are very important in OA together with pharmacological treatments. These treatments should be individually devised and should undergo rigorous randomized controlled trials in a similar manner to pharmacological studies. One of the widely used nonpharmacological treatment options is balneotherapy. The beneficial effects of the thermal mineral waters and/or medicinal mud on OA were investigated by several randomized controlled trials. However, these studies were focusing on the inorganic compounds of the thermal mineral waters (Branco et al. 2016; Fioravanti et al. 2014; Fioravanti et al. 2015; Kovacs et al. 2012; Kulisch et al. 2014).

In our previous clinical trial (Hanzel et al. 2018), we have already proven the positive health effects of Szigetvár thermal mineral water on patients suffering from osteoarthritis of the hips and the knees. Several other studies did the same with other thermal waters, spa therapies (Pittler et al. 2006; Franke et al. 2007; Kulisch et al. 2009; Horvath et al. 2012). In a recent systematic review, Morer et al. described these health effects as well and emphasized that double-blind randomized clinical trials are needed to study the role of mineral elements and other chemical compounds appropriately (Morer et al. 2017).

Fulfilling this requirement, the aim of the present study was to assess the therapeutic effect of the organic fraction of Szigetvár thermal mineral water in a double-blind, randomized, controlled clinical trial on patients suffering from OA of the hips and the knees. This is a completely new approach providing insight into the mechanism of action of thermal mineral waters.

Patients and methods

We performed the study again at Szigetvár Spa between August 2015 and September 2017, at the same place like we did it in our previous study (Hanzel et al. 2018). The same Regional Ethics Committee of University of Pécs, Hungary, approved the study protocol (Permission No. 5351), in accordance with the 2008 Helsinki declaration. The study was observed by medical professionals.

Inclusion and exclusion criteria were the same as in our previous study (Hanzel et al. 2018) to ensure comparability with our former results. All experimental circumstances had to be the same to prove our hypothesis that the beneficial effects of medicinal waters originate from their organic components.

Regular medications of comorbidities were administered to the patients as usual.

We paid special attention to include only those patients who had never received underwater jet massage either with tap water, or with medical water.

Recruitment of patients

The maximum travel distance required for involved patients to reach the spa was 15 km, to minimalize dropout. Informed written consent was obtained from every patient. Parameters applied in patient selection were age, sex, and diseases. The sample size had to be comparable to the sample size of our previous study (Hanzel et al. 2018). A sample size of 24 patients in the organic fraction group was required. Patient recruitment was continued until reaching 24 patients.

Preparation of organic fraction

Organic concentrate from medicinal water was prepared according to Varga (1991). Samples of thermal mineral water concentrates were isolated by adsorption–elution cycles on macroreticular adsorbent resins. A stainless steel pilot chromatography column (size 103.5 mm × 1000 mm, own product) was filled with a mixture of two adsorbent resin types (XAD-4 (Serva) and XAD-1180 (Rohm&Haas) in a rate of 1:1 in a volume of 5 l). Fifty cubic meters of thermal mineral water was passed over the column at an average flow rate of 1 bed volume per minute. Inert gas was used to eliminate the residual water from the column. Adsorbed organic substances were eluted with 96% ethanol of 1 bed volume to produce a 5000-fold concentration of the original thermal mineral water. The concentrate contained the vast majority of organic substances of the water, but not inorganic components. During the jet massage treatment in bath tub, the organic concentrate was diluted to the original concentration and temperature with tap water.

Interventions

We applied the same protocol like in our former study (Hanzel et al. 2018). Patients received a 30-min thermal water (34 °C) treatment in a bath tub, 5 times a week for 3 weeks. (Patients received solely underwater jet massage treatment (15 min per occasion) in tubs; afterwards, they stayed another 15 min in the tub.) All treatments were performed ambulatory.

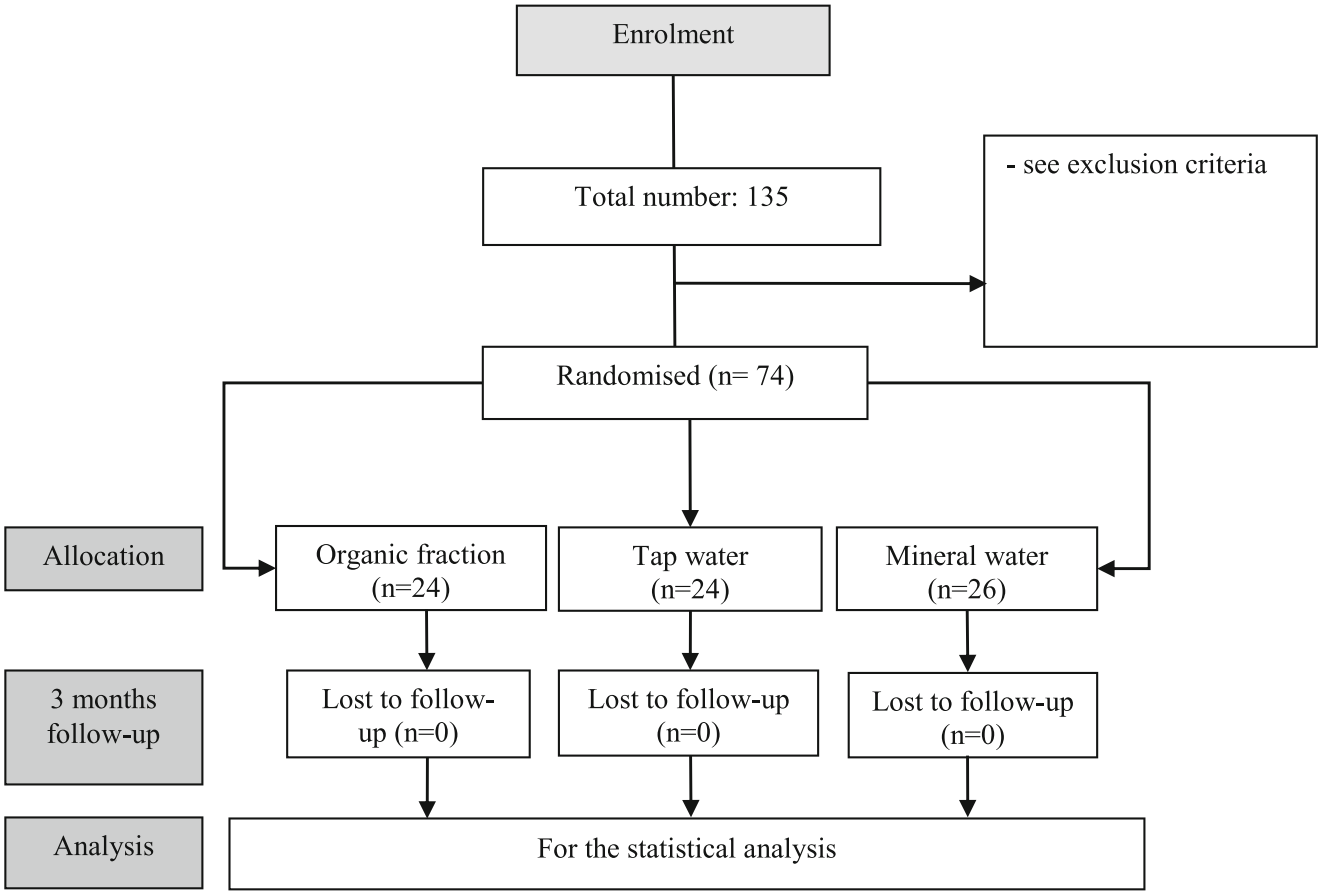

Fig. 1 Study flowchart

Analgesic medications were suspended during the 3-week-long treatment. Patients were randomly divided into three groups according to the type of the water used for the treatment. Tap water group patients received the jet treatment in tap water, mineral water group patients were treated in thermal mineral water (see Hanzel et al. 2018), and the third group in tap water containing the redissolved organic concentrate. All the three water types were colored by commercially available water coloring tablets to minimalize the experienced difference between the three different types of waters. Treatments were carried out in the same room; hence, all patients smelled the odor of the thermal water. With proper pH adjustment, differences in sensation were also eliminated. All treatments were performed in individual bathtubs. Water temperature was 34 °C. Neither the patients nor the investigators knew which type of water was filled in the tub; this was only known by the study assistant. A medical professional was responsible for the examination of patients, taking the medical history and selection.

Outcome parameters

Patients' condition was measured with both objective and subjective methods like in our previous study (Hanzel

Table 1 Clinical characteristics of the patients. BMI, body mass index

	Tap water ($n = 24$) (Hanzel et al. 2018)	Mineral water ($n = 26$) (Hanzel et al. 2018)	Organic fraction ($n = 24$)	p value
Mean age (years)	67.43 ± 4.95	66.22 ± 4.68	68.46 ± 3.58	0.206
Male, n (%)	8 (33.3)	9 (34.6)	7 (29.2)	0.912
BMI (kg/m^2)	27.08 ± 3.42	26.66 ± 3.05	26.33 ± 3.19	0.725
Diabetes type 2, n (%)	12 (50)	13 (50)	11 (45.8)	0.908
Hypertension, n (%)	18 (75)	20 (76.9)	17 (70.8)	0.850

Comparing the three groups, no significant differences were found between age, sex distribution, body mass index, and number of hypertensive patients. Mean age, years, and BMI estimates are from Kruskal–Wallis test; and Male, Diabetes, and Hypertension estimates are from chi-square test

Table 2 Baseline, short-term, and long-term measurements in range of joint movements

	Organic fraction		
	Mean	Std. deviation	*p* value
Hip flexion before treatment	102.38	5.35	
Hip flexion after 3 weeks	109.46	5.21	0.001
Hip flexion after 3 months	108.00	5.00	0.015
Hip extension before treatment	6.54	2.70	
Hip extension after 3 weeks	4.77	1.92	0.004
Hip extension after 3 months	5.46	1.90	0.02
Hip abduction before treatment	25.08	4.09	
Hip abduction after 3 weeks	28.23	5.05	0.001
Hip abduction after 3 months	26.92	4.86	0.004
Hip adduction before treatment	108.91	11.92	
Hip adduction after 3 weeks	115.18	10.03	0.001
Hip adduction after 3 months	114.09	9.74	0.003
Knee flexion before treatment	7.18	2.36	
Knee flexion after 3 weeks	4.82	1.47	0.003
Knee flexion after 3 months	5.18	1.54	0.003
Knee extension before treatment	102.38	5.35	
Knee extension after 3 weeks	109.46	5.21	0.003
Knee extension after 3 months	108.00	5.00	0.005

Baseline values were compared to short-term values, and baseline values were compared to long-term values. All estimates are from Wilcoxon signed-rank test

et al. 2018) to be able to compare the possible beneficial effects of the redissolved organic concentrate with the healing effect of medicinal water or tap water control. Range of movement (ROM) (Soucie et al. 2010) of the involved joints, Western Ontario and McMaster University Osteoarthritis Index (WOMAC) (Péntek et al. 1999), visual analog scale (VAS) for pain severity (Gould et al. 2001), and Short Form 36 questionnaire (SF-36) (Czimbalmos et al. 1999) were applied. ROM score, WOMAC index, and VAS were measured before the first treatment (baseline), after the last treatment (short-term), and at the end of the 3-month follow-up period (long-term). SF-36 questionnaire was filled in before the first treatment and after the last treatment. Interobserver error was also ruled out (Hanzel et al. 2018). Goniometer was used to measure movement of the joints; the mean value of three measurements was documented for further calculation. Goniometry plays an essential role in the clinical measurement of range of motion (Gajdosik and Bohannon 1987; Pazira et al. 2016). It is apparent from several papers that traditional plastic goniometer evaluates hip and knee joint angles efficiently and reliably; however, use of goniometer requires careful attention in evaluation (Kim 2018; Marques et al. 2017; Charbonnier et al. 2015; Gajdosik and Bohannon 1987; Rheault et al. 1988).

Randomization

Random number generator was used to allocate the patients into groups upon arrival (Suresh 2011).

Statistical analysis

Statistical analyses were performed with IBM SPSS Statistics for Windows Version 22 (IBM Corp., New York, NY, USA). Significance of the results was analyzed by Kruskal–Wallis, Mann–Whitney, Wilcoxon signed-rank test, and chi square tests. $p < 0.05$ was considered the criterion of significance.

Results

Among 135 patients, suffering from OA of the hips and the knees, enrolled into the study 61 were excluded and 74 (24 males, 50 females, mean age 67.3 ± 4.48 years) were randomized and treated (Fig. 1). After randomization, patients were divided into three groups according to the water type used for treatment: tap water group ($n = 24$), mineral water group ($n = 26$), and organic fraction group ($n = 24$). Table 1 shows the clinical characteristics of the patient groups. Comparing the three groups, there were no significant differences between age, sex distribution, body mass index, and number of hypertensive patients.

ROM score

Baseline–short-term–long-term comparison of the effect of organic fraction

There were significant ROM changes in the organic fraction group. Hip flexion ($p = 0.001$), hip extension ($p = 0.004$), hip abduction ($p = 0.001$), hip adduction ($p = 0.001$), knee flexion ($p = 0.003$), and knee extension ($p = 0.003$) showed significant improvement when baseline values were compared to short-term values. Furthermore, when comparing baseline values to long-term values, hip flexion ($p = 0.015$), hip extension ($p = 0.020$), hip abduction ($p = 0.004$), hip adduction ($p = 0.003$), knee flexion ($p = 0.003$), and knee extension ($p = 0.005$) showed significant improvement (Table 2).

Tap water–mineral water–organic fraction comparison

When comparing the ROM measured in the organic fraction group to the ROM measured in the tap water group after 15 treatments, significant improvements were detected in all parameters, except changes in hip extension. We

performed the same comparison between the organic fraction and the mineral water group. There was no significant change in parameters (Fig. 2).

When comparing the ROM of organic fraction group patients to the ROM of tap water group patients after 3 months, significant improvements were detected in all parameters (hip flexion $p = 0.028$, hip abduction $p = 0.004$, hip adduction $p = 0.002$, knee flexion and extension $p < 0.001$), except changes in hip extension ($p = 0.059$). But only knee flexion had a significant difference ($p = 0.027$) in the value of organic fraction group compared to the mineral water group (Fig. 3).

WOMAC score

Baseline–short-term–long-term comparison of the effect of organic fraction

Patients in the organic fraction group presented significant improvement in the dimensions of the WOMAC score during the short-term period, and in the long-term period, as well, except stiffness parameter. Table 3 shows the organic fraction group's detailed WOMAC index results.

Tap water–mineral water–organic fraction comparison

Comparing the WOMAC scores determined in the organic fraction group to the tap water group, no significant differences were detected in the short-term. However, 3 months after the treatment, we found significant improvements in the organic fraction group concerning pain ($p = 0.004$), activity ($p < 0.001$), and the WOMAC total score ($p < 0.001$) (Table 4).

Comparing the organic fraction group to the mineral water group in the short-term period, significant difference was not found in pain ($p = 0.551$), stiffness ($p = 0.521$), activity ($p = 0.399$), and total ($p = 0.749$) WOMAC scores. In the long-term period, there were no significant differences, either (Table 4).

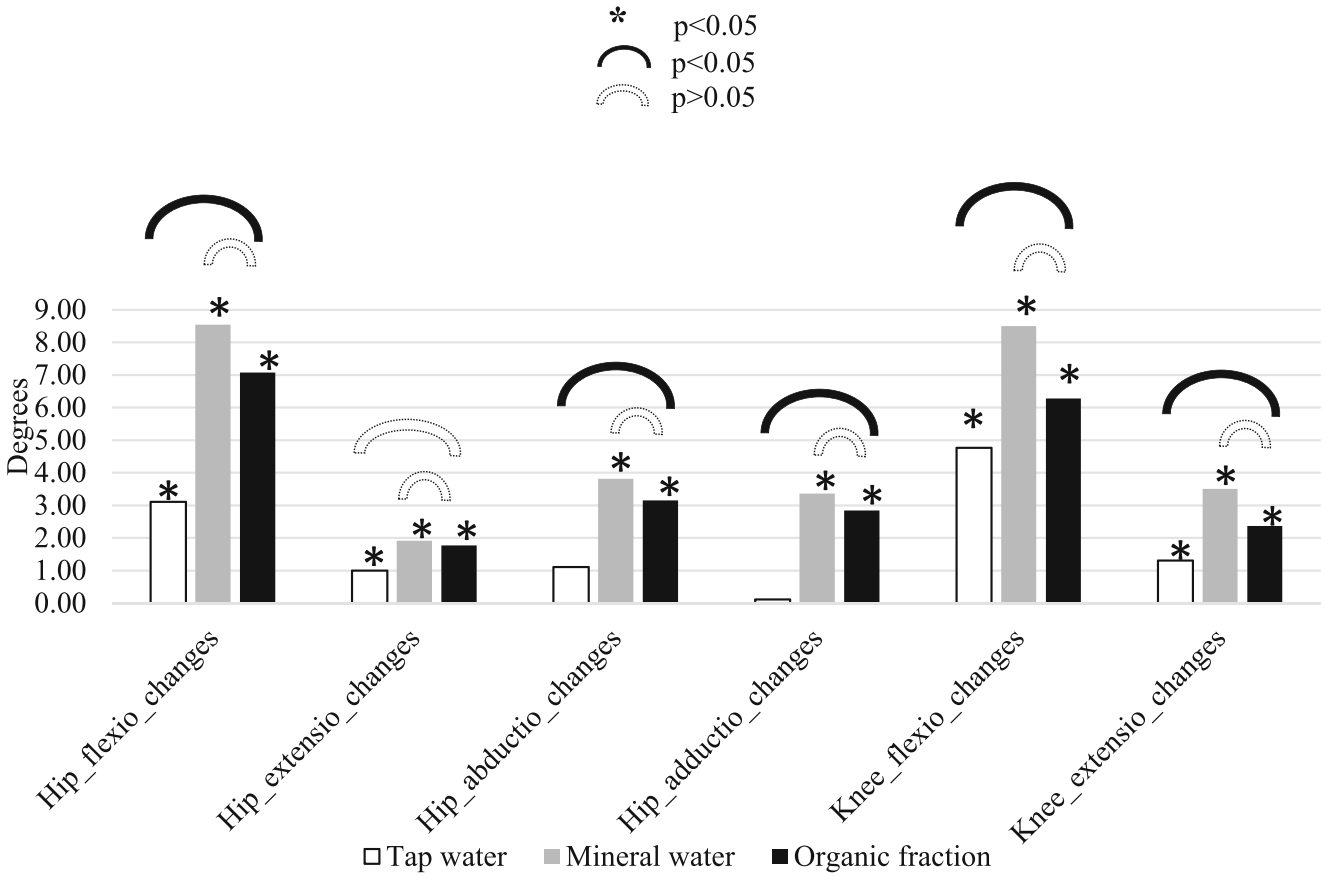

Fig. 2 Short-term changes in range of joint movements (ROM). Organic fraction group was compared to tap water and mineral water group after 15 treatments. *The three types of waters causing statistically significant changes in ROM parameters short-term. All estimates are from Wilcoxon signed-rank test. Statistically significant changes between groups. All estimates are from Mann–Whitney test. No statistically significant difference between groups. All estimates are from Mann–Whitney test

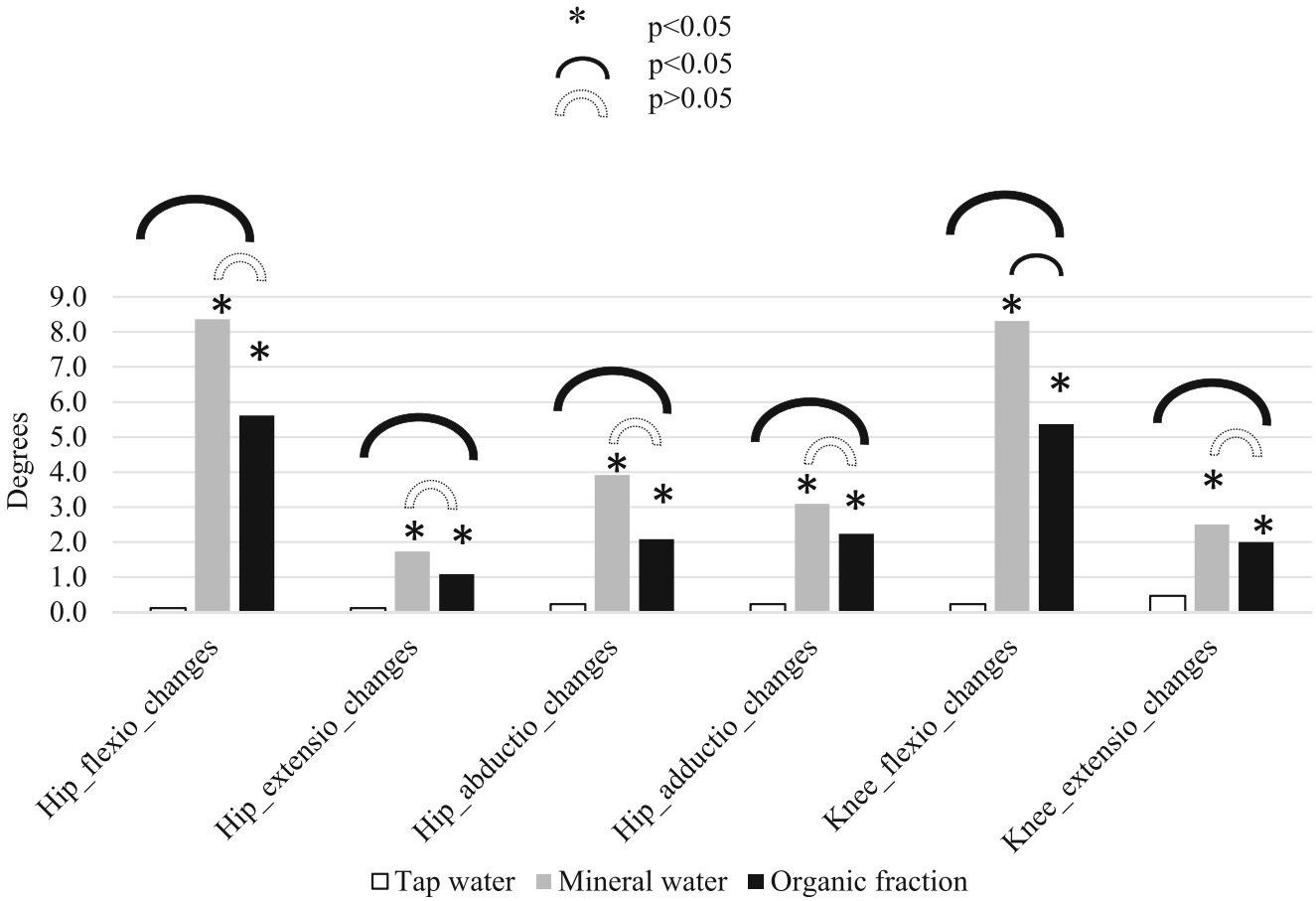

Fig. 3 Long-term changes in range of joint movements (ROM). Organic fraction group was compared to tap water and mineral water group after 3 months.*The three types of waters causing statistically significant changes in ROM parameters short-term. All estimates are from Wilcoxon signed-rank test. Statistically significant changes between groups. All estimates are from Mann–Whitney test. No statistically significant difference between groups. All estimates are from Mann–Whitney test

SF 36 questionnaire

Baseline–short-term–long-term comparison of the effect of organic fraction

We found improvement in all dimensions of the SF 36 questionnaire, except in the dimension of "General health perceptions," both short- and long-term. The "Emotional role functioning" dimension showed positive change only in the long-term period.

Tap water–mineral water–organic fraction comparison

Three months after the treatment, there were significant improvements only in the dimension of "Physical functioning" when comparing the results of the SF 36

Table 3 WOMAC scores in the organic fraction group

	Parameter	Before treatment (baseline)		After 3 weeks (short-term)		*p* value	After 3 months (long-term)		*p* value
		Mean	± Std. deviation	Mean	± Std. deviation		Mean	± Std. deviation	
Organic fraction	WOMAC pain score	6.83	2.07	4.71	1.80	< 0.001	4.96	1.85	0.001
	WOMAC stiffness score	1.83	1.49	1.00	0.93	0.001	1.83	1.34	1.000
	WOMAC activity score	26.62	8.64	18.46	7.59	< 0.001	19.708	7.07	< 0.001
	WOMAC total score	35.29	10.36	24.17	9.06	< 0.001	26.50	8.18	< 0.001

Baseline values were compared to short-term values, and baseline values were compared to long-term values. All estimates are from Wilcoxon signed-rank test

Table 4 WOMAC scores comparing organic fraction group to tap water and mineral water groups

Parameter	Tap water (Hanzel et al. 2018)		Mineral water (Hanzel et al. 2018)		Organic fraction		Organic fraction vs tap water	Organic fraction vs mineral water
	Mean	± Std. deviation	Mean	± Std. deviation	Mean	± Std. deviation	*p* value	*p* value
WOMAC pain score diff. 3 weeks	1.909	3.866	2.320	3.250	2.125	2.455	0.649	0.551
WOMAC stiffness score diff. 3 weeks	1.091	1.743	1.000	1.581	0.833	1.129	0.485	0.521
WOMAC activity score diff. 3 weeks	6.545	10.613	6.600	7.089	8.167	6.850	0.316	0.399
WOMAC total score diff. 3 weeks	9.545	14.097	9.920	8.831	11.125	9.611	0.27	0.749
WOMAC pain score diff. 3 months	0.045	1.090	2.520	2.694	1.875	2.525	0.004	0.332
WOMAC stiffness score diff. 3 months	0.045	0.653	0.040	0.539	0.000	0.659	0.668	0.632
WOMAC activity score diff. 3 months	0.136	1.754	6.080	7.000	6.917	6.852	< 0.001	0.631
WOMAC total score diff. 3 months	0.227	2.266	8.640	7.713	8.792	9.012	< 0.001	0.992

Organic fraction group was compared to tap water and mineral water group. All estimates are from Mann–Whitney test

questionnaire of organic fraction group to the tap water group ($p = 0.020$).

VAS

Baseline–short-term–long-term comparison of the effect of organic fraction

Regarding the results of VAS, redissolved organic fraction treatment significantly reduced the pain both in short-term ($p = <0.001$) and long-term ($p = 0.025$). Figure 4 shows changes of pain measured by VAS together with the previous results of tap water group and mineral water group (Hanzel et al. 2018).

Tap water–mineral water–organic fraction comparison

There were no significant differences when comparing organic fraction group to tap water group or mineral water group, either in short-term ($p = 0.107$; $p = 0.670$) or in long-term ($p = 0.525$; $p = 0.564$).

Discussion

This double-blind, randomized, controlled clinical trial proved the therapeutic effect of the redissolved organic fraction of the Szigetvár mineral water according to international standards in patients suffering from OA of the knee and hip. To the best of our knowledge, previous researches were only limited to the inorganic components of the thermal mineral water, e.g., sulfur (Kovacs et al. 2012; Carbajo and Maraver 2017), Rn^{222} (Nagy et al. 2009a; Nagy et al. 2009b), Dead Sea salt solution (Holló et al. 2004), and CO_2 (Fabry et al. 2009) in humans. No researcher has examined the possible healing effects of the organic fractions of mineral waters.

Along our initial hypothesis, the redissolved organic substance concentrate could partially provide the therapeutic effect of the original medicinal water. Our finding is the first direct evidence for the so-called Varga's organic hypothesis (Varga and Szuetta 2009; Varga 2010; Varga 2012), namely that the biological effects of thermal waters are caused by bioactive organic molecules more likely than by the inorganic salt content. Inorganic ion absorption through the skin is either unproven or insignificant due to higher ion concentrations in the human body. (This does not apply to the high-ionic mineral water consumption as course of treatment.) However, for example, hormone-like molecules with high biological activity can be found among the organic substances. These molecules that are absorbed can be highly active at very low concentrations. Furthermore, Bender et al. (2014) in their meta-analysis concluded that the beneficial effects of Hungarian thermal mineral waters were independent of their inorganic salt content.

Interpreting ROM results, when only the effect of the redissolved organic fraction was examined short- and long-term, it caused significant improvements in ROM score, just like in our previous study where the possible beneficial effects

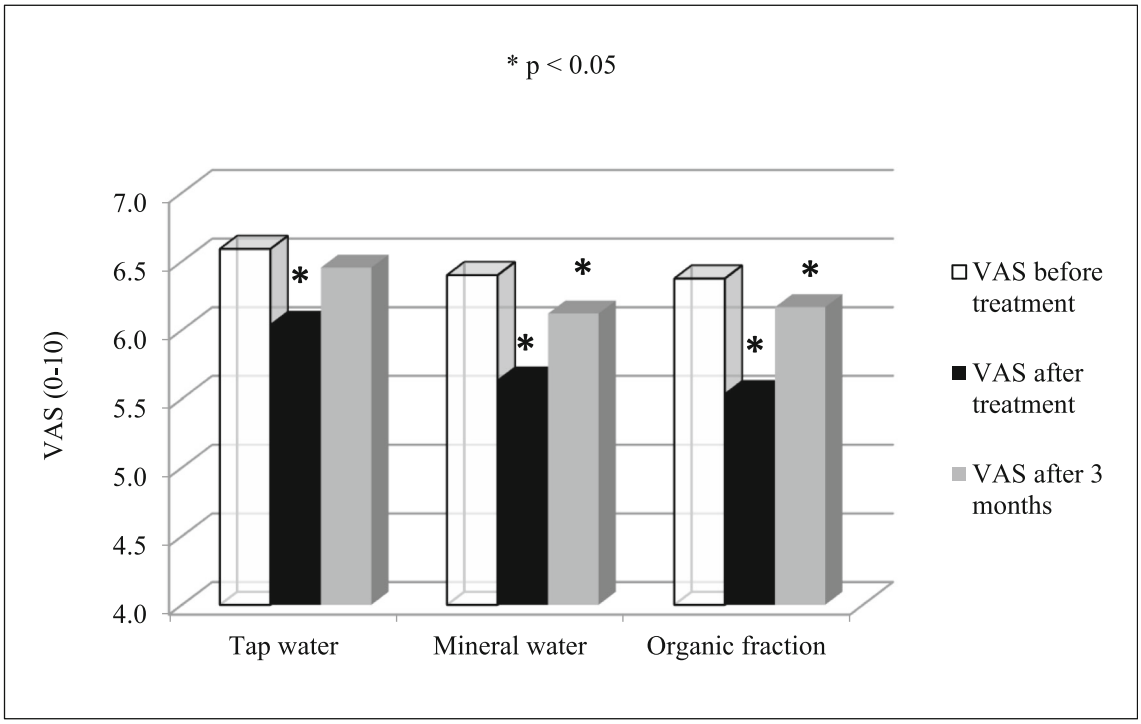

Fig. 4 Changes of pain measured by visual analog scale (VAS). Results of tap water and mineral water are from Hanzel et al. (2018). All estimates are from Wilcoxon signed-rank test. *Statistically significant reduction of pain

of the original mineral water were studied (Hanzel et al. 2018). So, in this case, the positive effect of the concentrate is very similar. When the three groups were compared, changes in ROM scores were higher in the organic fraction group than in the tap water group, both in short- and long-term. Results refer again to the same favorable effect of the redissolved organic fraction as the original mineral water, both short- and long-term.

WOMAC scores also indicated significant positive effects in the organic fraction group, short- and long-term, too. Comparing the three types of water-treated group, tap water group showed significantly worse WOMAC scores after 3 months of follow-up than the organic fraction group. WOMAC scores indicated similar beneficial or no effects of the mineral water compared to the organic fraction, both short- and long-term.

In several dimensions of the SF 36 questionnaire, the organic fraction induced positive changes both short- and long-term.

Regarding the VAS results, the organic fraction decreased the pain severity significantly also short- and long-term.

These novel findings emphasize the role and positive effects of the organic fraction of Szigetvár thermal mineral water.

Limitations

Questionnaires were self-reported; this could lead to misunderstanding and bias. Some other objective outcome parameters could have been involved, such as biomarkers of inflammation or oxidative stress. Higher number of patients could increase the strength of evidence.

Conclusion

On the field of balneology science, this unique idea is to suggest the beneficial healing effects of the organic substances in Szigetvár thermal mineral water. However, this phenomenon also needs to be proven in other medicinal waters. Once it is confirmed in numerous other investigations, our theory can lead to paradigm shift in the science of balneology. The line of further research is set for our team, as several medicinal waters in Hungary contain considerable amount of organic matter according to previous gas chromatography studies (Varga 2010). The presented concentration method also provides the opportunity to produce medicinal water-based products with therapeutic effects, which can be used both bedside and homeside.

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Compliance with ethical standards

The Regional Ethics Committee of University of Pécs, Hungary, approved the study protocol (Permission No. 5351), in accordance with the 2008 Helsinki declaration.

Conflict of interests The authors declare that they have no conflict of interest.

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