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Research article

Multidisciplinary non-pharmacological treatments with effects on pain modulation and functioning in spondyloarthropathies – a systematic review

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Abstract: Treatment for chronic rheumatic diseases, included various modalities for pain management and for functioning modulation, has the main gole to increase the quality of life and to improve also the activities of daily living. Seronegative spondyloarthropathies (SpA) are a group of rheumatologic disorders that include ankylosing spondylitis, psoriatic arthritis, entheropatic SpA, reactive arthritis and undifferentiated SpA. Treatment methods include clasically pharmacological modalities. Physical therapy should also be highlighted as being part of the treatment. Balneotherapy and spa therapy are increasingly taken into account in evidence-based treatment guidelines for multiple rheumatic diseases, for specific effects on functional parameters and also for the involvement in cartilage regeneration. Balneotherapy is universally defined as the treatment method which uses bathing in thermal and mineral waters. Other balneological treatments include peloidotherapy, balneological gases and therapeutic waters in various forms of bathing, inhalation or drinking. Spa therapy comprises complementary and alternative treatment modalities including balneotherapy, hydrotherapy, exercises, and massage therapy. This systematic literature review aims to highlight the effects of balneotherapy in spondylarthropathies. The review is based on the internationally accepted method, the "PRISMA" methodology- "Preferred Reporting Items for Systematic Reviews and Meta-Analysis".

Keywords: balneotherapy; spondylarthropathies; regeneration; articular cartilage.

1. Introduction

Seronegative spondyloarthropathies (SpA) are a group of rheumatologic disorders that include ankylosing spondylitis, psoriatic arthritis, and the less common subgroups: arthritis associated with inflammatory bowel disease (Crohn's disease or ulcerative colitis) or entheropatic SpA, reactive arthritis and undifferentiated SpA. Furthermore, they have recently been classified into three other categories, namely: non - radiographic axial SpA, peripheral SpA, and juvenile-onset SpA [1, 2].

The precise etiology and pathogenesis of SpA remain unknown up to this time. From a genetic point of view, SpA is connected with a highly polymorphic molecule, the human leukocyte antigen B27 (HLA B-27) , the major histocompatibility complex class I antigen. Although considerable research has been done in this regard, the exact role of HLA-B27 in SpA pathogenesis is still unknown [3].

Pharmacological treatment modalities include NonSteroidal Anti-Inflammatory Drugs (NSAIDs), tumour necrosis factor alpha (TNF) inhibitors, interleukin 17 (IL-17) inhibitors and Janus Kinase (JAK) inhibitors [4, 5]. Physical therapy should also be highlighted as being part of the treatment [6]. Important evidence from the literature supports its use in the treatment course, as an integral part of standard care of the patient [7 - 15]. Balneotherapy and spa therapy are increasingly taken into account in evidence-based treatment guidelines for multiple rheumatic diseases, and are investigated in dermatology and other indications [16].

Balneotherapy is universally defined as the treatment method which uses bathing in thermal and mineral waters. Other balneological treatments include peloidotherapy or mud therapy, balneological gases and healing waters in various forms of bathing, inhalation or drinking [17, 18]. Spa therapy comprises complementary and alternative treatment modalities including balneotherapy, hydrotherapy, exercise, and massage [19].

Balneotherapy triggers neuroendocrine and immunological responses, generating anti-inflammatory, analgesic, anabolic, antioxidant, chondroprotective effects and neuroendocrine-immune regulation [20]. The mechanisms by which balneotherapy exerts its beneficial effects in rheumatological diseases are not yet fully discovered, but the combination of mechanical, thermal and chemical factors are of significant importance. The decrease in pain perception may be due to the pressure and temperature of the water, according to the gate theory. A muscle spasm reduction and an incresed pain threshold can be explained by the effects of hot stimuli [21]. Mud-bath therapy has multiple positive effects, increasing circulating concentrations of b-endorphin levels, adenocorticotropic hormone (ACTH), cortisol, prolactin, growth hormone and noradrenaline. The mud-pack therapy method reduces levels of TNF-a, prostaglandin E2, leukotriene B4 and interleukin-1b. Also, mud-packs and thermal baths have the ability to reduce the release of reactive oxygen and nitrogen species. Spa therapy can also stimulate cartilage metabolism through increasing insulin-like growth factor-1 (IGF) [21, 22].

2. Materials and Methods

This systematic literature review was designed using the "PRISMA" methodology- "Preferred Reporting Items for Systematic Reviews and Meta-Analysis"- the method accepted at international level. The protocol for this review was registered in PROSPERO (International Prospective Register of Systematic Reviews). Protocol registration: CRD42023431772.

For the selection of eligible articles for our research we scoped the following databases: Cochrane, Elsevier, Physiotherapy Evidence Database- PEDro, Center for Biotechnology Information (NCBI) - PubMed and Springer. The following keywords were used initially to search the databases: balneotherapy- spondyloarthropathies, balneotherapy - spondyloarthritis, balneotherapy - ankylosing spondylitis, balneotherapy - psoriasic arthritis, balneotherapy - reactive arthritis, balneotherapy - enteropathic arthritis, balneo-

therapy - enteropathic spondyloarthritis, balneotherapy - undifferentiated spondyloarthritis, mud therapy - spondyloarthropathies, mud therapy- spondyloarthritis, mud therapy - ankylosing spondylitis, mud therapy - psoriasic arthritis, mud therapy - reactive arthritis, mud therapy - enteropathic arthritis, mud therapy - enteropathic spondyloarthritis, mud therapy - undifferentiated spondyloarthritis, hydrotherapy - spondyloarthropathies, hydrotherapy - spondyloarthritis, hydrotherapy - ankylosing spondylitis, hydrotherapy - psoriasic arthritis, hydrotherapy - reactive arthritis, hydrotherapy - enteropathic spondyloarthritis, hydrotherapy - enteropathic arthritis, hydrotherapy - undifferentiated spondyloarthritis. Additional keywords added were: human, aquatic therapy, peloid therapy (Table 1).

Table 1. The keyword combinations used for scoping the international databases

	COCHRANE	ELSEVIER	PEDro	PUBMED	SPRINGER
Balneotherapy + spondyloarthropathies	0	0	0	141	23
balneotherapy + spondyloarthritis	0	18	0	151	43
balneotherapy + ankylosing spondylitis	1	81	7	138	82
balneotherapy + psoriasic arthritis	0	4	0	42	4
balneotherapy + reactive arthritis	0	91	1	24	143
balneotherapy + enteropathic arthritis	0	5	0	2	13
balneotherapy + enteropathic spondyloarthritis	0	5	0	1	5
balneotherapy + undifferentiated spondyloarthritis	0	3	1	0	18
mud therapy + spondyloarthropathies	0	29	0	24	44
mud therapy + spondyloarthritis	0	10	0	25	36
mud therapy + ankylosing spondylitis	0	89	3	19	176
mud therapy + psoriasic arthritis	0	3	0	13	4
mud therapy + reactive arthritis	0	397	1	6	655
mud therapy +enteropathic arthritis	0	6	0	1	13
mud therapy + enteropathic spondyloarthritis	0	3	0	1	7
Mud therapy + undifferentiated spondyloarthritis	0	3	0	0	21
hydrotherapy + spondyloarthropathies	0	91	0	28	64
hydrotherapy spondyloarthritis	0	48	0	34	57
Hydrotherapy ankylosing spondylitis	1	278	4	34	221
hydrotherapy psoriasic arthritis	0	1	0	7	3
hydrotherapy reactive arthritis	0	378	0	21	289
hydrotherapy enteropathic spondyloarthritis	0	14	0	0	6
hydrotherapy enteropathic arthritis	0	31	0	0	8
hydrotherapy + undifferentiated spondyloarthritis	0	8	1	0	25

TOTAL	**4259**	**2**	**1567**	**18**	**712**	**1960**

Articles have been sorted by title and abstract using the following criteria for inclusion: population - patients suffering from either ankylosing spondylitis, psoriasic arthritis, reactive arthritis, enteropathic arthritis or undifferentiated spondyloarthritis- and intervention- balneotherapy or spa therapy.

Exclusion criteria were articles written in a language other than English, books and book chapters, conference abstracts. Initially we did not have a date criteria, but later we sorted the articles from 2010 to 2022. Articles regarding exercise programs and physical therapy were removed because the aim of this review is to investigate the effects of balneotherapy on spondylarthropathies.

Methodological quality of the included studies was evaluated by two independent authors using the PEDro scale, which represents a validated tool for assessing clinical trials quality. Two articles showed fair quality, and the other ones showed high quality. Any disagreement was resolved by consulting a third reviewer if consensus could not be reached by the first two reviewers (Table 2).

Table 2. Representation of the gradings

Article	**Grading** (first reviewer)	**Grading** (second reviewer)	**Mean grading** (average of both grades)
Aydemir et al.	5	5	5
Ciprian et al.	7	8	7.5
Franke et al	11	11	11
Dundar et al	7	8	7.5
Cozzi et al.	7	8	7.5
Garcia et al.	5	8	6.5
Karagülle et al.	6	6	6
Bestaș et al.	10	10	10
Van der Zee et al.	5	5	5

The question on which this review was based, using the PICO (patient/problem, intervention, comparison and outcome) strategy is: what effects does balneotherapy have on patients suffering from spondyloarthropathies compared to other treatment methods or no intervention on pain, disease activity, functional capacity, flexibility, quality of life or other parameters?

3. Results

The general search revealed 4259 articles: 2 in Cochrane, 1567 in Elsevier, 18 in PEDro, 712 in PubMed and 1960 in Springer. After duplicate removal, 3960 papers remained. A total of 3876 studies were excluded after screening the titles and the abstracts. From the remaining 84 papers, a selection was made and only those published between 2010 - 2022 were chosen, resulting in 47 articles. Of these, 26 articles on physical therapy or exercise programmes were excluded, and, in addition, 12 reviews, which will be addressed at a later stage, leaving for analysis only those articles referring to balneotherapy or spa therapy, in total 9 research articles. (Figure 1).

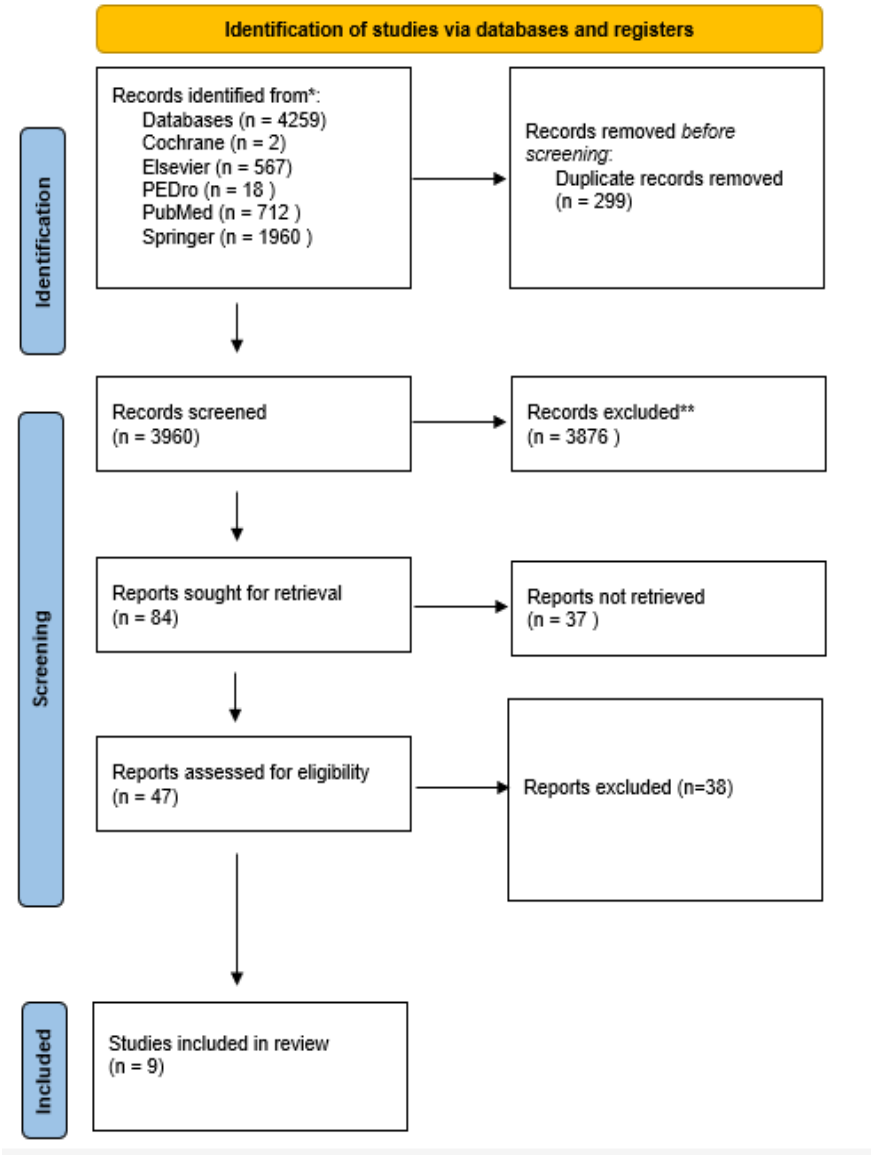

Figure 1. Our adapted PRISMA flow diagram

The resulting research articles (9) were listed in the table below, including authors, the countries in which they were conducted, the year they were published, the study design, the number of patients included in the study, the type of intervention and references (Table 3).

Table 3. The centralised researche articles resulted from our search

Authors	Country	Year	Pathology	Study design	Patients	Treatment	References
Aydemir et al.	Turkey	2010	Ankylosing spondylitis	Not specified	28	Therapeutic pool with underwater exercises	32
Ciprian et. al	Italy	2013	Ankylosing spondylitis	Randomized controlled study	30	Thermal water and mud packs	25
Franke et al.	Germany	2013	Rheumatic diseases, including ankylosing spondylitis	Randomised, blinded, controlled trial	681- 39 AS patients	Radon baths; tap water baths	42
Dundar et al.	Turkey	2014	Ankylosing spondylitis	Randomized controlled trial	69	Aquatic exercises; home-based exercises	27
Cozzi et al.	Italy	2015	Psoriasic arthritis	Randomized, open-labelled study	36	Mud-bath treatment	34
Garcia et. al	Spain	2015	Ankylosing spondylitis	Randomized, single blind study	30	Aquatic fitness and relaxation progran	28
Karagülle et al.	Turkey	2017	Musculoskeletal diseaseas, AS patients	Retrospective observational study	819- 22 AS patients	Spa therapy, including balneotherapy	79
Bestaș et al.	Turkey	2021	Ankylosing spondylitis	Prospective, randomized study	60	Spa pool, in-pool exercises, physical therapy	44
Van der Zee et al.	Austria	2022	Ankylosing spondylitis	A longitudinal analysis of prospectively collected registry data	469	Low-dose radon balneo and speleotherapy	36

In 2010, Aydemir et al. conducted a study on 28 AS patients who underwent balneotherapy 30 min a day, 5 days per week, for 3 weeks. The patients also followed treatment with sulfasalazine and indomethacin for at least 6 months prior the intervention. Balneotherapy treatment has included spa treatment (therapeutic pool), plus underwater exercises, followed by 20 minutes ventilation and 20 minutes of posture exercises. The patients were evaluated before treatment and after one month. After intervention, global index

scores and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) decreased, although not significantly. Tragus-wall distance and intermalleolar distance decreased. Schober's test, chest expansion, cervical rotation and spinal lateral flexion increased, but not significantly excepting Bath Ankylosing Spondylitis Metrology Index (BASMI). Pulmonary function testing showed no major difference before and after balneotherapy [23].

Ciprian et al. published in 2011 a randomised controlled trial (RCT) carried on 30 ankylosing spondylitis (AS) patients, where 15 patients underwent 10 sessions of spa therapy- mud packs, thermal baths and rehabilitation (exercises in a thermal pool) and 15 were the control group. The patients also received anti-TNF agents for at least three months before intervention. They were evaluated at the beginning, end, at 3 and 6 months. The treatment took place in a spa center in Montegrotto Terme near Padova, Italy for a duration of 2 weeks. The spa and balneotherapy group had an improvement in Bath Ankylosing Spondylitis Functional Index (BASFI) and Health Assessment Questionnaire HAQ [24].

Another RCT was published in 2013 by Franke et al. investigating radon spa therapy compared to control interventions in rheumatic out-patients. The study included 681 patients (39 AS patients) who were treated in 7 health resorts in Austria and Germany. The treatment has consisting in 12 radon baths with a duration of 20 minutes for 2-3 days within 3-4 weeks and 10 radon speleotherapy for 3 weeks. After treatment, the radon therapy group had more significant pain relief, but with a slight decline in the 3 to 9 months follow-up. The patients with inflammatory rheumatism and multiple rheumatic indications had more pain than the other groups and almost returned to baseline values after 9 months. The study concluded that radon spa therapy has better effects than radon free therapy in terms of pain relief [25].

In 2014, Dundar at al. conducted a RCT regarding the effects of aquatic therapy versus land-based exercises on 69 AS patients. The aquatic group consisted in 25 patients who underwent 20 treatment sessions, 5 times a week for 4 weeks in total in a swimming pool. The control group included 34 patients who received a home based exercise program for 4 weeks. The follow up at 4 and 12 weeks post intervention showed improvements for all parameters for both groups. The aquatic group had better outcomes in parameters of the Short Form – 36 (SF-36) scale [26].

Another study by Cozzi et al. from 2015, researched the effects of mud-bath therapy on patients suffering from psoriasic arthritis. The randomised, open-labelled, controlled clinical study included 36 psoriasic arthritis patients, also treated with TNF inhibitors. Half of them were treated with mud-bath therapy alongside medication and the other half maintained treatment with TNF inhibitors alone. The intervention consisted in mud-baths therapy, 12 mudpacks and 12 thermal baths on a 2 week period, in a spa resort near Padova, Italy. 45 days after treatment, the first group showed a significant improvement in Psoriasis Area Severity Index (PASI), HAQ, disease activity score (DAS) 28, swollen joint and tender joint count. Also, contrast enhanced ultrasound (CEUS) demonstrated significant appearance delay and faster washout of contrast dye in the same group [27].

Garcia et al. conducted a randomized single blind study on 30 AS patients (16 men and 14 women) for 2 months. They were randomized equally in 2 groups of 15 participants. The intervention consisted in a relaxation technique, breathing technique, active joint exercises, training 3 times per week. The aquatic sessions in a heated pool were effectuated 3 times per week, with a 30 minutes duration, for 8 weeks. The experimental group undewent a relaxation program and aquatic fitness. The control group did not participate in supervised exercises program. At the end of the treatment, the aquatic group had post-intervention improvement in quality of life, BASDAI, BASFI, morning stiffness versus the control group [28].

Karagulle et al. led a retrospective study on 819 patients to demonstrate the positive effects of spa therapy on musculoskeletal diseases. Of these, 22 were diagnosed with AS. The study found statistically relevant improvements in parameters in the whole sample, regarding pain, function, patient's general evaluation. The study also concluded that spa therapy is used less for AS [29].

Bestaș et al. performed a single-center, prospective, randomized study on 60 patients, who were randomized equally in 3 groups. First group underwent balneotherapy (20 minutes, whole body bath in spa pools), second, water based exercises (WBE) therapy (60 minutes in-pool exercise) and third, land based exercises (LBE) therapy (60 minutes exercises). The treatment consisted in sessions for 5 days a week in groups of 5-6 patients, for a total duration of 4 weeks. Follow up was effectuated at 4 and 12 weeks post-intervention. The results showed that all three groups had improvements in all variables, with no significant difference between them. The WBE group had a better result in chest expansion 4 and 12 weeks after treatment. LBE group showed better outcomes in Fatigue Severity Scale (FSS), sleep duration and Ankylosing Spondylitis Disease Activity Score with C- Reactive Protein (ASDAS-CRP) [30].

The most recent study was conducted by van der Zee-Neuen et al. who performed an analysis of collected data from "Radon indication registry for the assessment of pain reduction, increase of quality of life and improvement in body functionality throughout low-dose radon hyper-thermia therapy". The effects of spa therapy, including low dose radon therapy were studied on 291 AS patients using quality of life (Qol) forms. The questionnaire was completed at baseline, after the treatment and 3, 6, and 9 months post-intervention. The treatment included 10 low-dose radon baths for 20 minutes and speleotherapy (a process of relaxation while being exposed to a low-dose radon, high umidity and mild hyperthermia in a former gold mine) for 60 minutes on alternate days, with a total of 11 sessions. Regarding the EuroQol - 5 Dimension (EQ - 5D) utility index, the values indicated improvements at all timepoints. Nine months after treatment, values were still increased, but non clinically relevant. Regarding euroQol Visual Analogue Scale (VAS), for all points in time evaluated, values have been significantly increased [31].

In our search we found a number of 12 reviews [32 - 43] describing the effects of balneotherapy on spondylarthropathies, and further on we have centralized the results of these reviews on each pathology belonging to the spectrum of spondylarthropathies we could find: ankylosing spondylitis (Table 4), psoriasic arthritis (Table 5), reactive arthritis and enteropathic arthritis. It should be mentioned that in these tables we have not included the studies mentioned and detailed above.

Table 4. The articles regarding ankylosing spondylitis included in the reviews mentioned above

Ankylosing spondylitis	
Helliwell et al. (1996)	A small randomized, controlled study revealed that the group assigned to 6 weeks hydrotherapy plus home exercises had better results on VAS, stiffness and neck mobility versus the group assigned to 6 weeks of home exercises. After 6 months, no significant differences remained [44].
van Tubergen et al. (2001)	Van Tubergen et al. conducted a randomized trial which compared 3 options of treatment: spa therapy in Arcen- The Netherlands, spa therapy in Bad Hofgastein-Austria and home exercises (the control group). Both spa groups had significant better results in terms of BASFI, patient's global assesment, pain, morning stiffness, quality of life, results that remained significant for both groups until week 16, and until week 40 for the Austrian spa group [45].
Barnatskii et al. (2005)	An uncontrolled small trial reported benefits of peloid therapy and bathing in radon water [46].

Codish et al. (2005)	Codish et al. conducted a randomized prospective researcher-blinded trial on 28 AS patients, where 14 underwent treatment with mud packs and sulfur pools and 14 used the fresh water pools. The results were positive, showing an improvement in disease activity and VAS for pain and spinal movement. In the mud pack and sulfur pools group, there was a reduction in pain, improving the quality of life [47].
Yurtkuran et al. (2005)	A study in a spa resort demonstrated the beneficial effects of balneotherapy on pain, spine mobility, functional index, morning stiffness and patient's evaluation, effects that were present 6 months later [48].
Altan et al. (2006)	A study compared 28 AS patients, who received 30 minutes sessions over 3 weeks plus a daily 30 minutes home exercise program with 26 AS patients, who followed a home exercise program alone. After 3 weeks of treatment, the balneotherapy group had better results in disease activity and quality of life. After 6 months, only modified Schober's test and patient global evaluation had better results. No significant group differences were observed in terms of pain, stiffness, physical function and spinal mobility [49].
Lubrano et al. (2007)	Lubrano et al. postulated that in-patient rehabilitation showed a strong positive effect on pain and BASFI [50].
Dagfinrud et al. (2008)	Dagfinrud et al. compared AS patients who effectuated aquatic exercises in spa resorts and home based exercises with only home based exercises, with the conclusion that there is a beneficial effect in the aquatic group in terms of pain and global perceived effect after 4 and 16 weeks, but no differences were shown after 28 and 40 weeks. There was no differences on function [8].
Falagas et al. (2009)	In a systematic review, regarding the effects of balneotherapy on ankylosing spondylitis, fibromyalgia, osteoarthritis, chronic low back pain and rheumatoid arthrtitis, was concluded that balneotherapy may have a positive effect on multiple rheumatological conditions, but the existing evidence is not enough to draw a conclusion [51].
Karapolat et al. (2009)	Karapolat et al. studied the effects of hydrokinesiotherapy, walking and conventional exercise (groups 1, 2 and 3), and discovered statistically significant improvements in the first 2 groups in the 6-minute walk test and maximal oxygen uptake. There were observed improvements in both groups regarding respiratory function, mobility and pain [52].
Kuĉuķdeveci et al. (2013)	Kuĉuķdeveci et al. analyzed 27 RCTs, 6 involving rheumatoid arthritis, 2 AS and 19 including both and showed weak to moderate evidence of balneotherapy on functional limitation and pain [53].

Table 5. The articles regarding psoriasic arthritis included in the reviews mentioned above

Psoriasic arthritis	
Sukenik et al. (1994, 2001)	Sukenik et al. conducted a study on 166 psoriasic arthritis patients treatet with balneotherapy and phototherapy at the Dead Sea. 146 of them also received mud packs and sulfur baths treatment. After 3 weeks, although both groups showed significant improvement, in the mud packs and sulfur baths groups additional benefits were observed in terms of spine pain reduction and range of mevement of the lumbar spine [54].
	In another study, Sukenik et al. led an noncontrolled prospective trial on 28 patients psoriasic patients who also suffered from fibromyalgia. The treatment consisted in mudpacks, sulfur baths, balneotherapy and phototherapy at the Dead Sea for 3,5 weeks, with beneficial results in morning stiffness, tender points and number of inflamed joints [55].
Elkayam et al. (2000)	Elkayam et al. treated 42 psoriasic arthritis patients with balneotherapy and phototherapy at the Dead Sea. Of these, 23 were also treated with mud packs and sulfur baths. Both groups had improvements in morning stiffness, right and left grip, patient self-assesement and axial skeleton movements. Benefits over time were observed in the mud packs and sulfur baths [56].

Regarding reactive arthritis, Barnatskii et al. (2006,2007), in 2 different studies, one mentioned above, also including AS patients [46], demonstrated that thermal baths and mud packs at a low temperature had a positive result, leading to an improved functional condition and quality of life [46, [57].

As for, enteropathic arthritis, Cozzi et al. (2007) included in this study 24 patients with enteropathic spondylitis, 13 suffering from ulcerative colitis and 11, from Crohn's disease. 17 patients also underwent drug treatment with sulfasalazine and 5-ASA (aminosalicylic acids) for at least 3 months before the study. Half of the patients underwent mud baths treatment and half were the control group. The mud bath group had significant improvements in spondylitis at the end of the treatment, at 12 and 24 weeks post intervention [58].

4. Discussion

There are multiple non-pharmacological methods of treatment in spondyloarthritis, with more published studies on physiotherapy than balneotherapy. Most of them are small observational studies, concluding that larger studies and more controlled are needed further on. There is not a general consensus for the optimum exercise therapy. The systematic review regarding the combined use of TNFa inhibitors and rehabilitation treatment for AS patients seems to have a synergistic effect [59].

A study from 2016 regarding physical therapy shows that this type of treatment is underprescribed. Even if the beneficial effects of exercise are well-known, there is a need for standardized protocols [60].

The use of balneotherapy in treating various rheumatic diseases has a long-term tradition, and is based on settled scientific principles [61]. This type of treatment is probably as old as mankind and was used for centuries in Europe. In the present days, it is widely used in Central and Eastern Europe [62]. Thermal waters used for bathing have an important and impressive history. In the present days, spa therapy is having a recovery, by

receiving revived attention from health tourists and numerous medical specialties. Nonetheless, the exact therapeutic mechanisms of spa therapy is still broadly unknown [63]

Spa therapy seems to have an important role in treating a broad range of musculoskeletal diseases. Although it can not substitute the conventional therapy, it can definitely complement it. A study reported that the beneficial improvements can last for months post treatment [64].

The American College of Rheumatology positioned balneotherapy, in a statement released in 2000, as an essential complementary therapy in treating rheumatic diseases [65]. In various rheumatic diseases, balneotherapy causes a reduction in serum concentrations of TNF-α, interleukin-1β (IL-1β) and IL-6, IL-8, tumor grouth factor-β (TGF-β), having an anti-inflammatory effect and an increase in IGF-1. Mud therapy can also decrease adiponectin and resistin, adipokines found in osteoarthritis patients. All mentioned cytokines and adipokines are inflammation mediators and cartilage metabolism mediators. Their modulation induced by balneotherapy has anti-inflammatory-mediated chondroprotective beneficial effects. Matrix metalloproteinases (MMP) are also involved in the degradation of cartilage. MMP-3 or stromelysin-1, which are produced by chondrocytes and other different cell types in development of cartilage distruction, decreases in osteoarthritis patients after mud therapy. Cartilage oligomeric matrix protein (COMP) concentration, which represents a cartilage turnover indicator, also decreases after balneotherapy, concluding that balneotherapy has chondroprotective effects and it can stimulate cartilage metabolism through increasing insulin-like growth factor-1 [21, 22].

A study regarding H_2S, the main active molecule of sulfurous mineral waters on in vitro studies on animal and human samples, concluded that it showed chondroprotective, antioxidant, anti-inflammatory, and immunosuppressive effects, despite the various differences in cell cultures, experimental procedures and treatment modalities. H_2S seems to have a positive effect, counteracting the inflammation in fibroblast-like synoviocytes and chondrocytes affected by arthritis. Osteoarthritis cartilage might benefit from H2S due to the antioxidant and chondroprotective effects [66].

Another study demonstrated that mud baths might have beneficial effects on and inflammatory reactions and cartilage homeostasis, by significantly decreasing nitric oxid (NO) and myeloperoxidase values [67].

A study on osteoarthritis in vivo murine models demonstrated that balneotherapy in sulfur-rich water has the ability to reduce oxidative damage and cartilage destruction [68].

The present information in the literature shows that spa therapy in combination with physical therapy generates clinical improvements in AS patients. However, no definitive conclusions are available, given the small and imperfect design studies. Though, the evidence suggests that spa therapy should be considered as an alternative therapeutic option, especially in patients who fail conventional therapy [69]. A systematic review postulated that potentially helpful modalities such as land based and water based exercises should be prescribed in AS patients, since they are safe, beneficial and cost-effective [70].

A RCT was published in 2002 aiming to evaluate the cost effectiveness and cost utility of spa therapy combined with exercise therapy over a course of 3 weeks on 120 AS patients. The patients were randomly allocated to 3 separate groups: one in a spa resort (in Bad Hofgastein), one in another spa resort (in Arcen, The Netherlands), and the control group performed their usual activities and treatment at home. The study period was 40 weeks. Of 120 patients, 111 completed weekly a diary comprising absence from work and resource utilization. According this study, spa- exercise treatment has demonstrated cost-utility and cost-effectiveness ratios when compared to standard treatment alone. The 2 intervention groups demonstrated cost savings when compared to the control group regarding visits to health care professionals, medication and physiotherapy [71].

In our review, we found that the numerous effects of balneotherapy have been studied more in Turkey, a country with a vivid balneotherapy and spa therapy tradition, used in most cases in rheumatic diseases [72]. Also, several studies have been carried out in Italy, another country with a well known balneotherapy tradition. The Roman society was using therapeutic waters for medicinal purposes, in the popular Roman thermal baths

[73]. We found in our research that here are more studies regarding balneotherapy in ankylosing spondylitis than in psoriasic arthritis. For reactive arthritis there were only 2 studies mentioned, and for enteropathic arthritis, we only found one study. As for balneotherapy interventions in undifferentiated spondyloarthritis, we could not find any study regarding this matter.

5. Conclusions

From the studies included in this review, we can conclude that balneotherapy interventions could be beneficial and can be recommended especially for ankylosing spondylitis patients, because it showed improvements in the quality of life, overall well-being of the patients, pain perception and other parameters. The current level of evidence from the literature is not plentiful enough to draw reliable conclusion in other spondyloarthropathies, such as psoriatic arthritis, reactive arhritis and enteropathic arthritis.

More studies are needed on the effects of balneotherapy on patients with spondyloarthropathies, in larger groups of patients, with longer follow-up periods and better validity. Effects of different types of therapeutic waters and various types of mud should be studied to form a broader perspective.

The patients suffering from spondyloarthropathies, aside from drug treatments, could benefit from this non-pharmacological type of treatment, that has the ability to improve their quality of life and disease activity.

Therefore, balneotherapy and spa therapy interventions should represent an important purpose in further studies because this type of treatment has an important role in rheumatological conditions, such as spondyloarthropathies.

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References

1. Sen R, Goyal A, Hurley JA. Seronegative Spondyloarthropathy. 2022 Jul 18. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. PMID: 29083692.
2. Terenzi R, Monti S, Tesei G, Carli L. One year in review 2017: spondyloarthritis. Clin Exp Rheumatol. 2018 Jan-Feb;36(1):1-14. Epub 2018 Feb 5. PMID: 29461959.
3. Sharip A, Kunz J. Understanding the Pathogenesis of Spondyloarthritis. Biomolecules. 2020 Oct 20;10(10):1461. doi: 10.3390/biom10101461. PMID:33092023; PMCID: PMC7588965.
4. Danve A, Deodhar A. Treatment of axial spondyloarthritis: an update. Nat Rev Rheumatol. 2022 Apr;18(4):205-216. doi: 10.1038/s41584-022-00761-z. Epub2022 Mar 10. PMID: 35273385.
5. Ritchlin C, Adamopoulos IE. Axial spondyloarthritis: new advances in diagnosis and management. BMJ. 2021 Jan 4;372:m4447. doi: 10.1136/bmj.m4447. PMID: 33397652.
6. Ku CH, Lee YH, Wei JC, Braun J. Current aspects for the treatment of axial spondyloarthritis. Int J Rheum Dis. 2023 Jan;26(1):5-7. doi: 10.1111/1756-185X.14473. PMID: 36591903.

7. Nikiphorou E, Santos EJF, Marques A, Böhm P, Bijlsma JW, Daien CI, Esbensen BA, Ferreira RJO, Fragoulis GE, Holmes P, McBain H, Metsios GS, Moe RH, Stamm TA, de Thurah A, Zabalan C, Carmona L, Bosworth A. 2021 EULAR recommendations for the implementation of self-management strategies in patients with inflammatory arthritis. Ann Rheum Dis. 2021 Oct;80(10):1278-1285. doi: 10.1136/annrheumdis-2021-220249. Epub 2021 May 7. PMID: 33962964; PMCID: PMC8458093.
8. Dagfinrud H, Kvien TK, Hagen KB. Physiotherapy interventions for ankylosing spondylitis. Cochrane Database Syst Rev2008;1:Cd002822. [PMC free article] [PubMed] [Google Scholar]
9. Philipp Klemm, Paulina Preusler, Ole Hudowenz, Thomas Asendorf, Ulf Müller-Ladner, Elena Neumann, Uwe Lange, Ingo H. Tarner, Multimodal rheumatologic complex treatment in patients with spondyloarthritis - a prospective study, European Journal of Internal Medicine, Volume 93, 2021, Pages 42-49, ISSN 0953-6205, https://doi.org/10.1016/j.ejim.2021.07.005.
10. Lim HJ, Moon YI, Lee MS. Effects of home-based daily exercise therapy on joint mobility, daily activity, pain, and depression in patients with ankylosing spondylitis. Rheumatol Int 2005;25:225e9.
11. Durmus D, Alayli G, Cil E, et al. Effects of a home-based exercise program on quality of life, fatigue, and depression in patients withankylosing spondylitis. Rheumatol Int 2009;29:673e7.
12. Masiero S, Bonaldo L, Pigatto M, et al. Rehabilitation treatment in patients with ankylosing spondylitis stabilized with tumor necrosis factorinhibitor therapy: a randomized controlled trial. J Rheumatol 2011;38:1335e42.
13. RodríguezLozanoC,JuanolaX,CruzMartínezJ,etal.Outcomeofaneducationandhomebasedexerciseprogrammefor patients with ankylosingspondylitis: a nationwiderandomized study. Clin Exp Rheumatol 2013;31:739e48.
14. Alonso-Blanco C, Fernandez-de-las-Penas C, Cleland JA. Preliminary clinical prediction rule for identifying patients with ankylosingspondylitis who are likely to respond to an exercise program: a pilot study. Am J Phys Med Rehabil 2009;88:445e54.
15. Karapolat H, Akkoc Y, Sari I, et al. Comparison of group-based exercise versus home-based exercise in patients with ankylosing spondylitis: effects on bath ankylosing spondylitis indices, quality of life and depression. Clin Rheumatol 2008;27:695e700.
16. Matsumoto S. Evaluation of the Role of Balneotherapy in Rehabilitation Medicine. J Nippon Med Sch. 2018;85(4):196-203. doi: 10.1272/jnms.JNMS.2018_85-30. PMID: 30259887.
17. Z.Karagülle,Hydrotherapy,spa,balneotherapy,thalassotherapy,TurkiyeKlinikleri J. Med. Sci. 28 (2008) 224–229.
18. Karagülle MZ, Karagülle M. It is not just balneotherapy; it is spa therapy consisting of balneological treatments including balneotherapy as well. Int J Biometeorol. 2021 Jul;65(7):1273-1274. doi: 10.1007/s00484-021-02098-w. Epub 2021 Feb 22. PMID: 33619663.
19. Baysal E, Leblebicioğlu H, Khorshid L, Sarı D. Why individuals choose balneotherapy and benefit from this kind of treatment. Complement Ther Clin Pract. 2018 Aug;32:157-162. doi: 10.1016/j.ctcp.2018.06.010. Epub 2018 Jun21. PMID: 30057044.
20. Gálvez I, Torres-Piles S, Ortega-Rincón E. Balneotherapy, Immune System, and Stress Response: A Hormetic Strategy? Int J Mol Sci. 2018 Jun 6;19(6):1687.doi: 10.3390/ijms19061687. PMID: 29882782; PMCID: PMC6032246.
21. Fioravanti A, Cantarini L, Guidelli GM, Galeazzi M. Mechanisms of action of spa therapies in rheumatic diseases: what scientific evidence is there? Rheumatol Int. 2011 Jan;31(1):1-8. doi: 10.1007/s00296-010-1628-6. Epub 2010 Dec 1.PMID: 21120502.
22. Gálvez I, Torres-Piles S, Ortega-Rincón E. Balneotherapy, Immune System, and Stress Response: A Hormetic Strategy? Int J Mol Sci. 2018 Jun 6;19(6):1687.doi: 10.3390/ijms19061687. PMID: 29882782; PMCID: PMC6032246.
23. Aydemir K, Tok F, Peker F, Safaz I, Taskaynatan MA, Ozgul A. The effects of balneotherapy on disease activity, functional status, pulmonary function and quality of life in patients with ankylosing spondylitis. Acta Reumatol Port. 2010 Oct-Dec;35(5):441-6. PMID: 21245812.
24. Ciprian L, Lo Nigro A, Rizzo M, Gava A, Ramonda R, Punzi L, Cozzi F. The effects of combined spa therapy and rehabilitation on patients with ankylosing spondylitis being treated with TNF inhibitors. Rheumatol Int. 2013 Jan;33(1):241-5. doi: 10.1007/s00296-011-2147-9. Epub 2011 Sep 27. PMID: 21947374.-
25. Annegret F, Thomas F. Long-term benefits of radon spa therapy in rheumatic diseases: results of the randomised, multicentre IMuRa trial. Rheumatol Int. 2013 Nov;33(11):2839-50. doi: 10.1007/s00296-013-2819-8. Epub 2013 Jul 18. PMID: 23864139.-
26. Dundar U, Solak O, Toktas H, Demirdal US, Subasi V, Kavuncu V, Evcik D. Effect of aquatic exercise on ankylosing spondylitis: a randomized controlled trial. Rheumatol Int. 2014 Nov;34(11):1505-11. doi: 10.1007/s00296-014-2980-8. Epub 2014 Mar 14. PMID: 24626605.
27. Franco Cozzi, Bernd Raffeiner, Valeria Beltrame, Luca Ciprian, Alessandro Coran, Constantin Botsios, Egle Perissinotto, Enrico Grisan, Roberta Ramonda, Francesca Oliviero, Roberto Stramare, Leonardo Punzi, Effects of mud-bath therapy in psoriatic arthritis patients treated with TNF inhibitors. Clinical evaluation and assessment of synovial inflammation by contrast-enhanced ultrasound (CEUS), Joint Bone Spine, Volume 82, Issue 2, 2015, Pages 104-108, ISSN 1297-319X, https://doi.org/10.1016/j.jbspin.2014.11.002.

28. Rubén Fernández García, Laura de Carmen Sánchez Sánchez, María del Mar López Rodríguez, Gema Sánchez Granados, Effects of an exercise and relaxation aquatic program in patients with spondyloarthritis: A randomized trial, Medicina Clínica (English Edition), Volume 145, Issue 9, 2015, Pages 380-384, ISSN 2387-0206, https://doi.org/10.1016/j.medcle.2016.03.001.
29. Karagülle, M., Kardeş, S. & Karagülle, M.Z. Real-life effectiveness of spa therapy in rheumatic and musculoskeletal diseases: a retrospective study of 819 patients. Int J Biometeorol 61, 1945–1956 (2017).
30. Bestaş E, Dündar Ü, Köken T, Koca B, Yeşil H. The comparison of effects of balneotherapy, water-based and land-based exercises on disease activity, symptoms, sleep quality, quality of life and serum sclerostin level in patients with ankylosing spondylitis: A prospective, randomized study. Arch Rheumatol. 2021 Dec 24;37(2):159-168. doi: 10.46497/ArchRheumatol.2022.9024. PMID: 36017205; PMCID: PMC9377174
31. van der Zee-Neuen, A., Strobl, V., Dobias, H. et al. Sustained improvements in EQ-5D utility scores and self-rated health status in patients with ankylosing spondylitis after spa treatment including low-dose radon – an analysis of prospective radon indication registry data. BMC Musculoskelet Disord 23, 743 (2022).
32. Andreas M. Reimold, Vinod Chandran, Nonpharmacologic therapies in spondyloarthritis, Best Practice & Research Clinical Rheumatology, Volume 28, Issue 5, 2014, Pages 779-792, ISSN 1521-6942, https://doi.org/10.1016/j.berh.2014.10.003.
33. Romain Forestier, Fatma-Begüm Erol-Forestier, Alain Francon, Current role for spa therapy in rheumatology, Joint Bone Spine, Volume 84, Issue 1, 2017, Pages 9-13, ISSN 1297-319X, https://doi.org/10.1016/j.jbspin.2016.05.003.
34. Uriel Katz, Yehuda Shoenfeld, Varda Zakin, Yaniv Sherer, Shaul Sukenik, Scientific Evidence of the Therapeutic Effects of Dead Sea Treatments: A Systematic Review, Seminars in Arthritis and Rheumatism, Volume 42, Issue 2, 2012, Pages 186-200, ISSN 0049-0172, https://doi.org/10.1016/j.semarthrit.2012.02.006.
35. Arianne P. Verhagen, Jefferson R. Cardoso, Sita M.A. Bierma-Zeinstra, Aquatic exercise & balneotherapy in musculoskeletal conditions, Best Practice & Research Clinical Rheumatology, Volume 26, Issue 3, 2012, Pages 335-343, ISSN 1521-6942, https://doi.org/10.1016/j.berh.2012.05.008. (https://www.sciencedirect.com/science/article/pii/S1521694212000599).
36. Kocyigit, B.F., Sagtaganov, Z., Yessirkepov, M. et al. Assessment of complementary and alternative medicine method in the management of ankylosing spondylitis, rheumatoid arthritis, and fibromyalgia syndrome. Rheumatol Int (2022). https://doi.org/10.1007/s00296-022-05267-1.
37. Cozzi, F., Ciprian, L., Carrara, M. et al. Balneotherapy in chronic inflammatory rheumatic diseases—a narrative review. Int J Biometeorol 62, 2065–2071 (2018). https://doi.org/10.1007/s00484-018-1618-z-
38. Bernetti, A., Mangone, M., Alviti, F. et al. Spa therapy and rehabilitation of musculoskeletal pathologies: a proposal for best practice in Italy. Int J Biometeorol 64, 905–914 (2020). https://doi.org/10.1007/s00484-019-01731-z-
39. Cozzi, F., Galozzi, P., Ciprian, L. et al. Mud-bath treatment of seronegative spondyloarthritis: experience at the Euganean Thermal Area. Int J Biometeorol 64, 937–941 (2020). https://doi.org/10.1007/s00484-019-01761-7-.
40. Küçükdeveci AA, Oral A, Ilıeva EM, Varela E, Valero R, Berteanu M, Chrıstodoulou N. Inflammatory arthritis. The role of physical and rehabilitation medicine physicians. The European perspective based on the best evidence. A paper by the UEMS-PRM Section Professional Practice Committee. Eur J Phys Rehabil Med. 2013 Aug;49(4):551-64. PMID: 24084414.
41. van den Berg R, Baraliakos X, Braun J, van der Heijde D. First update of the current evidence for the management of ankylosing spondylitis with non-pharmacological treatment and non-biologic drugs: a systematic literature review for the ASAS/EULAR management recommendations in ankylosing spondylitis. Rheumatology (Oxford). 2012 Aug;51(8):1388-96. doi: 10.1093/rheumatology/kes066. Epub 2012 Apr 17. PMID: 22513148.
42. Zão A, Cantista P. The role of land and aquatic exercise in ankylosing spondylitis: a systematic review. Rheumatol Int. 2017 Dec;37(12):1979-1990. doi: 10.1007/s00296-017-3829-8. Epub 2017 Oct 5. PMID: 28983663.
43. Zejun Liang, Chenying Fu, Qing Zhang, Feng Xiong, Lihong Peng, Li Chen, Chengqi He & Quan Wei (2019): Effects of water therapy on disease activity, functional capacity, spinal mobility and severity of pain in patients with ankylosing spondylitis: a systematic review and meta-analysis, Disability and Rehabilitation, DOI: 10.1080/09638288.2019.1645218.)
44. Helliwell PS, Abbott CA, Chamberlain MA. A randomized trial of three different physiotherapy regimes in ankylosing spondylitis. Physiotherapy 1996;82:85e90.
45. van Tubergen A, Landewe R, van der Heijde D, et al. Combined spa-exercise therapy is effective in patients with ankylosing spondylitis: a randomizedcontrolled trial. Arthritis Rheum 2001;45:430e8.
46. BarnatskiiVV.Effects of radon and peloid therapy on functional condition and quality of life in patients with seronegative spondyloarthritis. Vopr KurortolFizioter Lech Fiz Kult 2005;3:26e30.
47. Codish S, Dobrovinsky S, Abu Shakra M, Flusser D, Sukenik S. Spa therapy for ankylosing spondylitis at the Dead Sea. Isr Med Assoc J 2005;7(7):443-6.
48. Yurtkuran M, Ay A, Karakoc Y (2005) Improvement of the clinical out- come inankylosing spondylitis by balneotherapy. Joint Bone Spine 72:303–308.
49. Altan L, Bingol U, Aslan M, et al. The effect of balneotherapy on patients withankylosing spondylitis. Scand J Rheumatol 2006;35:283e9.
50. Lubrano E, D'Angelo S, Parsons WJ et al. Effectiveness of rehabilitation in active ankylosing spondylitis assessed by the ASAS response criteria. Rheumatology2007;46: 16725.

51. Falagas ME, Zarkadoulia E, Rafailidis PI. The therapeutic effect of balneotherapy: evaluation of the evidence from randomised controlled trials. InternationalJournal of Clinical Practice 2009;63:1068–84.
52. Karapolat H, Eyigor S, Zoghi M, Akkoc Y, Kirazli Y, Keser G (2009) Are swimming or aerobic exercise better than conventional exercise in ankylosing spondylitis patients? A randomized controlled study. Eur J Phys Rehabil Med 45(4):449–457.
53. Kuçukdeveci AA, Oral A, Ilıeva EM, Varela E, Valero R, Berteanu M, Chrıstodoulou N (2013) Inflammatory arthritis. The role of physical and rehabilitation medicine physicians. The European perspective based on the best evidence. A paper by the UEMS-PRM Section Professional Practice Committee. Eur J Phys Rehabil Med 49(4):551–564.
54. Sukenik S, Giryes H, Halevy S, et al. Treatment of psoriatic arthritis at the Dead Sea. J Rheumatol 1994;21:1305e9.
55. Sukenik S, Baradin R, Codish S, Neumann L, Flusser D, Abu- Shakra M, et al. Balneotherapy at the Dead Sea area for patients with psoriatic arthritis and concomitant fibromyalgia. Isr Med Assoc J 2001;3(2):147-50.
56. Elkayam O, Ophir J, Brener S, Paran D, Wigler I, Efron D, et al. Immediate and delayed effects of treatment at the Dead Sea in pa- tients with psoriatic arthritis. Rheumatol Int 2000;19(3):77-82.
57. Barnatskiĭ VV (2007) Peloid therapy in various temperature modes in rehabilitation of patients with seronegative spondylarthritis. Vopr Kurortol Fizioter Lech Fiz Kult 2:7–12
58. Cozzi F, Podswiadek M, Cardinale G, et al. Mud bath treatment in spondylitis associated with inflammatory bowel disease – a pilot randomised clinical trial. Joint Bone Spine 2007;74:436–9.
59. Lubrano E, Spadaro A, Amato G, Benucci M, Cavazzana I, Chimenti MS, Ciancio G, D Alessandro G, Angelis R, Lupoli S, Lurati AM, Naclerio C, Russo R, Semeraro A, Tomietto P, Zuccaro C, De Marco G. Tumour necrosis factor alpha inhibitor therapy and rehabilitation for the treatment of ankylosing spondylitis: a systematic review. Semin Arthritis Rheum. 2015 Apr;44(5):542-550. doi: 10.1016/j.semarthrit.2014.09.012. Epub 2014 Sep 28. PMID: 25450240.
60. Zarco P, Florez M, Almodóvar R; Working Group of GRESSER. Expert opinion of Spanish rheumatologists about the role of physical exercise in ankging spondylitis and other rheumatic diseases. Reumatol Clin. 2016 Jan-Feb;12(1):15-21. English, Spanish. doi: 10.1016/j.reuma.2015.01.001. Epub 2015 May 8. PMID: 25964018.
61. Lange U, Müller-Ladner U, Schmidt KL. Balneotherapy in rheumatic diseases--an overview of novel and known aspects. Rheumatol Int. 2006 Apr;26(6):497-9. doi: 10.1007/s00296-005-0019-x. Epub 2005 Jul 12. PMID: 16010560.
62. Tishler M, Brostovski Y, Yaron M. Effect of spa therapy in Tiberias on patients with ankylosing spondylitis. Clin Rheumatol. 1995 Jan;14(1):21-5. doi: 10.1007/BF02208080. PMID: 7743740.
63. van Tubergen A, van der Linden S. A brief history of spa therapy. Ann Rheum Dis. 2002 Mar;61(3):273-5. doi: 10.1136/ard.61.3.273. PMID: 11830439; PMCID: PMC1754027.
64. Shaul Sukenik, Dan Flusser, Mahmud Abu-Shakra, THE ROLE OF SPA THERAPY IN VARIOUS RHEUMATIC DISEASES, Rheumatic Disease Clinics of North America, Volume 25, Issue 4, 1999, Pages 883-897, ISSN 0889-857X, https://doi.org/10.1016/S0889-857X(05)70108 (https://www.sciencedirect.com/science/article/pii/S0889857X05701083)
65. American College of Rheumatology Position Statement (2000). Complementary and alternative therapies for rheumatic dis- ease. Rheum Dis North Am 26:189192
66. Cheleschi S, Gallo I, Tenti S. A comprehensive analysis to understand the mechanism of action of balneotherapy: why, how, and where they can be used? Evidence from in vitro studies performed on human and animal samples. Int J Biometeorol. 2020 Jul;64(7):1247-1261. doi: 10.1007/s00484020-01890-4. Epub 2020 Mar 21. PMID: 32200439; PMCID: PMC7223834.
67. Bellometti S, Poletto M, Gregotti C, Richelmi P, Bertè F. Mud bath therapy influences nitric oxide, myeloperoxidase and glutathione peroxidase serum levels in arthritic patients. Int J Clin Pharmacol Res. 2000;20(3-4):69-80. PMID:11314241
68. Vaamonde-García C, Vela-Anero Á, Hermida-Gómez T, Fernández-Burguera E, Filgueira-Fernández P, Goyanes N, Blanco FJ, Meijide-Faílde R. Effect of balneotherapy in sulfurous water on an in vivo murine model of osteoarthritis. Int J Biometeorol. 2020 Mar;64(3):307-318. doi: 10.1007/s00484-019-01807-w. Epub 2019 Nov 1. PMID: 31828429.
69. Claudepierre P. Spa therapy for ankylosing spondylitis: still useful? Joint Bone Spine. 2005 Jul;72(4):283-5. doi: 10.1016/j.jbspin.2005.01.003. Epub 2005 Mar 22. PMID: 16038839.
70. Zão A, Cantista P. The role of land and aquatic exercise in ankylosing spondylitis: a systematic review. Rheumatol Int. 2017 Dec;37(12):1979-1990. doi: 10.1007/s00296-017-3829-8. Epub 2017 Oct 5. PMID: 28983663.
71. Van Tubergen A, Boonen A, Landewé R, Rutten-Van Mölken M, Van Der Heijde D, Hidding A, Van Der Linden S. Cost effectiveness of combined spa-exercise therapy in ankylosing spondylitis: a randomized controlled trial. Arthritis Rheum. 2002 Oct 15;47(5):459-67. doi: 10.1002/art.10658. PMID: 12382292.
72. Karagülle MZ, Karagülle M. Balneotherapie und Kurorttherapie rheumatischer Erkrankungen in der Türkei: Ein systematischer Review [Balneotherapy and spa therapy of rheumatic diseases in Turkey: a systematic review]. Forsch Komplementarmed Klass Naturheilkd. 2004 Feb;11(1):33-41. German. doi: 10.1159/000077194. PMID: 15004446.
73. Moss GA. Water and health: a forgotten connection? Perspect Public Health. 2010 Sep;130(5):227-32. doi: 10.1177/1757913910379192. PMID: 21086819.