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Therapeutic properties of thermal water in rheumatic diseases: A narrative review

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Abstract

The use of thermal water therapy or balneotherapy as a complementary form of non-pharmacological treatment is common in clinical practice and has sparked some renewed interest in research the past few years. Aim of this narrative review was to investigate the therapeutic properties of thermal water therapy in patients with rheumatic diseases. The keywords that were used were thermal water therapy, balneotherapy, spa therapy and rheumatic diseases and the search was done in databases such as PubMed, Cochrane, and Scopus for systematic and narrative reviews as well as for clinical trials and RCTs. Thermal water therapy or balneotherapy or spa therapy is used for its anti-inflammatory effect as a supplement to the pharmacological treatment of patients with rheumatic diseases with or without skin symptoms to improve pain, functionality and QoL and the patients' wellbeing. There is a consensus that double-blinded RCTs are missing to evaluate the primary and secondary outcomes of the trials. Researchers are reporting a high amount of heterogeneity in both research design and methodology as well as in the quality of samples. Further research is required to address the limitations and to verify the beneficial properties of this therapeutic modality to be used in the treatment of rheumatic diseases.

Key words: *Thermal water treatment; therapeutic properties; balneotherapy; rheumatic diseases*

INTRODUCTION

The use of water for medical purposes is probably as old as humanity itself. Spas, including hydrotherapy and bathing, remained popular until effective analgesics became available. However, no analgesic can eliminate pain, and severe adverse reactions led to renewed interest in spa therapy. There is some confusion about hydrotherapy and spa therapy. The former uses plain, cool water. The latter uses natural thermal mineral water. Due to methodological difficulties and lack of research funding, the effects of "water therapies" on pain have rarely been evaluated with randomized control trials-RCTs. However, existing RCTs show that pain can be relieved in inflammatory and non-inflammatory rheumatic diseases, chronic low back pain and fibromyalgia with results lasting from three to nine months [1]. The adjective "thermal" indicates that the water has a temperature of 20º C or higher. The term balneotherapy used interchangeably to thermal water is difficult to study, as it is usually part of the overall spa therapy treatment. However, it has been possible to compare the effects of balneotherapy with those of hot tap water therapy in double-blind trials in knee osteoarthritis and rheumatoid arthritis. In controlled studies, ambulatory bath therapy was tested in patients for pain due to chronic low back pain [2] and fibromyalgia [3] making an effort to exclude the "spa atmosphere". Balneotherapy (BT) is a popular treatment for many diseases. The mechanisms by which

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mineral or thermal water immersion, or in several cases combined with mud application, relieve symptoms, are not fully understood. The net benefit is probably the result of a combination of factors. Buoyancy, immersion, resistance and temperature all play important roles. According to the gateway theory [4], pain relief may be due to water pressure and temperature on the skin; hot stimuli may affect muscle tone and pain intensity, helping to reduce muscle spasm and increase pain threshold. Spa therapy has been found to cause an increase in insulin-like growth factor-1 (IGF1), which stimulates cartilage metabolism, and transforming growth factor-β (TGF-β). There is also evidence for the positive effect of mud baths and spas on the oxidative/antioxidant system, with a reduction in the release of reactive oxygen species (ROS) and nitrogen (RNS). Overall, heat stress has an immunosuppressive effect. Many other non-specific factors may also contribute to the beneficial effects observed after spa therapy in certain rheumatic diseases, including effects on cardiovascular risk factors and changes in environment, pleasant surroundings and absence of work obligations [5].

In BT the whole or part of the body is immersed in water bathing in individual or group baths or douches, i.e. for a certain period the body is exposed to thermometallic water, which comes at a low or high pressure. This is mainly of interest for skin diseases, arthropathies and rheumatic diseases. Peloid therapy is the application of cured clay (usually mixed with mineral water) to the points indicated for rheumatism and skin diseases. Three types of stimuli are applied during spa therapy. First, the mechanical stimuli, which are due to the physical properties of water. A mechanical stimulus is hydrostatic pressure, which is the effect of the water pressure on the body of the bather. Secondly, the thermal stimuli, which are due to the heat of the water and causes vasodilation or vasoconstriction. Finally, the chemical stimuli that facilitate the change of the internal state of the body through transdermal absorption [6].

One systematic review aimed primarily at evaluating whether BT, mud therapy and spa therapy can affect cortisol levels. The secondary aim was to understand whether these interventions can improve stress resilience. Five studies investigated the biological effects of spa therapy alone. Ten studies investigated the biological effects of spa therapy with or without the inclusion of mud/peloid treatment and all, but two studies reported significant changes in cortisol levels. The main findings suggest that spa therapy may have the potential to affect cortisol levels in healthy individuals in a way that improves stress resilience, hence bathing and spa therapy can be considered useful interventions for the management of stressful situations [7]. There is also increased interest in using preclinical models to investigate the effects of BT on inflammation, immunity, cartilage, and bone metabolism. The aim of another comprehensive analysis was to summarize current knowledge on in vitro studies in BT and to review the results obtained on the biological effects of thermal mineral waters. Particular attention was paid to main rheumatological and dermatological diseases, as well as to the regulation of the immune response. Human and animal samples were used. In particular, the properties of a thermal water, as a whole, of an inorganic molecule such as hydrogen sulfide, in different cell cultures (keratinocytes, erythrocytes, chondrocytes and peripheral blood cells), or of the organic component were analyzed. The results confirmed the scientific value of in vitro studies demonstrating the anti-inflammatory, antioxidant, chondroprotective and immunosuppressive role of thermal water therapy at the cellular level. However, the validity of the cell culture model is limited by several sources of bias, such as differences in experimental procedures, high heterogeneity among available studies, and difficulties in considering all chemical and physical factors of BT [8]. The validity of such results depends on the experimental procedure and the particular and complex composition of the mineral waters used to perform the preclinical studies. Analyzing the inorganic composition of the waters may not be adequate rather than considering including the organic composite that may play a role in the observed therapeutic effect and other biological mechanisms like toxicity [9]. Finally, BTs benefits for chronic back pain (cLBP) were shown to also induce changes in proteins involved in functions such as modulation of gene expression, differentiation, angiogenesis, tissue repair, acute and chronic inflammatory response [10]. 66 patients with cLBP secondary to OA were randomly enrolled and treated with daily mud packs and bicarbonate-alkaline mineral water baths, or a thermal hydrotherapy rehabilitation scheme, the combination of the two regimens for two weeks. Control group of patients received only meditation sessions. Clinical variables were evaluated at entry level, in 2- and 12-weeks' time. 1000 serum proteins were tested before and after a two-week mud bath therapy. Spa treatment groups showed clinical benefits, shown from improved VAS scores, Roland Morris disability questionnaire and

neck disability indexes. A few serum proteins were increased (≥2.5 fold) after spa treatment: inhibin beta A subunit (INHBA), activin A receptor type 2B (ACVR2B), angiopoietin-1 (ANGPT1), beta-2-microglobulin (B2M), growth differentiation factor 10 (GDF10), C-X-C motif chemokine ligand 5 (CXCL5), fibroblast growth factor 2 (FGF2), fibroblast growth factor 12 (FGF12), oxidized low density lipoprotein receptor 1 (OLR1), matrix metallopeptidase 13 (MMP13). Three proteins were found greatly decreased (≤0.65 fold): apolipoprotein C-III (Apoc3), interleukin 23 alpha subunit p19 (IL23A) and syndecan-1 (SDC1). Balneophototherapy (BPT), further enhances the anti-inflammatory effects. In a review [11], authors described BT and BPT use in three different treatment sites, with unique climates and chemical properties of the mineral water which proved to be an effective complementary therapy for inflammatory and autoimmune skin diseases; however, the burden of the travel to the site and the long duration of therapy could be prohibitive for a wider use of this form of treatment.

Methodology

The scope of this narrative review was to focus on the therapeutic effects of BT for rheumatic and musculoskeletal diseases. Therefore, this was set as the basic research question and the related key terms used for the bibliographical research were balneotherapy, spa therapy including mud and/or peloid therapy and thermal water treatment, therapeutic properties, following the aforementioned clarifications and definitions. In that aspect, some inclusion and exclusion criteria were set, even though in narrative reviews the search protocol is not as strict as in systematic reviews and meta-analyses [12]. The rationale for the databases' search was to include clinical trials, especially RCTs, double blind and randomized, to be able to comment on their results. Apart from that, multicenter trials and systematic reviews and meta-analyses were also included due to the added benefits they could offer to the discussion on the therapeutic effects of these modalities [13]. On the other, one basic exclusion criterion was the modality of thermal water (BT) was clearly defined and differentiated from the use of hydrotherapy, where the use of water in most cases pool water (no minerals, mud, peloid, sulphur or any other ingredient added) and normal (room/environmental) temperature. Databases that were searched were Scopus, PubMed and Cochrane. Initially, 110 research articles were identified. Research articles were removed based on relativity, presence of key terms, meeting or not the inclusion/exclusion criteria. Finally, 21 articles were the ones used for this narrative review focusing specifically on the therapeutic effects of these modalities on RMDs [12].

RESULTS

In many European countries and in Turkey [1, 14], BT is used in daily clinical practice however, there are few studies on the effectiveness of spa therapy in real life [15]. Naiade, an Italian national project, was a longitudinal observational study aimed at providing knowledge on the social, epidemiological, efficacy and economic characteristics of spa treatments in eight disease subgroups one of them being the rheumatic disease subgroup including 11,437 patients with osteoarthritis. The results showed that spa therapy is beneficial and could be cost-effective. A wider range of RMDs population was included in a similar study and provided more detailed information on the effectiveness of spa treatment in daily clinical practice. Findings showed that spa therapy is prescribed and practiced mainly for osteoarthritis, then fibromyalgia, lumbar/cervical disc herniation, and nonspecific low back pain; and less for ankylosing spondylitis, rheumatoid arthritis and improvements were basically for pain and function [2].

Rheumatoid arthritis (RA) is the most common inflammatory rheumatic disease. The symptoms of RA make the disease disabling and strongly affect quality of life (QoL). Spa therapy appears to be one of the most common forms of non-drug treatment for RA which benefits the QoL of patients. There seem to be positive effects in both mineral baths and sand or mud immersion [16]. The sulphur mineral water has special benefits during active inflammatory phases. A systematic review aimed to summarize the available evidence on the effects of balneotherapy on patients with RA. The systematic search was done in articles, published from 1980 to 2014, which have compared balneotherapy with other therapeutic modalities or with no intervention considered. Eight RCTs were found and included for full review involving a total of 496 patients. The studies highlighted an important improvement and statistically significant in several clinical parameters. Improvement on functional capacity up to six months of follow-up (FU) was emphasized in one article. Some of the studies reveal an improvement on morning stiffness (five studies), number of active joints (three studies), Ritchie index (two studies) and activities of daily living (two studies) up to three months of FU. Three studies revealed the

improvement on handgrip strength up to one month of FU. Three studies evaluating the parameter of pain (VAS) were inconclusive about any improvement. This review comments on differences of methodologies, treatment modalities, outcomes and their analyses as issues to be taken into account when considering the strength of the data collected. Homogeneity of the studied population (patient's clinical heterogeneity, diverse clinical course of the disease, variety of the medications received), natural mineral water composition and their potential specific biological effects [17]. A prospective, observational study in 49 Spanish patients aged 60-80 years with RA aimed at analyzing the influence of this modality on patients' functionality and QoL. After 10 sessions of BT and an additional technique (a circular shower, footbath, mobilization in the pool, steam room), the outcome variables were the Health Related QoL (HRQoL), EuroQoL 5d-5l and the Health Assessment Questionnaire (HAQ). The scores obtained in the variable "current health state" of EuroQol 5D-5L increased by 6.73 in the first and by 6.26 points in the third month. The EuroQol index decreased by 0.121 and 0.098 points in the first [t] and the third month. In all cases, the differences were statistically significant. Regarding functionality, the mean scores obtained in the HAQ decreased in all the follow up periods, although statistical significance was only reached at three months after the end of the balneotherapeutic treatment. The beneficial effects of balneotherapy on health-related quality of life and functionality in individuals with rheumatoid arthritis can be positive, although the effect size seems to be slightly lower than that found in RCTs [18].

Similarly, overall evidence of another systematic review [19] assessing benefits and harms of BT for RA patients in terms of pain, improvement, disability, tender joints, swollen joints and adverse events was not sufficient to prove that BT is more effective compared to no treatment or that one type of bath is more effective than another or that it's more effective than exercise or relaxation therapy. The review was the update from the previous one, from 2004 and updated in 2008. RCTs were included with participants having a RA diagnosis. Two new studies were included, in total nine studies involving 579 participants. One study involving 45 participants with hand RA compared mudpacks versus placebo. There was a very low level of evidence of reduction in the number of tender joints on a scale from 0 to 28 (MD -4.60, 95% CI -8.72 to -0.48; 16% absolute difference). Two studies involving 194 participants with RA evaluated the effectiveness of additional radon in carbon dioxide baths. There was some benefit of additional radon at six months in terms of pain frequency (RR 0.6, 95% CI 0.4 to 0.9; 31% reduction; improvement in one or more points (categories) on a 4-point scale; moderate level of evidence) and 9.6% reduction in pain intensity on a 0 to 100-mm VAS (MD 9.6 mm, 95% CI 1.6 to 17.6; moderate level of evidence). Some benefit was found in one study including 60 participants in terms of improvement in one or more categories based on a 4-point scale (RR 2.3, 95% CI 1.1 to 4.7; 30% absolute difference; low level of evidence). Study authors did not report physical disability, tender joints, swollen joints, withdrawals due to adverse events or serious adverse events. One study involving 148 participants with RA compared balneotherapy (seated immersion) versus hydrotherapy (exercises in water), land exercises or relaxation therapy. One study involving 57 participants with RA evaluated the effectiveness of mineral baths (balneotherapy) versus Cyclosporin A. Some benefit of balneotherapy was observed in overall improvement on a 5-point scale at eight weeks of 54% (RR 2.35, 95% CI 1.44 to 3.83) and some benefit of Cyclosporin A in the number of tender joints (MD 8.9, 95% CI 3.8 to 14; very low level of evidence).

Despite advances in pharmacological treatment, physical therapy is important for the management of AxSpA. Aim of a study was to evaluate the effects and tolerability of combined spa therapy and rehabilitation with physical therapy in a group of 30 patients treated with TNF inhibitors: 15 were prescribed 10 sessions of spa therapy (mud packs and thermal baths) and rehabilitation (exercises in a thermal pool) and the other 15 were considered controls. The patients in both groups had been receiving anti-TNF agents for at least three months. Outcome measures were scores of BASFI, BASDAI, BASMI, VAS for back pain and HAQ. Assessments were done at entry level, after three and six months. Most of the evaluation indices were significantly improved at the end of the spa treatment, as well as at the three- and six-month follow-up assessments. The control group patients showed no differences. Combined spa therapy and rehabilitation caused a clear, long-term clinical improvement in AS patients being treated with TNF inhibitors with no shown disease relapses [20]. BT was also compared to water-based exercise and land-based exercise regarding their effects on disease activity, symptoms, sleep quality, quality of life, and serum sclerostin level (SSL) in patients with axial spondyloarthritis (AxSpA) and

were all found effective and beneficial with a duration of the benefits of up to 12 weeks [21]. Between January 2019 and January 2020, a total of 60 patients (35 males, 25 females; mean age: 40.9±11.2 years; range, 18 to 55 years) who were diagnosed with AS were randomly divided into the balneotherapy (n=20), WBE (n=20), and LBE (n=20) groups (20 sessions of treatment in groups of five to six patients). Evaluations were done at entry level, at 4 and 12 weeks with BASDAI, BASFI, BASMI, ASDAS-CRP, Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), Ankylosing Spondylitis Quality of Life (ASQoL) Scale, Fatigue Severity Scale (FSS), and Pittsburg Sleep Quality Index (PSQI). Serum sclerostin levels (SSL) were measured for all participants who had improved indices at four- and 12-weeks follow-up ($p<0.05$). A significant improvement in sleep latency was seen in the balneotherapy and WBE groups. Changes in SSL were not statistically significant in any group ($p>0.05$).

As discussed previously, BT is effective for fibromyalgia [16]. It has been found that patient education combined with a two-week application of BT has more beneficial effects in patients with fibromyalgia syndrome compared to patient education alone. Similarly, heat therapy may after all have a positive effect on specific symptoms. BTs effects for most patients appear after treatment, and are not noticeable after three months, mud bath therapy has longer lasting effects [22] when investigated in patients with primary fibromyalgia (FM) using rheumatological, psychiatric, biochemical, and proteomic approaches. 41 patients, 39 females and two males, with FM diagnosis, received a two-week thermal therapy once daily for six days/week. Twenty-one patients received mud-bath treatment, while the other twenty balneotherapy. Pain, symptoms, and quality of life were assessed. Oxytocin, brain-derived neurotrophic factor (BDNF), ATP and serotonin transporter levels during therapy were analyzed. Comparative whole saliva (WS) proteomic analysis was performed using a combination of two-dimensional electrophoresis (2DE) and mass spectrometry techniques. Both groups of patients showed reduction in pain, FIQ values and improvement of SF36, receiving either mud-bath or balneotherapy. The improvement of the outcome measures occurred with different timing and duration in the two spa treatments. Accordingly, patients in both groups showed a significant decrease in BDNF concentrations after twelve weeks, but no significant changes in oxytocin, ATP levels and serotonin transporter were detected. Significant differences were observed for phosphoglycerate mutase1 (PGAM1) and zinc alpha-2-glycoprotein 1 (AZGP1) protein expression.

In another RCT, a fibromyalgia-specific standardized spa therapy (SST) was assessed (through Fibromyalgia Impact Questionnaire-FIQ) for its efficacy and safety at six months in the context of a fibromyalgia-specific therapeutic patient education (TPE) program, compared to SST alone. The differences between groups were significant for primary parameters (pain and FIQ scores) at each time point. Similar results were obtained for the other secondary outcomes except for anxiety. Short- and long-term therapeutic efficacy of BT in FM is supported [23]. The beneficial effects of BT are supported also from a single blind RCT [3] that evaluated the effectiveness of BT in fibromyalgia management in fifty women under pharmacological treatment. Fifty women with FM under pharmacological treatment were randomly assigned to either the balneotherapy (n=25) or the control (n=25) group. The patients in the balneotherapy group had two thermomineral water baths daily/two weeks in Tuzla Spa Center. The patients in the control group received the standard of care for FM. Assessments were done four times, at entry level, at two weeks, in the first and third month. Outcome measures were pain intensity, Fibromyalgia Impact Questionnaire (FIQ), Beck Depression Inventory (BDI), patient's global assessment, investigator's global assessment, SF-36 scores, and tender point count. Balneotherapy was found to have an effect, and be a better modality, at the end of the cure period in terms of pain intensity, FIQ, BDI, patient's global assessment, investigator's global assessment scores, and tender point count as opposed to the standard of care. Benefits of BT lasted up to the end of the third month, except for the BDI score and the investigator's global assessment score [3].

Another rheumatic disease, Osteoarthritis (OA), is currently one of the leading causes of Disability Adjusted Life Year (DALY) indicators worldwide. BT is one of the most used non-pharmacological approaches for OA in many European countries, as well as in Japan and Israel. One review attempted to summarize the clinical effects and mechanisms of action of spa therapy in KOA. Several RCTs were conducted to evaluate the efficacy and tolerability of spa therapy and mud bath therapy in patients with KOA which support a beneficial effect of spa therapy on pain, functionality and quality of life that lasts over time, up to six-nine months after treatment. The net benefit is probably the result of a combination of factors, among which mechanical, thermal and chemi-

cal effects that are the most important and have been shown to be effective in the treatment and secondary prevention of KOA, reducing pain, consumption of NSAIDs and functional limitation while improving the QoL of patients [24]. Similarly, the results of another systematic review confirmed the beneficial effect for patients with chronic back pain, knee and hand osteoarthritis and chronic inflammatory pelvic disease of BT on pain with weight-bearing and at rest in patients with degenerative joint and spinal diseases. This review also revealed that spa therapy affects the antioxidant status and metabolic and inflammatory parameters [25].

A systematic review and meta-analysis on the effect of spa therapy and spa treatment on the QoL of patients with KOA when comparing spa therapy interventions with placebo interventions had results that favored the former in terms of long-term pain improvement, while no significant difference was found in terms of social functioning. The evidence suggested that spa therapy and treatment could significantly improve the quality of life of patients with KOA with reduction in medication consumption and improvement in algofunctional indicators [26]. The primary objective of a randomized RCT [27] was to evaluate the effectiveness of mud and thermal water baths compared with thermal water baths alone in Hand osteoarthritis-HOA and knee osteoarthritis-KOA. Investigators randomly assigned patients to either mud plus bath therapy (group 1) or balneotherapy (group 2). The primary outcome was a change in AUSCAN questionnaire for HOA and in the WOMAC for KOA at 12 months. Evaluations were performed at baseline (B), at week 2 (W2) after the interventions and after three (M3), six (M6), nine (M9) and 12 (M12) months. 37 patients with KOA and 52 with HOA participated. In HOA patients, AUSCAN pain improved more in group 1 compared to group 2 at M3, M6 and M12 ($p<0.001$, $p=0.001$ and $p=0.038$, respectively). AUSCAN stiffness improved more in group 1 at M3 ($p=0.001$). AUSCAN function improved more at M3, M6, M9 and M12 ($p=0.001$, $p=0.001$, $p=0.014$ and $p=0.018$, respectively). In KOA patients, WOMAC function decreased more prominently in group 1 compared to group 2 at M9 ($p=0.007$). The absolute values of WOMAC function at M6 and M9 were lower in group 1 compared to group 2 ($p=0.029$ and $p=0.001$, respectively). WOMAC pain absolute values were lower in group 1 at W2 ($p=0.044$) and at M9 ($p=0.08$). In conclusion, mud plus balneotherapy was more effective than balneotherapy alone on clinical outcomes of HOA. Differences in clinical outcomes of KOA were not significant, yet numerically higher [28]. Similarly, in a blind RCT, that evaluated the effectiveness of hot sulphur and non-sulphur waters in the treatment of KOA results showed that there was a significant reduction in VAS pain scores (pain on movement, at rest and at night) and use of pain medication, as well as improvement in WOMAC and LAFI scores ($P<0.05$) [29].

Among the available treatments, several health benefits of bathing in natural mineral water for a three-week bathing intervention in patients with KOA have been proposed for pain, functionality, emotional and social aspects and QoL. Those were the primary outcomes of this RCT in 120 patients with OA who were randomized in the experimental group (60 patients) and the control group (60 patients). Findings showed benefits for 45 patients of the experimental group who were found to benefit from the therapeutic intervention in terms of pain relief. Improvements were often clinically significant and, in most patients, persisted three months after the start of treatment [30]. Another review focused on preclinical studies, RCTs and clinical trials. The results of the clinical studies confirmed beneficial properties on various mediators and factors of inflammation, oxidative stress, cartilage metabolism and humoral and cellular immune responses in patients suffering from chronic degenerative musculoskeletal disorders. Data from mouse models of OA and RA revealed the efficacy of various BT therapies in reducing pain, inflammation and improving mobility, as well as reducing the expression of matrix-degrading enzymes and markers of oxidative stress damage. Different in vitro studies have analyzed the potential effect of a mineral water, as a whole, or a mineral element, demonstrating their anti-inflammatory, antioxidant and chondroprotective properties in OA cartilage, articular and chondrocytes, as well as osteoblast and osteoclast cultures. The data presented are promising and confirm BT as an effective complementary approach in the management of various low-inflammatory, degenerative and stress-related pathological conditions such as rheumatic diseases [31].

The short-term efficacy of different thermal modalities, such as BT, mud therapy and spa therapy in patients with OA were assessed in another systematic review. The primary outcomes for the included articles were pain, stiffness and QoL. BT was found to be effective in all three outcomes, mud therapy significantly reduced pain and stiffness, and spa therapy showed pain relief. However, heterogeneity of research designs, methodologies and quality of sample sizes raised serious consideration as

well as the lack of double-blind design RCTs. Still, some evidence was suggestive of these thermal modalities being effective at least for the long-term basis of treating patients with OA [32]. While the mechanism of spa therapy is yet to be defined clearly, it is suggested that adipocytokine, including leptin and adiponectin, may play an important role in the pathophysiology of OA. This RCT study [33] tried to assess whether during spa therapy there is evidence of plasma modified levels of leptin and adiponectin in thirty patients with knee OA treated with a cycle of a combination of locally applied mudpacks and bicarbonate-sulphate mineral bath water daily. Plasma levels of the adipocytokines leptin and adiponectin, which play an important mediating role on cartilage metabolism, were assessed at baseline and at week 2. Concentrations of leptin and adiponectin were measured by ELISA. At basal time, plasma leptin levels were significantly correlated with body mass index (BMI) and gender, but no significant correlation was found with age, disease duration, radiographic severity of knee OA, VAS score or Lequesne index as well as for the plasma adiponectin levels. For plasma adiponectin levels a correlation was found only with the Lequesne index. At the end of the mud-bath therapy cycle, serum leptin levels showed a slight but not significant increase, while a significant decrease ($P < 0.05$) in serum adiponectin levels was found. Data showed that spa therapy can modify plasma levels of the adipocytokines leptin and adiponectin. Whether this effect may play a potential role in OA needs to be further investigated and clarified.

BT applied in combination with physical therapy (PT) could have a more positive effect in patients. That was the aim of a study on 305 patients aged 65 years and older with knee osteoarthritis (KOA) compared to physical therapy (PT) alone. Findings supported the original hypothesis that BT plus PT would be more effective than PT in KOA for patients aged over 65 years supporting the notion that reducing pain is a treatment goal that positively contributes to functionality, quality of life, fatigue and sleepiness of patients living with knee osteoarthritis [34]. Similar findings showed that spa treatment reduced the level of pain in the majority of patients in the short- and long-term follow-up and contributed to improving the quality of life both in their social relations and their environment [35]. In this study, the aim was to evaluate the short- and long-term effects of spa therapy on quality of life and pain in 70 patients aged 60 years and older with OA. Spa treatment lasted three weeks (15 days of treatment) and was applied during a session lasting 120 to 150 minutes a day. BT can become an alternative to pharmacological treatment for KOA patients who do not tolerate pharmacological treatments well. In this prospective, single blind RCT BT with mineral sulphate-bicarbonate-calcium water was used for its potential to offer substantial symptomatic improvement, and to create any changes in the QoL of 60 patients with symptomatic KOA. A significant reduction of drug consumption was noted. The differences between the two groups were significant for all considered parameters already from the 15th day and persisted during follow-up. Tolerability of BT seemed to be good, with light and transitory side effects. Results confirmed that BT with mineral sulphate-bicarbonate-calcium water has beneficial effects on pain, function and QoL in patients with KOA who last over time [36]. On the same notion, BT as well as terrain therapy is making use of microclimate factors. In a study designed to assess the short- and long-term effects of spa therapy, 102 patients with osteoarthritis (OA) of the spine received treatment in health resorts. The main conclusion was that spa therapy reduces pain, improves functionality, and enhances life satisfaction in these patients. Notably, the positive effects were sustained for at least six months. Spa therapy was more effective long-term, than outpatient treatment for OA of the spine [37].

CONCLUSION

From all the above (Table 1), it becomes clear that there is evidence to support that thermal water therapy or balneotherapy or spa therapy have therapeutic properties and are beneficial for people living with rheumatic diseases. BT in particular is a beneficial therapeutic modality and can be used as a supplement or complementary treatment, but its mechanisms are yet to be defined [38]. There is also evidence to support the notion that BT has proven to be beneficial mainly for patients with OA, hand OA and/or knee OA [15,33,35,36,37,39]. Patients with rheumatoid arthritis also benefit from the use of BT alone or in combination with mud packs, peloid therapy or other therapeutic modalities such as physiotherapy [11,16,17,18,19]. There is evidence of BT being effective for FM patients alleviating pain and functionality having a positive effect even on mood indices [3,23.40,41]. For AxSpA patients BT has shown some efficacy when combined with physiotherapy or even alone and positive effects have been shown to last in time, for at least three months [42,20,21]. Still, there are not enough systematic reviews and RCTs for this group of patients. General consensus among researchers is that there is a lack of double-blind RCTs

Table 1. *Data from patient groups using BT alone or in combination with other modalities.*

Authors	Type of study	Aim of study	Methodology	Outcome measures	Conclusion
Coccheri et al. 2008	Multicenter Study	Investigate whether appropriately applied spa therapy in several indications could be associated with a subsequent fall in the need for costly health services and missed working days due to sick-leave	39,943 patients divided into eight diseases subgroups (rheumatic, respiratory, dermatologic, gynecologic, otorhlnologic, urinary, vascular and gastroenteric) underwent entry inquiry and appropriate spa treatment. 11,437 patients with OA	The Naiade project was a multicenter observational, longitudinal, questionnaire-based study comparing an "entry" inquiry addressed to patients before an entry thermal cycle, and a "return" inquiry after 1 year. Was carried in 297 Italian spa centers	The results showed that spa therapy is beneficial and could be cost-effective
Fraioli et al. 2018	Review	Investigate the evidence of the efficacy of BT, Mud-Pach therapy, Mud-Bath therapy on pain, functional limitation, drug use, and quality of life	Studies published between 2002 and 2017	35 studies were examined among which 12 were selected and included	The mud-pack therapy, balneotherapy, mud-bath therapy, and spa therapy have proved effective in the treatment and in the secondary prevention of knee osteoarthritis, by reducing pain, nonsteroidal anti-inflammatory drug consumption, and functional limitation and improving quality of life of affected patients
Antonelli et al. 2018	Meta-Analysis	Assess if balneotherapy and spa therapy can significantly improve Quality of Life (QoL) of patients with knee OA	Searched for articles about trials involving patients with knee OA and measuring the effects of balneotherapy and spa therapy on study participants' QoL with validated scales	Seventeen studies were considered eligible and included. Fourteen trials reported significant improvements in at least one QoL item after treatment	Evidence shows that BT and spa therapy can significantly improve QoL of patients with knee OA. Reduction of drug consumption and improvement of algofunctional indexes may be other beneficial effects.
Benini et al. 2021	RCT	Assess the efficacy of mud plus bath therapy in comparison to bath therapy alone in hand and knee osteoarthritis (HOA and KOA)	Patients were randomly assigned to either mud plus bath therapy (group 1) or balneotherapy (group 2)	The primary outcome was a change in AUSCAN questionnaire for HOA and in WOMAC for KOA at month 12. Evaluations were performed at baseline (B), immediately after the interventions (week 2, W2) and after 3 (M3), 6 (M6), 9 (M9) and 12 (M12) months. 37 patients with KOA and 52 with HOA were randomized in the study	Mud plus balneotherapy was more effective than balneotherapy alone on clinical outcomes of HOA. Differences in clinical outcomes of KOA were not significant, yet numerically higher
Cantista & Maraver 2020	RCT	(1) to identify possible health benefits (in terms of effects on dimensions of pain, functionality, emotional and social aspects, and quality of life) of a 3-week balneotherapy intervention in patients with knee osteoarthritis; (2) to assess the clinical relevance of any benefits detected; and (3) to determine if these effects persist	120 patients randomly assigned to (1) an experimental group (3 weeks of balneotherapy consisting of daily whirlpool baths, hydrokinesitherapy sessions, and knee shower/massages) or (2) control group in which no form of treatment apart from their usual analgesia medication was given	(1) visual analogue scale (VAS) of pain, (2) Timed Up & Go Test (TUG), (3) WOMAC osteoarthritis questionnaire, and (4) SF 36 health survey questionnaire. In the experimental group, these tests were conducted immediately before treatment, immediately after treatment, and at 3 months of follow-up. Patients assigned to the control group were assessed at the study start and 3 months later	Out of 60 patients in the experimental group, 45 were found to benefit from the treatment intervention in terms of pain relief among other aspects, and also when test scores were compared to those obtained in the control group. Improvements were often clinical relevant and in most patients persisted 3 months after treatment onset.

Table 1. *Data from patient groups using BT alone or in combination with other modalities (continued).*

Authors	Type of study	Aim of study	Methodology	Outcome measures	Conclusion
Branco et al. 2016	RCT	Evaluate the effectiveness of hot sulfurous and non-sulfurous waters in the treatment of knee osteoarthritis	140 patients, both genders, mean age of 64.8±8.9 years, with knee osteoarthritis and chronic knee pain. Patients were randomized into three groups: the sulfurous water (SW) group (N.=47), non-sulfurous water (NSW) group (N.=50), or control group (N.=43) who received no treatment. Treatment groups received 30 individual thermal baths (three 20-minute baths a week for 10 weeks) at 37-39 °C	Pain (visual analog scale, VAS), physical function (Western Ontario and McMaster Universities Osteoarthritis Index, WOMAC; Lequesne Algofunctional Index, LAFI; Stanford Health Assessment Questionnaire, HAQ), and use of pain medication. Patients were assessed before treatment (T1), at treatment endpoint (T2), and two months post-intervention (T3)	Both therapeutic methods were effective in the treatment of knee osteoarthritis; however, sulfurous baths yielded longer-lasting effects than non-sulfurous water baths.
Fernandez-Gonzalez et al. 2021	Review	Explore the effectiveness of balneotherapy for improving the quality of life of patients with RA	Spanish, English RCT or CCT until May 2021	A total 535 records were retrieved, and seven met the inclusion criteria	Balneotherapy benefits the quality of life of people with RA. Positive effects for both mineral bathing and immersion in sand or mud on the quality of life of people who suffer from RA
D' Angelo et al. 2021	Review	Evaluate the short-term efficacy of different thermal modalities in patients with osteoarthritis	Systematic Reviews from inception until October 2020, with no language restrictions, including: pain, stiffness and quality of life	Seventeen systematic reviews containing 27 unique relevant studies were included	BT was effective in reducing pain and improving stiffness and quality of life, mud therapy significantly reduced pain and stiffness, and spa therapy showed pain relief. The evidence supporting the efficacy of different thermal modalities could be seriously flawed due to methodological quality and sample size, to the presence of important treatment variations, and to the high level of heterogeneity and the absence of a double-blind design
Dilekçi et al. 2019	RCT	Investigate whether balneotherapy (BT) applied in combination with physical therapy (PT) has a more positive effect in patients aged 65 years and older with knee osteoarthritis (KOA) compared to PT alone	305 individuals were randomized into two groups. Group I was applied PT alone; group II was applied PT + BT	Assessments were made using the Pain (VAS), EQ-5D-3L Scale, Western Ontario And McMaster Universities Osteoarthritis Index (WOMAC), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) Scale, Epworth Sleepiness scale (EPWORTH) and the Outcome Measures in Rheumatology-The Osteoarthritis Research Society International set of responder criteria for osteoarthritis (OMERACT-OARSI) at the beginning (T0) and at the end (T1) of treatment	Balneotherapy plus physical therapy was more effective than physical therapy alone in KOA patients aged over 65 years. Reducing pain, especially, positively contributes to functionality, quality of life, fatigue and sleepiness of KOA patients

Table 1. *Data from patient groups using BT alone or in combination with other modalities (continued).*

Authors	Type of study	Aim of study	Methodology	Outcome measures	Conclusion
Fioravanti et al. 2011	RCT	Assess whether spa therapy modified plasma levels of leptin and adiponectin in thirty patients with knee OA treated with a cycle of a combination of daily locally applied mud-packs and bicarbonate-sulphate mineral bath water	30 patients with KOA	Leptin and adiponectin plasma levels were assessed at baseline and after 2 weeks, upon completion of the spa treatment period. The concentrations of leptin and adiponectin were measured by ELISA. Parameters: BMI, age, disease duration, radiographic severity of OA, VAS score, Lequesne index	Data showed that spa therapy can modify plasma levels of the adipocytokines leptin and adiponectin, important mediators of cartilage metabolism.
Zwolińska et al. 2018	CT	Evaluate the short- and long-term effects of spa therapy on quality of life and pain in patients aged 60 years and older with osteoarthritis	70 patients with generalized osteoarthritis were enrolled in the study. Spa treatment lasted 3 weeks (15 days of treatment) and was applied during a session lasting 120 to 150 minutes a day	Visual Analogue Scale (VAS) for pain, the Laitinen scale, and WHOQOL-BREF questionnaire were used to assess the condition of the patients. The examinations were performed three times: at the beginning of the spa treatment, after three months, and one year after the first examinations	Spa treatment reduced the level of pain in majority of the patients in short- and long-term follow-up and contributed to improving the quality of life in the domain of social relations and environment.
Zwolińska & Gasior 2022	CT	Assess short- and long-term effects of spa therapy administered to patients with osteoarthritis of the spine who received treatment in health resorts located in Poland	102 patients receiving treatment in health resorts, a group of subjects receiving outpatient treatment (100 patients) and a group receiving no therapy (100 patients)	Pain VAS and Laitinen, LISAT-9 and HAQ-20 questionnaires. Assessments three times: at the start of the therapy program, as well as one month and six months after the end of the program	Spa therapy reduces pain, improves functional efficiency and increases the level of life satisfaction in patients with osteoarthritis of the spine. Its effects are sustained for at least six months. Spa therapy is more effective long-term, than outpatient treatment.
Santos et al. 2016	Review	Summarize the available evidence on the effects of balneotherapy on patients with rheumatoid arthritis	Articles published from 1980 to 2014, RCTs, English, French, Spanish, Italian, Portuguese, participants with RA	A total of eight articles documenting RCTs, involving 496 patients	There are very few published studies about the use of natural mineral water in RA. International multicentre studies, using the same methodologies, could be achieved by carrying the scientific arguments
Verhagen et al. 2015	Review	Evaluate the benefits and harms of balneotherapy in patients with RA	Search various databases up to December 2014, BT the intervention under study, compared with another intervention or with no intervention. Pain, improvement, disability, tender joints, swollen joints and adverse events among the main outcome measures	Nine studies were included involving 579 participants	Overall evidence is insufficient to show that balneotherapy is more effective than no treatment; that one type of bath is more effective than another or that one type of bath is more effective than exercise or relaxation therapy
Ciprian et al. 2013	RCT	Evaluate the effects and tolerability of combined spa therapy and rehabilitation in a group of AS patients being treated with TNF inhibitors	30 AxSpA patients being treated with TNF inhibitors for at least 3 months were randomized: 15 were prescribed 10 sessions of spa therapy (mud packs and thermal baths) and rehabilitation (exercises in a thermal pool) and the other 15 were considered controls	BASFI, BASDAI, BASMI, VAS for back pain and HAQ. Assessments at entry, end of treatment, 3 months, 6 months	Combined spa therapy and rehabilitation caused a clear, long-term clinical improvement in AS patients being treated with TNF inhibitors. Thermal treatment was found to be well tolerated and none of the patients had disease relapse

Table 1. *Data from patient groups using BT alone or in combination with other modalities (continued).*

Authors	Type of study	Aim of study	Methodology	Outcome measures	Conclusion
Bestaş et al. 2021	prospective randomized study	Compare the effects of balneotherapy, water-based exercise (WBE), and land-based exercise (LBE) on disease activity, symptoms, sleep quality, quality of life, and serum sclerostin level (SSL) in patients with ankylosing spondylitis (AS)	Between January 2019 and January 2020, a total of 60 patients (35 males, 25 females; mean age: 40.9±11.2 years; range, 18 to 55 years) who were diagnosed with AS were randomly divided into the balneotherapy (n=20), WBE (n=20), and LBE (n=20) groups (20 sessions of treatment in groups of five to six patients)	Evaluations before treatment and at 4 and 12 weeks using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Metrology Index (BASMI), Ankylosing Spondylitis Disease Activity Score-C-reactive protein (ASDAS-CRP), Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), Ankylosing Spondylitis Quality of Life (ASQoL) Scale, Fatigue Severity Scale (FSS), and Pittsburg Sleep Quality Index (PSQI), and SSL were measured	Balneotherapy, WBE, and LBE are effective in the treatment of AS, and the beneficial effects may last for at least 12 weeks.
Ozkurt et al. 2012	RCT	Effectiveness of balneotherapy in fibromyalgia management	BT group (n=25) Control group (n=25) BT daily/2 weeks vs standard of care patients with FM	Pain intensity, Fibromyalgia Impact Questionnaire (FIQ), Beck Depression Inventory (BDI), patient's global assessment, investigator's global assessment, SF-36 scores, and tender point count.	Balneotherapy was found to be superior. The superiority of balneotherapy lasted up to the end of the 3rd month, except for the Beck Depression Inventory score and the investigator's global assessment score.
Bazzichi et al. 2013	RCT	Study the effects of both balneotherapy and mud-bath therapy treatments in patients affected by primary fibromyalgia (FM) using rheumatological, psychiatric, biochemical and proteomic approaches	41 FM patients (39 female and 2 male) received a 2-week thermal therapy programme consisting of therapy once daily for 6 days/week. Twenty-one patients received mud-bath treatment, while the other twenty balneotherapy	Pain, symptoms, and quality of life were assessed. Oxytocin, brain-derived neurotrophic factor (BDNF), ATP and serotonin transporter levels during therapy were assayed. Comparative whole saliva (WS) proteomic analysis was performed using a combination of two-dimensional electrophoresis (2DE) and mass spectrometry techniques	Thermal treatment might have a beneficial effect on the specific symptoms of the disease. In particular, while balneotherapy gives results that in most patients occur after the end of the treatment but which are no longer noticeable after 3 months, the mud-bath treatment gives longer lasting results.
Fioravanti et al. 2018	RCT	Assess the efficacy and tolerability of balneotherapy (BT) in patients with primary fibromyalgia syndrome (FS)	100 FS patients were randomized to receive a cycle of BT with highly mineralized sulfate water (BT group) or with tap water (control group)	Primary outcome measures were the change of global pain on the Visual Analogue Scale (VAS) and Fibromyalgia Impact Questionnaire total score (FIQ-Total) from baseline to 15 days. Secondary outcomes included Widespread Pain Index, Symptom Severity Scale Score, Short Form Health Survey, State-Trait Anxiety Inventory (STAI), and Center for Epidemiologic Studies Depression Scale	The differences between groups were significant for primary parameters at each time point. Similar results were obtained for secondary outcomes except for the STAI outcome. Our results support the short- and long-term therapeutic efficacy of BT in FS

and studies to confirm the mechanisms of this type of therapy and its therapeutic properties [9,16,17,18,37,33]. In addition to that, lack of homogeneity in study designs, methodologies, quality of sample sizes and analysis and parameters to be considered create discrepancies in the findings and the need for further research on the subject area to confirm findings [17,31,32]. Despite all that, evidence suggests that there are benefits and apparent therapeutic potential to this modality for patients with rheumatic diseases and could become a valid supplement to the available pharmacological treatment to be used in daily clinical practice.

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