

treatment mild improvement was observed in patients treated with Dead sea salts compared with those treated with common salts. However, saline spa water alone at Salies de Bearn in France (sodium concentration, 250 g/l; magnesium, 980 mg/l) was reported to have a minor therapeutic effect on psoriasis compared with UV-B exposure in an RCT on 90 patients (12).

Acne vulgaris is another dermatologic disease that benefits from balneotherapy. A non-randomized clinical study of 86 patients treated for acne vulgaris in the Dead sea area showed a significant improvement manifested by a reduced number of comedones and pustules (9).

Sulfur-rich spas are especially in the interest for their dermatologic effects. The sulfur that penetrates the skin is oxidized and evokes various physiologic responses in the skin, such as vasodilation in the microcirculation, an analgesic influence on the pain receptors, and inhibition of the immune response. Sulfur also interact with oxygen radicals in the deeper layers of the epidermis, producing sulfur and disulfur hydrogen, which may be transformed into pentathionic acid, and this may be the source of the antibactericidal and antifungal activity of sulfur water (2). The therapeutic action of sulfur water is related mainly to sulfur's keratolytic effect, resulting in peeling (13).

Schempp et al. (14) demonstrate in both in vivo (a 5% concentration of $MgCl_2$) and in vitro (a 1% concentration of $MgCl_2$) studies that magnesium ions specifically inhibit the antigen-presenting capacity of Langerhans cells and may thus contribute to the efficacy of magnesium-rich spa water in the treatment of inflammatory skin diseases.

Therapeutic activities of CO₂ water bathes (700~1300 mg CO₂ per kg water) are explained by a synergism between hydrostatic pressure and chemical properties of carbon dioxide that acts directly on the blood vessels of the skin, causing vasodilation and increased oxygen utilization (15).

Balneotherapy with arsenical-ferruginose (no evidence on concentrations) water from the spa at Terme di Levico (Italy) showed effectiveness in the treatment of cervico-vaginitis (n=20) in comparison to placebo suppositories (n=10). Both clinical signs and symptoms reduced in the intervention group with good tolerability (16).

Apart from immersion, drinking spa water has also been investigated for treatment of dermatologic conditions. Drinking of low-salt Avene (France) Spring water (sodium, 4.9 mg/l; magnesium, 22.5 mg/l; calcium, 44.3 mg/l; bicarbonate, 234.8 mg/l) for a period of 18 days normalized the intestinal permeability in patients with atopic dermatitis (17). Drinking and immersion in a selenium-rich spa water (selenate 70 μ g/l) for three weeks at the care center of La Roche-Posay (France) demonstrated an improvement in patients with psoriasis (18). Patients who responded to treatment had a significant increase in their plasma selenium level. In patients with psoriasis, inflammatory reactions in the skin may lead to an increased loss of selenium (18).

Chronic musculoskeletal effects:

Balneotherapy has been practiced for centuries in the management of chronic musculoskeletal diseases. It is based on the indigenous natural remedies of the spas, such as thermal and mineral water and gases (CO₂,

radon). The net beneficial effect of balneotherapy on musculoskeletal diseases is probably a result of mechanical, thermal and chemical effects.

Inflammatory diseases:

Sukenik et al. (19) reported from an RCT that a two-week period of therapy with sulfur baths or mud packs (no evidence on mineral concentration), alone or in combination, was effective in the treatment of patients with RA. Forty patients with active RA were allocated at random to 4 groups of 10 patients each. The first group was treated with daily mud packs, the second group with daily sulfur baths, the third with a combination of daily mud packs and sulfur baths, and the fourth group served as controls. Statistically significant improvements in most clinical indices were observed for a period of up to 3 months in all the three treatment groups. Improvement in the control group was minor in comparison and did not reach statistical significance.

In a similar study Elkayam et al. (20) allocated 41 RA patients at random to 2 groups. One group was treated with a combination of mineral baths (rich in sodium chloride and sulfate (no evidence on concentrations)) and mud packs for 20 minutes in Tiberias (Israel), while the second group was treated with tap water only. Both groups showed a significant but only temporary improvement. The first group showed significant improvement in grip strength.

Sukenik et al. (21) again reported from a randomized trial that daily bath in Dead sea or daily sulfur bath (no evidence on sulfur ions concentration) or combination of both resulted to improvements in clinical indices such as

duration of morning stiffness, grip strength and number of active joints in 36 patients with RA during a 3 months follow-up period compare to controls that neither bathed in the Dead sea nor took sulfur baths.

Radon spa therapy was found to be effective in treatment of RA (22). Sixty patients were grouped to take baths with either radon-carbon dioxide water (1.3 KBq/l and 1.6 g/l) or artificially enriched carbon dioxide water for four weeks. After six months of follow-up pain intensity remained lower in patients receiving radon-carbon dioxide bath than the other group (23).

In a non-randomized clinical (24) study 14 patients with ankylosing spondylitis were treated for 2 weeks at a Tiberias spa with combination of hot mineral water baths (38°C) and mud packs (45°C) for 20 minutes (no evidence on mineral concentration). A significant improvement was observed in morning stiffness, finger to floor distance, and overall well-being as assessed by patients and physicians. Tubergen et al. (25) also found that in 120 outpatients with ankylosing spondylitis, a 3-week course of combined spa-exercise therapy at a spa resort (no evidence on mineral components) in Bad Hofgastein (Austria), in addition to drug treatment and weekly group physical therapy, provide beneficial effects which may last for 40 weeks. Also combined spa-exercise therapy (Bad Hofgastein, Austria) besides standard treatment with drugs and weekly group physical therapy has been shown to be more effective and showed favorable cost-effectiveness and cost-utility ratios compared with orthodox treatment alone in patients with ankylosing spondylitis (26).

The beneficiary effect of balneotherapy was also observed in patients with

fibromyalgia. Forty-eight patients with fibromyalgia were randomly assigned to a treatment group receiving sulfur baths (sulfur ions concentration of 2000 mg/l) for 20 minutes and a control group without receiving treatment. All participants stayed for 10 days at a Dead sea spa. Signs and symptoms of the disease improved in the patients receiving sulfur baths and it persisted for 3 months (27).

It should be mentioned that although balneotherapy does not replace but rather complements conventional drug therapy, it is certainly beneficial in suitable cases.

Non-inflammatory diseases:

The aim of balneotherapy in musculoskeletal diseases is to improve the range of joint movements, cause muscle strengthening, relieve muscle spasm, maintain or improve functional mobility, and as a consequence to relieve patients suffering.

A prospective randomized controlled study was conducted in patients with osteoarthritis of the hip, knee or lumbar spine (28). Treatment was either spa therapy (n=91) of three weeks duration at Vichy (France) (no evidence on mineral components) or usual therapy (n=97) at home. Changes in the assessment criteria after a 6 months follow-up period showed improvement in terms of pain, functional impairment and quality of life in the spa group. The effects of thermal water (36°C for 30 minutes) from Cserkeszolo (Hungary) were appraised in a randomized, double blind study on 58 patients with osteoarthritis of the knee (29). Balneotherapy was performed with spa water (Solute content of 1675 mg/l comprised primarily of sodium

bicarbonate along with silicic acid (48mg/l) and fluoride (1.8 mg/l)) and tap water. Both groups improved in signs and symptoms, but the magnitude of improvement was significantly greater in patients treated with spa water. In a study by Green et al. (30) after randomizing 47 patients with osteoarthritis of the hip into home exercise (n=23) and hydrotherapy with tap water in a deep pool twice weekly for a period of 6 weeks plus home exercise (n=24), they found improvement in both groups but no significant difference in effect between the interventions.

A double-blinded RCT was conducted by Wigler et al. (31) to observe the effects of spa therapy at Dead sea on osteoarthritis of the knee in 33 patients. Subjects were randomly assigned to three groups of mineral bath and mud pack, mineral bath and false mud packs, and tap water and false mud packs. Improvements were observed in all three groups after two weeks of intervention, with more improvements in the group of mineral bath and mud pack.

Low back pain is another non-inflammatory musculoskeletal disease that benefits from short and long-term effects of spa therapy (32,33). Constant et al. (33) assessed the overall effectiveness of spa therapy at Saint-Nectaire (France) compared with usual routine drug therapy in chronic low back pain. In an RCT, 121 patients were allocated to treatment (n=59) and control (n=62) groups. In the treatment group, patients underwent routine drug therapy and spa therapy (total mineral content of 8073 mg/l of mixed bicarbonate, chlorine and sodium composition) 6 days per week for 3 consecutive weeks. In control group, patients received routine drug therapy.

After 3 weeks of intervention and 6 months of follow-up, patients in the treatment group had significant improvement in signs and symptoms of the disease and also drug consumption (analgesic and anti-inflammatory).

Three treatments for non-specific lumbar pain- balneotherapy (total mineral concentration of 901 mg/l, mainly bicarbonate, 445.3 mg/l; sulfate, 109.9 mg/l and calcium, 117.2 mg/l electrolytes), underwater traction bath and underwater massage were assessed in a randomized prospective controlled trial in 158 outpatients (34). Each group was treated for 4 weeks and patients were reviewed at the end of this period and at 12 months following entry to the trial. The prescription of analgesics and pain score were significantly reduced in all three treated groups but there was no difference between the three groups. After 1 year, only consumption of analgesics remained significantly lower than in control group who received no treatment.

Strauss-Blasche et al. (35) reported seasonal variation in effect of spa therapy (including mud and CO₂ applications) on chronic pain. A total of 387 patients with non-inflammatory chronic pain stayed at a spa in Austria for 3 weeks and received 2-4 treatments per day, including mudpacks, massages, and exercise therapy. In different groups of patients for 2 years, pain was measured at the beginning, end, and 6 weeks after spa therapy. The effect of spa therapy on pain was best between April and June and medium decrease of pain was more likely between October and November. The magnitude of the seasonal variation was greater for back than for joint pain.

The effectiveness of balneotherapy in the management of patients with

arthritis attributes to physiological changes like increased diuresis and hemodilution as well as biomechanical changes like joint unloading, relaxation and increased muscle function (4,36,37).

Metabolic effects:

Water temperature has an important role for the metabolic effects of balneotherapy. In Japan, the most outstanding features of balneotherapy is repeated whole body immersion in hot water (42°C or higher) . Ohtsuka et al. (38) reported that immersion in water at 42°C for 10 minutes resulted in oxidative stress by increasing the levels of lipid peroxides and decreasing the activities of glutathione peroxides in erythrocytes. Moreover, whole body bathing in hot water (42°C or higher for 10-15 minutes) is reported to induce a marked increase of blood viscosity and an enhancement of the blood coagulation system (39). However, drinking of an electrolyte water containing (meq/l) sodium, 21; potassium, 7; calcium, 1 and chloride, 18.5 at midnight associated with a decrease in blood viscosity from midnight to 8 AM (40).

Platelet glutathione metabolism is impaired among patients with diabetes mellitus and coronary heart disease, in which platelet aggregability is elevated (41,42). Ohtsuka et al. (43) reported from a clinical controlled trial on 12 type II diabetic patients that four weeks of twice or thrice daily balneotherapy at a spa in Hokkaido (Japan) with the water temperature between 39 to 40°C (no evidence on mineral compositions) resulted in partial improvement of platelet glutathione metabolism. They concluded that balneotherapy was beneficial for patients whose platelet antioxidative

defense system is damaged, such as those with diabetes mellitus and coronary heart disease. However, immersion in hot water (42°C or higher) for 10 minutes reported to cause an increase in the activity of erythrocyte aldose reductase which showed to have a positive good correlation with hemoglobin A1c (44). The change in erythrocyte aldose reductase activity might aggravate diabetic complications, and therefore, body exposure to hot environmental conditions is better to be avoided for diabetic patients.

To determine the involvement of activated platelets in the frequent thrombosis after hot hot-spring bathing, Take et al. (45) found that plasma levels of beta-thromboglobulin began to rise at 5 minutes and elevated significantly 10 minutes after the start of 47°C hot spring bathing at Kusatsu (Japan). This effect was not observed with bathing at 42 °C. Concentrations of beta-thromboglobulin were significantly correlated with intima-media thickness of common carotid artery (46). Acute hyperthermal stress due to hot hot-spring water may also decrease the fibrinolytic capacity, leading to the occurrence of thrombotic events (47).

Some spa resorts have larger place so that aerobic exercise can be applicable. Aerobic exercise in Ataturk spa resort (Turkey) for 6 months with the water temperature of 29-30°C determined to be effective to make anabolic effects on the bone of 41 postmenopausal, sedentary subjects in comparison to control group who were instructed to maintain their sedentary lifestyle for the duration (48).

Spa therapy has also been shown to have a lipid-lowering effect. Strauss-Blasche et al. (49) reported that a 3-week spa therapy (consisting of

mud packs, CO₂ baths and massage and exercise therapy) at Bad Tatzmannsdorf (Austria) in 395 patients with musculoskeletal chronic pain over a time of 2 years associated with a mild decrease of total cholesterol, HDL cholesterol and LDL cholesterol.

Kuczera et al. (50) also found in a non-randomized clinical study that spa therapy (no evidence on mineral components) in Wysowa (Poland) for 20 days was accompanied with a significant increase of plasma erythropoietin, iron, ferritin and saturation of transferrin with iron. These effects were especially marked in patients with essential hypertension. The same researchers also reported an increase in plasma concentration of stress reaction hormones (ACTH, cortisol, growth hormone and prolactin) after 20 days of spa therapy (51).

Leibetseder et al. (52) pointed out that sulfur baths (S⁻² concentration of 7.3 mg/l) exerts beneficial effects on plasma homocysteine. Plasma homocysteine is a risk factor for cardiovascular diseases (53). Forty patients with degenerative osteoarthritis were randomized into two equal groups, a treatment group, received stationary spa therapy plus daily sulfur baths and a control group received spa therapy alone. Plasma homocysteine was significantly reduced in sulfur bath and rose insignificantly in the control group after three weeks stay at the spa resort. The researchers did not find any significant change in the urinary levels of 8-hydroxydeoxy Guanosine in both groups (52). Studies on rats provided evidence to an increase in heat-shock protein expression after bathing for 15 minutes in 41°C hot water for 4 weeks (54,55). Heat-shock proteins are known as important endogenous

cell-protective proteins induced in response to a wide variety of stresses (56,57).

Psychological effects:

A few studies addressed the psychological effects of balneotherapy. Steam baths, saunas and whirlpools are standard equipment of many spa resorts, with the main objective being to relax and strengthen the body and mind, and to prevent development of disease. The spa resorts stay with medium (3-month intervention) and long term (6-month intervention) bathing accompanied with health education resulted in less psychological tension and self-rating depression and more vigorousness among a group of middle-aged and elderly women in an RCT (58,59).

Rest is an important element in spa resort treatment. The physical and emotional distance from the stress and concerns of daily life and worries over livelihood could be beneficial in reducing daily stress. Stress reduction has been shown to reduce disease activity by way of soluble interleukin-2 receptor level in RA (60).

General contraindications for balneotherapy should also be considered with importance. These contraindications include severe psychiatric conditions, acute alcoholic states, epilepsy, cardiac dysrhythmias, inadequate balance, severe varicose veins, open wounds and hypersensitivity to mineral baths (61). Furthermore, hyperthermic immersion might produce potentially dangerous cardiovascular effects, such as ectopic beats and excessive tachycardia (62).

Conclusion:

Although there is a tendency to publish statistically significant findings and there is a lack of access to many non-significant studies, existing data support the beneficial effects of spa therapy in several diseases and conditions. Apart from any specific effect of any natural waters, a proper regimen of treatment, rehabilitation with physiotherapy and hydrotherapy in an atmosphere free from stress will undoubtedly help many patients. In interpretation of the findings, the methodological aspects for each study should be taken into consideration. Can the tap water be adequately disguised? Can immersion be organized in a double-blind fashion? Can the wider aspects of climatotherapy be controlled? In addition, some other important questions should also be answered: Could the positive findings have resulted from patient expectations? How long the positive effects persist? Were the benefits worth the costs? It is not clearly recognizable whether the improvements seen were due to direct effect of spas or from resorts stay. Since temperature and chemical compositions of each spa is a characteristic for that spa resort, extrapolating the results to other spa resorts should be considered cautiously.

Most of the studies reported in this review were conducted on a small number of subjects. With a smaller number clinically relevant effects might be missed. Performing randomized studies using a larger study population is recommended so that statistical significance comes close to clinical relevance. Randomized studies performed and reported properly give a sound answer to the question whether balneotherapy is an effective treatment in different medical conditions.

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Table 1. Effects of balneotherapy in randomized controlled trials or clinical studies conducted on patients with dermatologic disorders.

Disease	Authors	Mode of therapy	n	Treatment duration	Efficacy	*Evidence (Design and journal type)
Atopic dermatitis	Kubota et al. (8)	Acidic hot-spring bath pH: 2.0 plus Mn 1.4 mg/l, I 0.3 mg/l	70	Median of 2 months	Significant clearing of skin lesions and reduction in itch	B(C)
	Shani et al. (9)	Balneotherapy In Dead sea	1408	4 to 6 weeks	Complete clearance of lesions in 90% of patients	A(D)
	Dupuy et al. (17)	Drinking spa water (sodium 4.9 mg/l, calcium 44.3 mg/l)	12	18 days	Normalizing the permeability of patients	B(C)
		low-salt	12	18 days	Normalizing the intestinal permeability of patients	B(C)
Psoriasis	Halvey et al. (11)	Dead sea balneotherapy	25	3 weeks	Mild improvement in comparison with those treated with common salts bath	B(A)
	Leaute-labreze et al. (12)	Saline water balneotherapy (sodium concentration, 250 g/l; magnesium, 980 mg/l)	71	3 weeks	Minor therapeutic effects with saline spa water alone, and no beneficial effect of bathing to enhance phototherapy	C(A)

Continued:

Disease	Authors	Mode of therapy	n	Treatment duration	Efficacy	*Evidence (Design and journal type)
	Pinton et al. (18)	Drinking and immersion in selenium rich spa (70 μ g/l)	92	3 weeks	Improvement in psoriatic plaques	A(C)
Acne Vulgaris	Shani et al. (9)	Dead sea balneotherapy	86	4 weeks	Reduced numbers of comedones and pustules	A(D)
Cutaneous microcirculation (15)	Hartmann et al.	Balneotherapy with CO ₂ (1200 mg/ kg water)	18	20 minutes	Cutaneous vasodilation and increased oxygen utilization	A(A)

* Evidence. A: effective, B: probably effective, C: may not be effective.

Journal type and design: A: Randomized clinical trial (RCT) in a major journal, a: RCT in a non-major journal, B: case-control study in a major journal, b: case-control study in a non-major journal, C: clinical study in a major journal, c: clinical study in a non-major journal, D: review article.

Table 2. Effects of balneotherapy in randomized controlled trials or clinical studies conducted on patients with chronic inflammatory musculoskeletal diseases.

Disease	Authors	Mode of therapy	n	Treatment duration	Efficacy	*Evidence (Design and journal type)
Rheumatoid arthritis	Sukenik et al. (19)	Sulfur baths, mud packs and combination	40	2 weeks	Improvement in clinical indices up to 3 months	A(A)
	Elkayam et al. (20)	Mineral water baths and mud packs (rich in sodium chloride and sulfate)	41	2 weeks	Temporary improvement in clinical indices	A(A)
	Sukenik et al. (21)	Dead sea, sulfur bath or combination	36	3 months	Improvement in clinical indices in all three intervention groups	A(A)
	Franke et al. (23)	Combined radon (1.3 KBq/l) carbon dioxide (1.6 g/l) spa	60	4 weeks	Lower pain intensity after 6 months comparing to taking only a carbon dioxide bath	B(a)
Ankylosing spondylitis	Tishler et al. (24)	Combination of hot mineral baths (38°C) and mud packs (45°C)	14	2 weeks	Improvement in morning stiffness and overall well-being	B(C)
	Tubergen et al. (25)	Combination of spa-exercise therapy	120	3 weeks	Improvement in clinical indices up to 40 weeks	A(A)