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A meta-analysis of the effectiveness of mud-bath therapy on knee osteoarthritis

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Abstract

Objective. Osteoarthritis (OA) results from loss of cartilage integrity in association with changes to the structure of the entire joint. Treatment of OA is based on different pharmaceutical and no pharmaceutical approaches and the latter include the use of spa-therapy. The biological effects of mud-bath therapy are mainly secondary to heat stimulation and to physic-chemical properties of mineral waters and mud-packs. Mud-bath therapy likely exerts its effects modulating several cytokines and other molecules involved in inflammation and cartilage degradation. Our aim was to perform an updated meta-analysis of the effectiveness of the mud-bath therapy on knee osteoarthritis and briefly to discuss the mechanisms of action of this treatment.

Materials and Methods. A MEDLINE on PubMed for articles on knee OA and spa therapy published from 1995 through up to April 2019 was performed. Then, we checked the Cochrane Central Register of Controlled Trials to find additional references included up to April 2019. Articles were included if in accordance with the eligibility criteria. Sample size and effect sizes were processed with the MedCalc software package.

Results. Twenty one studies met the inclusion criteria and were included in meta-analysis. We examined WOMAC Index and VAS pain. We found significant improvements in function scores and painful symptoms after mud-bath therapy in patients with knee joint osteoarthritis.

Conclusions. Spa therapy is a non-drug treatment modalities, non invasive, complication-free, and cost-effective alternative modality for the conservative treatment of knee osteoarthritis. It cannot substitute for conventional therapy but can integrated or alternated to it. Treatment with mud-bath therapy may relieve pain, stiffness and improve functional status in patients with knee OA. ***Clin Ter 2021; 172 (4):372-387. doi: 10.7417/CT.2021.2343***

Key words: *knee osteoarthritis, meta-analysis, mineral waters, mud-bath therapy, osteoarthritis, spa-therapy*

Introduction

Musculoskeletal disorders (MSDs) (low back pain, neck pain, osteoarthritis, rheumatoid arthritis (RA), low bone mineral density, musculoskeletal injuries, connective tissue diseases and vasculitis) constitute a group of pathologies affecting locomotors system and they are the most common cause of severe long-term pain, impaired physical function and lower quality of life (physical, mental and economic well-being) with major burden on individuals, health and social care financial consequences. Musculoskeletal conditions are the single biggest cause of physical disability in the EU; in Western Europe their prevalence has been estimated at 4–5% of the adult population and is higher among women, increasing markedly with age (1).

Estimates made in the two decades (1990-2010) MSDs were among the greatest cause of impaired functioning in nearly worldwide measured by years lived with disability globally (YLDs). Worldwide the total number of MSDs disability-adjusted life years (DALYs) increased from 1990 to 2010 of 40%, and median proportion of DALYs attributed to MSDs diseases was 6.66% in Europe compared to lower values in the others continents (2). The burden of musculoskeletal conditions increased significantly between 2010 and 2017 for growing and ageing of populations, changes in lifestyle factors, such as increased obesity and lack of physical activity. The MSDs are among the top ten cause of disability worldwide and comprised the second highest global volume of YLDs in EU (21.3% of all YLDs) (1,3,4).

Within this grouping with the highest frequency there is osteoarthritis (OA), which is a chronic condition characterized by progressive function loss linked to joint pain and stiffness, and by an lower quality of life with considerable social repercussions in terms of direct healthcare costs (drugs) and indirect costs (work disability); 80% of patients with osteoarthritis have some degree of limitation of movement, and 25% cannot perform their major daily activities of life (5). Worldwide estimates are that 10% of the population who

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are 60 years or older (9.6% of males and 18.0% of females) has symptomatic problems that can be attributed to OA (1,7). OA in 1990 was estimated to be the 10th leading cause of non-fatal burden in the world, accounting for 2.8% of total years of living with disability (YLDs) (1). In the Global Burden of Disease study 2000 OA was the 4th leading cause of YLDs at global level accounting for 3.0% of the total global of YLDs (1,6,7). In the 2010 WHO Global Burden of Disease Study OA was the 11th cause of years lived with disability in the world but only 15th in 1990. Years of living with disability for osteoarthritis increased by 64% between 1990–2010, and Osteoarthritis of the knee accounted for 83% of the total osteoarthritis burden (2). In Global Burden of Disease (GBD) studies, osteoarthritis due to his substantial contribution to non-fatal health loss appears in the top 20 causes of disability; was observed to have an increase of 46% mean change in number of YLDs from 1990 to 2016 show that OA was ranked as 8th in the leading causes of disease burden and the second most rapidly rising condition associated with disability (1,2,7,8). Increases in life expectancy and ageing populations are expected to make osteoarthritis the fourth leading cause of disability by the year 2020 (2).

Osteoarthritis (OA) of the knee and hip combined was the third most prevalent MSK disorder. OA is the leading cause of lower extremity disability in older adults; hip and knee OA was ranked as the 11th highest contributor to global disability, and hip and knee OA has accounted for 2.4% of all years lived with disability (YLDs) (3,9). In Italy musculoskeletal disorders are on the among most important rank of cause of years lived with disability (YLDs). Percentage change in number of years lived with disability (YLDs) between 1990 and 2017 in the general adult population is 26.7% being significantly higher among women than men (10). In the Italy's GBD 2017 the OA is on the 14th rank of cause of number years lived with disability with percentage change between 1990 and 2017 51.8% (10). Population deemed most at risk include the obese, and those with abnormal biomechanics, a history of joint injury, intense sporting activities or certain occupations. For both males and females the incidence of osteoarthritis rises steeply after the age of 50 peaking in the 70-79 age groups. Especially osteoarthritis affects 16.4% of the population (21.3% females versus 11.3% males): 45% of women over the age of 65 years have symptoms while radiological evidence is found in 70% of those over 65 of age (11). The prevalence of osteoarthritis increases indefinitely with age, because the condition is not reversible (1). The main anatomical districts affected by degenerative rheumatic process are the spine and weight bearing joints. Knee and hip pain are the major causes of difficulty in walking and as many as least 40% of people over 65 years of age (12,13). Osteoarthritis of the knee is a major cause of impaired mobility and lost work time particularly among women; particularly about 13% of females and 10% of males aged 60 years and older have symptomatic knee OA. The incidence of knee osteoarthritis is high in both sexes after the age of 50 peaking in the 70-79 age groups with women experiencing particularly high levels. The standardized prevalence rate for symptomatic knee osteoarthritis per 100 populations is different by age group included: 5.39% (18-91 age group) or 29.80% (65-99 age group) in Italy (2,12,13). Knee OA can make it hard to do many everyday activities, such as walking or climbing stairs is among the most common and disabling forms of OA with high socio-economic impact in terms of drug spending and work productivity (14). The risk factors of OA consists of combination of local biomechanical (muscle strength, specific bone/joint shapes, joint loads and alignment, joint overload and joint injury), into person-level factors (sociodemographic characteristics, obesity, genetic predispositions, bone density and mass, sedentary lifestyle, diet-related factors) and metabolic disorders factors. There is growing evidence of the association between OA and metabolic syndrome rather than obesity itself has the greatest impact on the initiation and progression of disease severity (15-23). Traditionally OA has been considered a degenerative "tear and wear" disease leading to loss of cartilage, but today this view changed. Osteoarthritis (OA) is a low-grade chronic inflammatory disease of synovial membrane joints mediated primarily by the innate immune system (non-specific immune system), and characterized by neuroendocrine-immune deregulations with release of soluble mediators (cytokines, prostaglandins and adipokines) into the blood during metabolic disorders (obesity, insulin resistance, lipid abnormalities, hypertension) or aging (secretory senescence) thus initiating the OA process (23-29). OA joint cells in turn release inflammatory mediators into the joint cavity and once degraded, cartilage fragments fall into the joint and contact the synovial. Synovial cells react by producing inflammatory mediators, found in synovial fluid and OA synovitis perpetuates the cartilage degradation (23). OA is characterized by changes to the structure of the entire joint due to an imbalance between catabolic phenomena and chondrocytic repair phenomena. Histologically the disease is characterized early by loss of joint cartilage integrity gradually wears away fissures, ulceration and by vertical clefts associated with hypertrophy of bone (osteophytes and subchondral bone sclerosis), thickening of the capsule, synovial angiogenesis at the subchondral bone level, and periarticular ligament damage as well as loss of normal function (7,28). A complex network of proinflammatory cytokines [tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-1 receptor antagonist (IL-1Ra), interleukin-4 (IL-4), interleukin-6 (IL-6), interleukin-15 (IL-15), interleukin-17 (IL-17), chemokines], cyclooxygenase-2 (COX-2), matrix metalloproteinases (MMPs), prostaglandins (PGE2), leukotriene B4 (LTB4), adipocytokines (such as leptin, adiponectin, resistin, and visfatin), nitric oxide (NO), reactive species of oxygen (ROS), high-sensitivity C-reactive protein (hsCRP), elevated eHsp72 concentrations, cartilage extracellular matrix (ECM)-derived biomarkers [fragments of C-terminal cross-linked telopeptide type II collagen (CTX-II), cartilage oligomeric matrix protein (COMP)], and other important molecules are involved in inflammation and cartilage damage (27,30-32). Genetic predisposition, injury/surgery, thigh flexor muscle weakness, joint overload, vitamin D insufficiency, specific bone/joint shape, malalignment, repetitive activities inherent in certain occupations and sports participation (soccer, long-distance running, weight lifting, wrestling) increase the risk for the development of knee OA (15). Age in itself cannot be considered a trigger in the development of osteoarthritis; however changes that relate to aging and activities requiring repeated knee bends increase the risk. Particularly the progression of the knee OA is accelerated by obesity; it rep-

resents a biomechanical factor responsible for the onset and evolution of OA in joints subjected to load due to the effect of chronic mechanical stress induced on the chondrocyte. This increased risk cannot certainly be explained alone by the mechanical effect of overload but also by systemic factors released mainly by abdominal adipose tissue and able to reach and then activate joint cells. The infrapatellar fat pad, an adipose tissue localized in the knee, was found to be a potential source of adipokines (23). However, obesity is associated with an increased prevalence of OA even in non-bearing joints. The impact of obesity on OA has some metabolic and inflammatory systemic effects caused by gut microbiome dysbiosis (13,33,34).

The pain is typically mechanical and movement-related accompanied by short-term joint morning stiffness (<30 minutes), tenderness, joint swelling (synovitis), warmth, redness, crepitation and decrease of movement amplitude (35-37). The goals of therapy for the management of knee osteoarthritis are reduce pain and to improve functional mobility initially through noninvasive and nonsurgical means. Treatment approaches is based on pharmacologic therapies delivered topically, orally and intra-articulary, and non-pharmacologic options, often in combination, strongly and conditionally recommended: symptomatic drugs [paracetamol, cyclooxygenase-2-selective inhibitors (COX-2), acetaminophen, oral and topical no steroidal anti-inflammatory drugs (NSAIDs), tramadol, duloxetine, topical capsaicin], physical therapy (ultrasonography, laser, short wave), range of motion aerobic exercises (walking, cycling on stationary bicycles), balance training, self-efficacy and self-management programs, cognitive behavioral therapy (CBT), stretching and isometric-isotonic strengthening exercises, yoga, intra-articular hyaluronic acid, I-A steroids, kinesiotaping, assistive devices (walking aids, wearing shock-absorbing shoes or inserts insoles, knee bracing), tibiofemoral bracing for tibiofemoral knee OA (TF Knee Brace) and patellofemoral bracing for patellofemoral knee OA (PF Knee Brace), modified shoes, acupuncture, Tai Chi, radiofrequency ablation, education on weight loss (overweight or obese) and work ability, health education programs, lifestyle changes (38). A open retrospective observational study evaluated effectiveness of adapted physical activity (APA) on physical and functional health in elderly patients with osteoarthritis. A highly significant differences between the pre-APA and the post-APA value was found for various clinical indexs, showing that physical exercise improves physical function and reduces pain intensity (39). Particulary an extensive meta-analysis compared effects of exercise and analgesics on pain in knee osteoarthritis. There was no statistically significant difference between the two treatments, therefore the effects from exercise and from oral analgesics are comparable (40).

Surgical procedures (arthroscopy, cartilage grafting, osteotomy (HTO- DFVTO), uni-compartment knee replacement (UCKR) or total knee replacement (TKR) should be considered for end-stage joint damage that is causing unacceptable pain or limitation of function and used in those for whom medical therapy other treatment modalities have failed and who generally have more severe disease (41). The no pharmaceutical approaches include the use of spa-therapy (comprises a broad spectrum of therapeutic modalities including hydrotherapy, balneotherapy, mud-pack therapy, mud-bath therapy adding and supervised water exercises in spa resorts), to supplement or alternate conventional therapy (42,43). Some forms of hydrotherapeutic applications (e.g. hot showers, water jets, underwater massage, whirlpool bath and exercise in thermal water pools), as well as other treatments complementary (health education, nutrition therapy, massage therapy, exercise, physio-kinesitherapy, and lifestyle changes) can also be combined within the SPA-therapy programs (44,45). This kind of therapy can be classified under the label of traditional medicine (TM) as specified in WHO's "General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine" and used in the treatment, as well as in the prevention and rehabilitation of chronic diseases to improve the health-related quality of life for people. The terms complementary/alternative/non-conventional medicine are used interchangeably with traditional medicine in some countries (46,47). The Traditional and Complementary Medicine (T&CM) is used not only to treat diseases, especially chronic diseases; it is also widely used in disease prevention, health promotion (recreational and social activities) and health maintenance, and it has proved to be cost-effective into national health systems. Spa-therapy is a very common treatment for osteoarthritis in South and Eastern Europe, Middle Asia, Japan, South America and North Africa and involves all the medical activities that are originated and employed in spa resorts. Particularly in Italy it is applied in 320 SPAs, and each year about 2,790,000 people attend italian health resorts (fonte: Federterme). In 2013 the World Health Organization included spa-therapy in the strategies and objectives of traditional medicine for the period 2014-2023 (48).

Mineral water and peloids are both natural resources. Healing mud is a mixture of a solid of geologic origin, mainly clay, with various types of natural mineral water and organic compounds, used for packs (local application of peloids) full body or to specific areas, such as over joints, after an adequate maturation period for six months (organic compounds and chemical elements are transferred from the water to the mud), directly applied onto the skin warmed up, as a rule, to 45°C-50°C for the duration of 20-30 minutes (47,49-53). The baths with full immersion of body (head-out water immersion) or bathing of body parts consist of diving a patient in a bathtub with hot medical mineral water (with a temperature of 36°C–38°C) from natural springs which specific features according with the source (47). In addition, they may be in an agitated state, as with a whirlpool or hydro massage bath. Mineral water and healing mud obtained after maturation involve the transfer of chemical elements from the healing mud to the human body, across the skin (51,52). Tolerability of mud-bath therapy seemed is good, with light and transitory side effects.

Numerous studies produced high quality scientific evidence for the efficacy of spa-therapy regimens (balneotherapy and/or mud-pack therapy at spa resorts) for knee osteoarthritis, and recently a large systematic review was published by Forestier et al. (54).

Thus, our aim was to perform an updated meta-analysis could provide better evidence on the effectiveness of mud-bath therapy practiced in the health resort area on treating knee osteoarthritis, and briefly discuss the possible mechanisms of action of crenobalneotherapy in knee OA.

Methods

The methodology involved searching the PubMed/MEDLINE bibliographic database for articles on knee OA and SPA-therapy published from 1995 through up to April 2019 was performed. We used the MeSH terms: spa-therapy, mud-pack therapy, mud-bath therapy, balneotherapy, balneology, mineral water, hydrotherapy, osteoarthritis, gonarthrosis, and knee osteoarthritis. Then, we checked the Cochrane Central Register of Controlled Trials to find additional references included up to April 2019. More, we found several studies that were publicized in "grey" literature that is not admitted into the main scientific magazines usually selected by the Medline database. Articles were included if in accordance with the eligibility criteria: clinical trials with patients conforming to the American College of Rheumatology (ACR) criteria relating to knee OA (55); randomized controlled trials (RCTs) and controlled studies that investigated the clinical efficacy of mud-bath therapy in treating knee OA (pain, functional status, quality of life, drug intake) compared to any other intervention or no treatment; articles available in full text and publications in English only. We removed studies that did not meet the inclusion criteria: clinical trials that were not related to OA and to spa therapy, that did not study perceived pain and functional capacity, all the narrative or systematic reviews, the case reports, the open studies, retrospective analyses, observational studies perspective or retrospective, non-randomized and non-controlled trials, studies of water exercises performed without mineral water by reading the titles and abstracts. Then, the full text of the remaining articles was obtained, and only trials of knee OA were analyzed. Data were extracted from the full text and then reviewed.

Statistical Analysis

Statistical validity was evaluated by checklists described by Forestier et al. (54). Mean values and standard deviations (SD), were recorded for each of the selected study, and effect sizes were computed using the standardised mean difference (SMD) technique. The SMD is a scale-free measure of the ratio of the difference in mean outcomes between the groups to the SD of the outcome in the study population. The intervention effect expressed in SMD units is a standardised value rather than the original unit of measure. Sample size and effect sizes were processed with the MedCalc software package. Funnel plots were used to assess publication bias.

Results

The results of the search strategy and screening process according to the Prisma Statement are reported in Fig. 1 (56). Initially, a total of 1.588 records were identified from database searching. After duplicates were removed, the remaining 470 articles were screened, after 405 articles were considered ineligible, 33 articles assessed in full text were considered eligible. We excluded articles with high risk of bias. Moreover the studies in which data are expressed as median, with percentage but without absolute values or only with a graphic representation were excluded. From these we identified 21 assessable articles reporting randomized controlled trials (RCTs) on mud-bath therapy in knee OA including a total number of participants of 1.816. Of 21 studies included in the meta-analysis 3 were carried out in Italy,18 studies were carried out in other European or non-European countries, namely 2 in France, 5 in Hungary, 1 in Spain, 4 in Turkey, 5 in Israel, 1 in Brazil (57-77). Different modalities of treatment delivered in spa centers were employed for patients with knee joint osteoarthritis enrolled in the randomized controlled clinical trials (RCTs). Patients have been assessed at different time points after spa-therapy, and the methods used for the assessment of efficacy vary, although the most used are a 10-cm visual analog scale (VAS pain) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Study characteristics are reported in Table 1.

We found 4 references with low risk of bias, 17 with median risk. We examined in the selected studies as outcome measures: WOMAC in the experimental groups before start of treatment and after end of treatment, at the final follow-up visits of each study of intervention, and visual analogue scale (VAS) assessment of pain as the measurement tool between experimental groups and control groups (Table 2-3). The funnel plot of the WOMAC scores reporting estimation of heterogeneity and publication bias across studies due to heterogeneous follow-up timing is reported in Figure 2. The results of the studies under the arrows seem to have results not consistent with the other studies (57,62-64,73). The maximum follow-up time for an outcome measure varied significantly between studies with the longest reported follow-up of an outcome measure being 12 months. There was a significant improvement between T0 and T last follow-up in WOMAC scores in all studies but for 5, thus suggesting that these results seem to confirm the beneficial effect of mud-bath therapy on functional capacities in patients with knee OA (Fig. 3). An analogous improvement of VAS pain score has been also observed at the last end point of the studies compared to controls (Fig. 4). The improvement for both outcomes was maintained until 9 months into follow-up period.

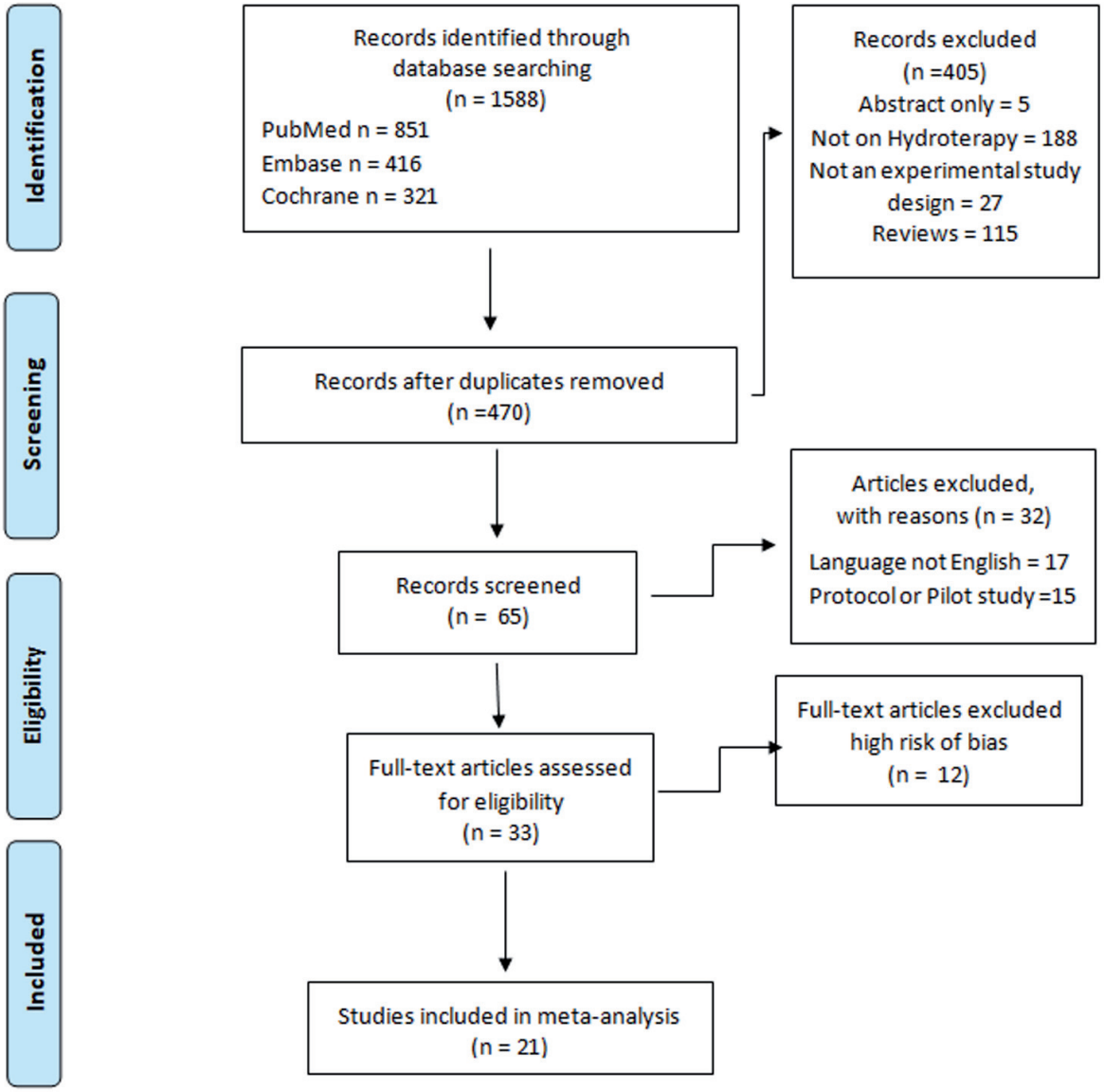

Fig.1 Flow chart of systematic search, screening and selection process

Table 1. Characteristics of analyzed studies

Authors	Treatment	Control	Sample size		Outcome measures	Follow-up
Ozkuk et al. 2019	30 patients treated for 3 weeks vs 30 patients treated for 2 weeks. Mineral water bath in the session pool for 20 min at 38 °C, rest for 30 min and then whirlpool therapy with 35 °C mineral water to both knee regions. Subsequently, 45 °C hot pack and TENS were performed for 20 min.	No	60	N	VAS pain, WOMAC, NHP	0, 30 days
Branco et al. 2016	Sulphurous water group (N.=47) vs non-sulphurous water (NSW) (N.=50) 30 individual thermal baths (three 20-minute baths a week for 10 weeks) at 37-39 °C	No treatment (N=43)	140	N	VAS pain, physical function, WOMAC; LAFI; HAQ, use of pain medication	0, 2 months
Fioravanti et al. 2015	53 patients daily local mud-packs on both knees for 20 min at an initial temperature of 42 °C and with Sillene water at 37 °C for 15min in a bathtub for a total of 12 applications carried out over a period of 2 weeks + usual care	Usual treatment (N=50)	103	Y	VAS Global pain score, WOMAC, W-TPFS	7 days before enrollment, T0-2 weeks-3, 6, 9, 12 months
Kulish et al. 2014	38 patients bathed at 34 °C for 30-minute, five times a week for three weeks.	Tap water at 34 °C for 30-minute, five times a week for three weeks (N=39)	77	Y	VAS pain, active flexion degree, knee circumference, stair-climb time, WOMAC, EQ-5D	T0, after treatment-15 weeks
Forestier et al. 2014	94 patients 18 days of spa therapy over 3 weeks with mineral hydro jet sessions at 37°C for 15 minutes, manual massages of the knee and thigh under mineral water at 38°C by a physiotherapist for 10 minutes, applications of mineral matured mud at 45°C to the knees for 15 minutes and supervised general mobilisation in a collective mineral water pool at 32°C in groups of six patients for 25 minutes + home exercise	Home exercise (N=88)	182	Y	VAS pain, WOMAC, SF-36	T0-1, 3 and 6 months
Tefner et al. 2013	27 patients hot mineral mud-pack therapy 45°C for 30 mins for 2 weeks on 10 occasions	Hot packs (45°C) of a substance manufactured on 10 occasions for 2 weeks for 30 mins (N=26)	53	Y	WOMAC, EuroQoL-5D, and use of pain medication	T0-2 weeks-6 weeks-12 weeks
Espejo Antúnez et al. 2013	61 patients, 11 consecutive sessions of peloid by brush at 30°C, followed by a drying period of 30 min in the solarium spa. Subsequently, patients received a thermal water bath for 15 min with peloid, ending with the removal of the same with a thermal jet for 2 min	Usual treatment (N=60)	121	Y	SF-36, VAS pain and changes in drug use	0-11 days
Fioravanti et al. 2012	30 patients daily sulphate-bicarbonate-calcium mineral water bath; 12 sessions in 2 weeks for 20 minutes at 38°C	Usual treatment (N=30)	60	Y	VAS pain, Lequesne, WOMAC, SF-36, AIMS and use of pain medication	T0-15 days-12 weeks
Fioravanti et al. 2010	40 patients daily mud packs applied on both knees for 20 minutes at temperature of 45°C and with bicarbonate-sulphate mineral water bath at 38°C for 15 minutes, for a total of 12 applications carried out over a period of 2 weeks + usual care	Usual treatment (N=40)	80	Y	VAS pain, WOMAC; LAFI, use of pain medication, AIMS	T0, 2 weeks- 3, 6, 9 months

(table follows)

Forestier et al. 2010	195 patients 18 days of spa therapy over 3 weeks with mineral hydro jet sessions at 37°C for 15 minutes, manual massages of the knee under mineral water at 38°C by a physiotherapist for 10 minutes, applications of mineral matured mud at 45°C to the knees for 15 minutes and supervised general mobilisation in a collective mineral water pool at 32°C for 25 minutes + home exercise	Home exercise (N=187)	382	Y	VAS pain, WOMAC, SF-36	T0-1, 3 and 6 months
Mahboob et al. 2009	25 patients received mineral mud therapy for 30 days	30 days Placebo (N=25)	50	Y	WOMAC, VAS pain	T0-30 days
Sherman et al. 2009	24 patients treated twice weekly for 6 consecutive weeks in a sulphur pool heated to 35–36°C	Jacuzzi filled with tap water heated to 35–36°C (N=20)	44	Y	Lequesne, WOMAC, SF-36, VAS pain	T0-6 weeks
Odabasi et al. 2008	30 patients had mud application 15 times to both knees with heated mud, up to 43°C applied to skin directly for 30 mins	Nylon-covered mud pack (N=30)	60	Y	WOMAC, VAS pain, patient's assessment of disease severity index, physician's assessment of disease severity index, and use of drug	T0-24 weeks (every 4 weeks)
Balint et al. 2007	32 patients thermal mineral water at 34°C for 30-min sessions of bathing, 5 days a week for four consecutive weeks	Tap water (N=32)	64	Y	WOMAC	0-4 weeks
Karagulle et al. 2007	10 patients 10 days thermal pool baths at 37°C for 20 min two times daily.	NSAIDs and paracetamol (N=10)	20	N (investigator)	LAFI, VAS pain, patient's and investigator's global evaluation VAS, ten-stairs stepping up and down time, 15 m walking time and three times squatting up and down time	T0-2 weeks-12 weeks-24 weeks
Tishler et al. 2004	48 patients 30 mins intermittent once weekly treatment with mineral bath for 6 weeks	Usual treatment (N=24)	72	Y	VAS pain, WOMAC, Lequesne, patients' and physician's disease severity score, and use of pain medication	T0-4, 6 weeks, and 4 weeks following end of the study
Kovács et al. 2002	29 patients balneotherapy over a 15-day course of 30-min daily sessions performed with thermal water at 36°C	Tap water (N=29)	58	Y	Pain, range of motion, tenderness on palpation, stair climbing, physicians' opinion and subjective rating by patients, and ambulation	0-3 months
Odabasi et al. 2002	24 patients had a thermal mineral water at 39°C for 20 mins for 8 days + mineral mud at 45 °C for 20 mins	Two mineral water baths at 39 °C for 20 mins per day for 8 days (N=25)	49	Y (investigator unblinded)	Lequesne, VAS pain, 10 meters walking time, 3 times squatting down and up time, 10 stairs stepping down and up time	T0-8days
Flusser et al. 2002	40 patients natural mineral-rich mud compresses applied 5 times each week during 3 weeks for a total of 15 treatments	Mineral-depleted mud compresses 30-35°C 3x5 (N=18)	58	Y	Lequesne, patient self-assessment of pain, VAS pain	T0-3 weeks-1 month-3 months
Ozkuk et al. 2017	Consecutive Treatment (n=25) for 2 weeks versus intermittent Treatment (n=25) for 5 weeks. Ten sessions of bath-mud therapy.	No	50	Y	VAS pain, WOMAC, SF-36	T0, after treatment-12 weeks
Wigler et al. 1995	11 patients had mineral water baths and hot native mineral mud packs, and 12 had mineral water baths and rinsed mineral-free mud packs for 2 weeks	Tap water baths and mineral-free mud packs (N=10)	33	Y	Index of severity of the knee, night pain scores, physical findings and VAS pain, use of pain medication	T0-2 weeks-20 weeks

Abbreviations: Nottingham Health Profile (NHP); Arthritis Impact Measurement Scale (AIMS); EuroQoL Group 5-Dimension Self-Report Questionnaire score (EQ-5D); Stanford Health Assessment Questionnaire (HAQ); Lequesne Algofunctional Index (Lequesne); Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC); Short Form-36 (SF-36); visual analogue scale (VAS)

Table 2. WOMAC Data represent means (S.D.)

Study Womac	Pre-Treated N	Pre-Treated mean	Pre-Treated SD	Post-Treated N	Post-Treated mean	Post-Treated SD
Ozkuk 2019	30	33,2	15,2	25	26,1	16,7
Branco 2016	47	40,2	14,2	43	3,8	2,3
Fioravanti 2015	53	10,2	10,7	50	1,7	14,8
Kulish 2014	38	15,5	23,5	39	2,7	19,9
Forestier 2014	94	8,7	16	88	4,1	16
Tefner 2013	27	17,9	15,2	26	12,6	18,5
Fioravanti 2010	40	16,5	14,7	40	1,1	15,7
Forestier 2010	195	8,5	14,7	187	3	15,4
Sherman 2009	24	8,3	10,4	20	5,9	11,4
Odabasi 2008	30	42,9	12,9	30	12,1	8,4
Balint 2007	64	11,2	3,2	32	2,3	1,6
Kovács 2002	29	4,3	0,6	29	1,6	0,6
Tishler 2004	48	52,7	15,4	24	54,3	16,8

Table 3. VAS pain Data represent means (S.D.)

Study VAS pain	Treatment N	Treatment mean	Treatment SD	Control N	Control mean	Control SD
Ozkuk 2017	25	43,1	23,8	25	70,6	19,7
Branco 2016	42	27	21	42	84	8
Fioravanti 2015	53	32	18	50	52	20
Kulisch 2014	38	30,5	18	39	45	19
Forestier 2014	113	43	19	101	44	23
Tefner 2013	27	28	23	26	33	19
Espejo Antúnez 2013	61	25	23	60	52	24
Fioravanti 2012	30	2,5	16	30	45	18
Fioravanti 2010	40	20	12	40	40	15
Forestier 2010	228	41,7	19	223	38,5	20
Mahboob 2009	25	19,8	10,6	25	25,2	10,6
Sherman 2009	24	50,1	27	20	55,1	30
Odabasi 2008	32	45,3	15,2	25	61,3	6,6
Karagulle 2007	9	30	28	8	59	35
Tishler 2004	48	24	20	24	64,7	21,3
Odabasi 2002	24	39,5	9,5	25	63,7	12,7
Flusser 2002	40	53	21,6	18	63,3	24,7
Wigler 1995	11	57	10	10	62	12

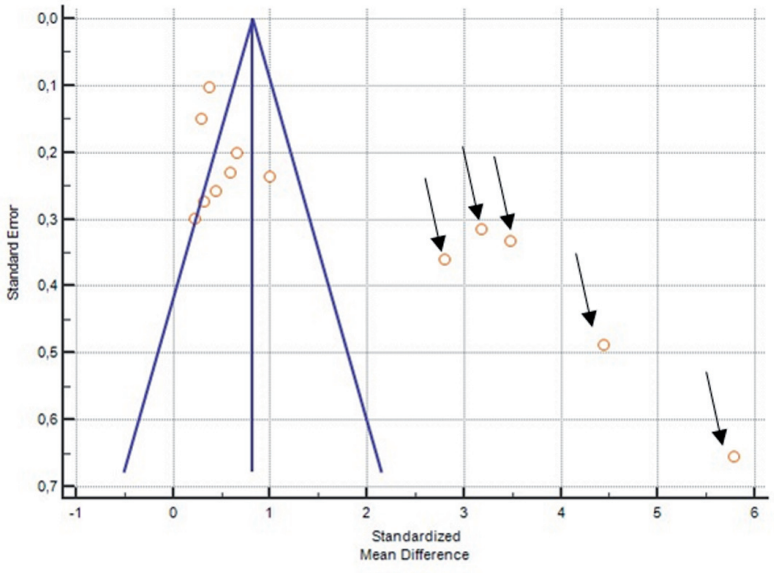

Fig. 2 Funnel plot of the WOMAC scores. Assessment of publication bias and heterogeneity

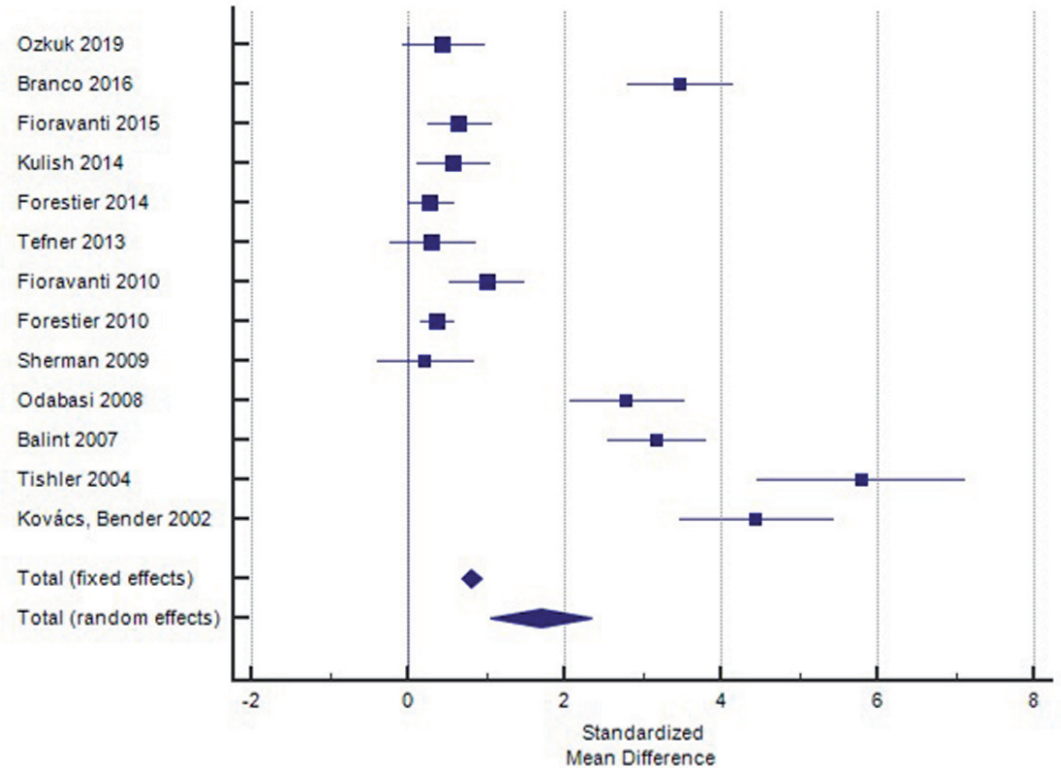

Fig. 3. Improvement of WOMAC scores at T0 and at T last follow-up in different studies

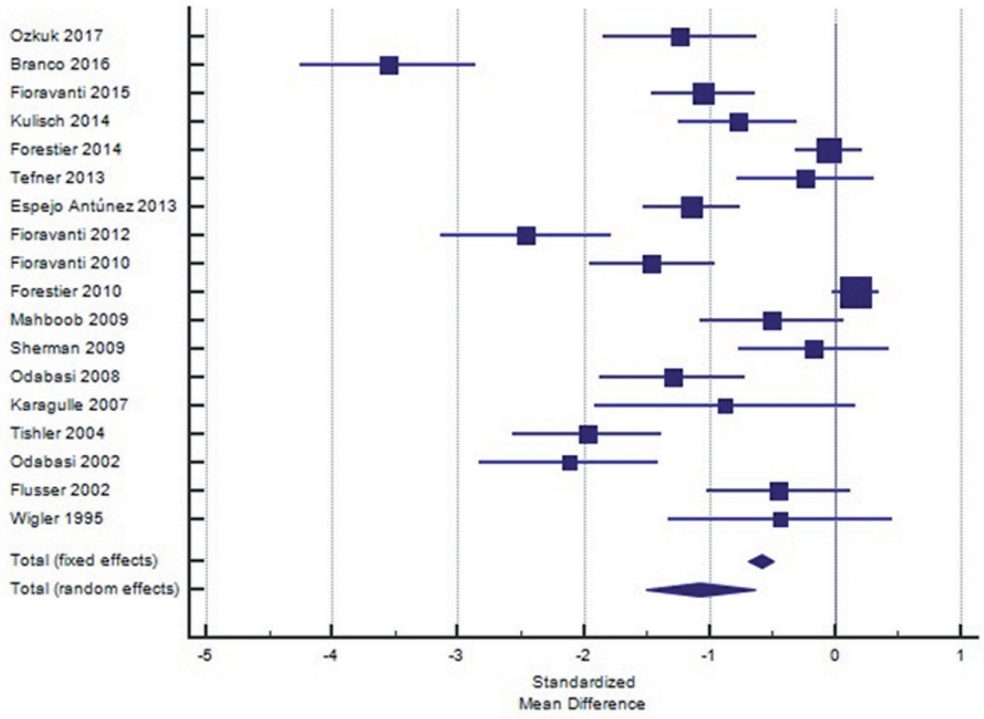

Fig. 4. Improvement of VAS pain at the last end point of the studies compared to controls

Discussion

Spa-therapy is recommended in relieving symptoms and improves joint function for individuals with musculoskeletal system disorders, especially osteoarthritis, fibromyalgia and low-back pain, aimed at improving quality of life by implementing effective prevention and treatment. Mechanisms of action of mud-bath therapy in OA are distinguished in specific (chemical and mineralogical features of the clay materials, chemistry of the waters used to mature and prepare the mud) and non-specific (hydrotherapeutic in a broad sense). The benefits are associated with mechanical, thermal, neuroendocrine, immunological (humoral and cell-mediated immunity), biological and chemical effects (51,53,78). The effects related to heat and to physical properties of all types of medical peloids (e.g. mud-packs) and mineral water used are approximately the same but chemical effects differ. The biological effects of mud-bath therapy in osteoarthritis are mainly secondary to heat stimulation, to the percutaneous absorption of chemical elements (ions and/or gases) dissolved in mineral-medicinal waters and/or are based on the physical properties of peloids (temperature, high heat capacity, heat keeping capacity, low thermal conductivity, viscosity, plasticity determinate by the clays minerals, good adhesiveness to skin, water-binding capacity) (47,78,79). The heat component plays a fundamental role together with the organic and inorganic properties of the thermal medium (80). The heat local or general corporal effects are characterized by increase in the temperature of the skin, subcutaneous tissue, muscles, stimulation of cardiac and respiratory frequency, and sweating increase. Heat of the thermal bath induces pain relief and muscle relaxation helping to increase the pain threshold in the nerve endings. Thermal stimuli and hydrostatic pressure of water on the skin also effect the pain sensation over the Melzack and Wall's gate control theory (78). The depolarization of the nervous fibers slows down the speed of nerve impulses, with a general antalgic effect. On the other hand, immersion of body parts in the thermal bath allows mobilization of joints more easily, and facilitates muscle strengthening (temperature, hydrostatic pressure, hydrodynamics, buoyancy, viscosity, and electric conductivity temperature) with positive effects on joint mobility (78,81). An increase in blood circulation is a physiological response to heat application at periarticular sites (capsules, ligaments, tendon insertions) of the thermal mud and can contribute to reduce chemical mediators of inflammation and sensitization of pain receptors (78).

In low-grade inflammation-related OA thermal mineral mud-bath exerts its effects influence chondrocyte activities modulating several cytokines, chemokines, metalloproteases, adipokines and other important factor of inflammation and chondrolysis mediators' cartilage metabolism, even with an antioxidant action. Several studies have shown a reduction in circulating levels of prostaglandin E2 (PGE2), leukotriene B4 (LTB4), tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8), transforming growth factor-beta (TGF-β), nitric oxide (NO), matrix metalloproteinase's (MMPs), particularly MMP-3 or stromelysin-1, high-sensitivity C-reactive protein (hsCRP), reduction in the release of reactive oxygen species (ROS) and Reactive Nitrogen Species (RNS), decrease in superoxide dismutase (SOD) and catalase activity (CAT), malondialdehyde (MDA), glutathione peroxidase (GSH-peroxidase), myeloperoxidase (MPO), micro-RNA, extracellular heat shock protein (eHsp72), adiponectin, resistin, modification serum levels of biomarkers cartilage turnover (increase of C-telopeptide fragment of type II collagen [sCTX-II] and decrease of cartilage oligomeric matrix protein [sCOMP]), as well as an increase production of synovial fluid, chemical mediators (anti-inflammatory growth factor [IGF-1], interleukin-10 [IL-10]) and in the circulating neutrophils' functional capacity (e.g. phagocytic and microbicidal activities) exerting a protective action on articular cartilage (82-108).

Experimental studies in animal models of arthritis induced by various pro-inflammatory agents in rats and in vitro on human OA chondrocytes cultures have demonstrated an anti-inflammatory and chondroprotective effect of mud-bath therapy (101,109-116). The general effect of mud-bath therapy in response to hyperthermia is achieved through influences on the hypothalamus-pituitary-adrenal axis and on the sympathetic nervous system (SNS), with increased circulating concentrations of adrenocorticotropic hormone (ACTH), cortisol, growth hormone (GH), prolactin, noradrenalin and greater production of endogenous opioids (β–endorphin) substances that by increasing the pain threshold have an analgesic effect and which may explain individual tolerance to thermal stress. Heat stress, caused by the elevated temperature of application, induces a cellular response, in which heat shock proteins (Hsp), particularly Hsp72, are synthesized and released. This stress response causes hormetic effects of could play a role in the effectiveness of mud-bath therapy (80). The mechanism of effectiveness by mud-bath therapy is neuroendocrine-immune stabilization that induce an anti-inflammatory response that is manifested by a decrease in the concentration of circulating pro-inflammatory cytokines (53,117-123). Moreover, patients benefit from staying in a spa resort with health-promoting environment and their perception of wellbeing (124-126).

Meta-analysis in spa-therapy is difficult because clinical trials included differed markedly from one another in terms of the methods of application and modalities used and for the lack of international accepted terms in the field (47). The studies used several different statistical tests, notably there was not a criterion of choice neither Bonferroni correction was applied thus ensuring that such results are truly meaningful is difficult. The other main limitation of the studies designs it was heterogeneity of clinical and demographic characteristics (age, sex, comorbidity) of the enrolled subjects and control groups, different protocol for mud-bath therapy (duration of treatment between 8 days and 10 weeks), the follow-up timing (the shortest duration of time to last follow-up after intervention was 11 days, and the longest time to last follow-up was 12 months), health resort medicine were located in different areas, and the chemical composition of mineral-medicinal waters and peloids varies among spa resorts. Only the study by Forestier et al. had proper control of alpha and beta risks, was performed on an intergroup comparison which showed a clinically relevant improvement on a relatively large well-defined cohort (73). The current literature provides enough robustness to data to

support the application of spa therapy in such patients. Well-established, randomized controlled clinical trials provide the highest level of evidence for efficacy. The topic of our study was for providing a better quality of evidence on the effectiveness of mud-bath therapy on the treatment knee osteoarthritis. Unlike what happens with the assessment of a drug, with spa therapy, organizing randomized controlled clinical trials is rather difficult, especially if we want to have a placebo control in a double blind study design. Indeed studies performed at health resort sites preclude the use of randomized placebo controls; the smell of the water, the perception of mud, are but a few factors that make it very hard to have a real placebo and a truly blind study.

Indeed, when considering WOMAC as the outcome measure, in all studies but five it is evident that such approach is favourable when compared to placebo. Even in those 5 studies in which statistical significance was not reached, a trend towards an improvement has been showed.

Our study followed previously well-performed meta-analyses with studies recently published that helped in strengthening the results obtained. Overall, similarly to previous studies, heterogeneity and a publication bias that might overestimate the treatment effect. Even in the most rigorous studies, bias related to the lack of blinding could not be prevented, which is particularly difficult to achieve in non-drug trials. The most challenging clue will be to have large and better performed randomized trials with very low risk of bias to finally cut off the doubts.

Nonetheless in this our meta-analysis, at the end of mud-bath therapy we observed a statistically significant improvement in VAS pain and WOMAC scores compared to no or others interventions, and we showed that a cycle of mud-bath therapy improve patients' outcome and had a beneficial effect, persisting also several months, on painful symptoms and impaired movement function in patients with knee OA.

Conclusions

Osteoarthritis is the most common musculoskeletal disease in the world. As there is no causative treatment for OA, spa-therapy is one of the methods to reduce pain and improve the patient's physical condition. The results obtained from the different studies included in meta-analysis to conclude that thermal mineral waters therapy is effective in the management of knee OA. Spa therapy regimens (e.g. mud-bath therapy) is an effective remedy in reducing pain and improving functional status compared to minimal or no interventions, in patients with knee osteoarthritis for health promotion aimed at improving general health, well being. A cycle of mud-bath therapy had this positive result by reducing inflammation and is related to heat and its chemical effect by organic substances and/or minerals that are absorbed through the skin. Spa therapy regimens (e.g. balneotherapy and/or mud therapy) are a non-drug treatment alternative, for individuals who do not tolerate pharmacologic treatments (gastrointestinal bleeding risk), non invasive, complication free, and cost effective modality for the conservative treatment of knee osteoarthritis with also positive effects on health-related quality of life (124,125). Today, this treatment is effective for secondary prevention, therapy and improvement of functioning (rehabilitation) of rheumatological diseases (osteoarthritis of various joints, fibromyalgia, ankylosing spondylitis, stabilized rheumatoid arthritis) and other musculoskeletal system disorders (chronic low back pain), to reduce or even avoid the burden and cost to individuals and society and degradation of patients' quality of life which are associated with events (46,127-141). A recent Dilekçi study showed that balneotherapy plus physical therapy was more effective than physiotherapy alone in knee osteoarthritis patients aged over 65 years (142). There are current guidelines developed by consensus from clinical experts about non-pharmacological management of knee osteoarthritis. The latest guidelines of Italian Society for Rheumatology for the diagnosis and treatment of patients with knee, hip and hand osteoarthritis recommend among the non-pharmacological and complementary therapeutic modalities also the mud-bath therapy (143). A Consensus Delphi has been applied for Spa-therapy management of musculoskeletal diseases to obtain opinion-based recommendations to be used in daily clinical practice. The study also showed that the mud-bath therapy is a good therapeutic option for patients with knee OA (144). Indications of spa therapy in rheumatologic diseases based on the clinical practice guidelines published by the French National Authority for Health (HAS) and the European League Against Rheumatism (EULAR), suggest that patients with knee osteoarthritis might gain the benefit of a persistent improvement of pain (145). Turkish League against Rheumatism states that mud-bath therapy if there is no contraindication may be recommended for the treatment of knee OA for at least two weeks of treatment. Additionally, a combination of balneotherapy with physical agents and exercises can also be performed (146). In the OARSI guidelines for the non-surgical management of knee osteoarthritis, balneotherapy was considered appropriate only in patients with multiple joint OA and co-morbidities for whom treatment options are limited (147,148). Despite this there is no general consensus on many aspects of this treatment. Unlike previous European League Against Rheumatism (EULAR) recommendations 2000 and 2003 for the non-pharmacological treatment of knee osteoarthritis in which spa-therapy was accepted as a valid option, in those published in 2013 it was not mentioned (149-151). We agree with other authors who are surprised to discover that spa-therapy was not even mentioned in the analyzed treatments, despite the historical role of the mud-bath therapy in the care of chronic degenerative rheumoarthropaties, namely osteoarthritis. There is good evidence on quality, safety and effectiveness to show that this treatment modality can decrease pain, stiffness, functional impairment, consumption of common analgesics or non-steroidal anti-inflammatory drugs (NSAIDs) to be considered associated with high rate gastrointestinal side effects, and improving functional disability and quality of life in patients with knee joint OA (152). It cannot substitute for conventional therapy but can be integrated or alternated to it and might support in the treatment and in to reduce the burden and the progression of this highly prevalent and debilitating condition aimed at improving general health, well being with cost-effectiveness in the health care system versus usual care.

Conflicts of Interest

The authors declare no conflict of interest

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