Scientific Evidence of the Therapeutic Effects of Dead Sea Treatments: A Systematic Review

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Objectives: The Dead Sea, the deepest and most saline lake on earth, has been known from biblical times for its healing properties. The aim of this systematic review was to present critically the level of evidence for the claims of therapeutic effects of Dead Sea treatments in several rheumatologic diseases and psoriasis as well as to review these treatments' safety.

Methods: All articles cited in MEDLINE under the query, "Dead Sea," were reviewed.

Results: We found bona fide evidence that Dead Sea treatments are especially effective in psoriasis due to both the special characteristics of solar ultraviolet radiation in the Dead Sea and the Dead Sea water balneotherapy. Dead Sea mud and Dead Sea balneotherapy have been found to be beneficial in rheumatologic diseases, including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and knee osteoarthritis. In the safety analysis, we found no evidence for an increase in skin neoplasia, although skin actinic damage seems to be increased in patients treated in the Dead Sea. Dead Sea treatments do not lead to worsening of blood pressure. Substantial ingestion of Dead Sea water (generally in unusual near-drowning cases) is toxic and can result in cardiac rhythm disturbances because of electrolyte concentration abnormalities. Laboratory analysis of Dead Sea mud did not reveal mineral concentrations that could represent a health concern for their intended use.

Conclusions: Dead Sea treatments are beneficial in several rheumatologic diseases and psoriasis and have a good safety profile.

 Semin Arthritis Rheum 42:186-200

Keywords: *Dead Sea, rheumatic diseases, autoimmune diseases, psoriasis, treatment, evidence, review*

The Dead Sea is the deepest and most saline lake on earth and it is estimated to be 50,000 years old(1). It is located at nearly 420 m below sea level, between the Judean Mountains in Israel and the Moab mountains in Jordan, along the Syrian-African rift. The Dead Sea is about 80 km long and 17 km wide. Mean maximal daily temperature at the Dead Sea is 32°C during the summer with peaks over 40°C. Mean maximal daily temperature is 19°C in the winter. Its humidity levels are low, at about 27% in the summer and 38% in the winter (compared to 85% in the corresponding Mediterranean coast) (1,2). Barometric and oxygen pressure are increased at the Dead Sea, being the highest on earth. For comparison, barometric pressure at the Dead Sea (420 m below sea level) is around 800 mm Hg, while in Jerusalem (800 m above sea level) it is 696 mm Hg (3). Oxygen tension is 10% higher than at sea level (1).

The Dead Sea water has 345 g of mineral per liter (34.5% or 34.5 g/100 mL). This salt concentration is about 7 to 10 times that of the oceans (2). The Dead Sea spring water has 180 to 215 g of mineral per liter (3). However, the water of the Dead Sea is not concentrated seawater. The relative proportion of salts as compared with the Mediterranean Sea may be no different regarding NaCl, but the content of others salts like $MgCl_2$, $CaCl_2$, KCl, and $MgBr_2$ is astonishingly higher. Interestingly, it is the $CaCl_2$ that provides the Dead Sea water that slimy ("oily") feel (1,2,4,5). In fact this property is well known for its cosmetic application: smoothing of the skin (6). In addition, the waters of the Dead Sea have moisturizing

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doi:10.1016/j.semarthrit.2012.02.006

properties because of its high magnesium content, which enhances the ability of the skin to retain water (7). The proportion of $CaSO_4$ is twice that of the Mediterranean Sea. Among the separate ions present in the Dead Sea water, chloride (212.4 g/l), magnesium (40.65 g/l), sodium (39.15 g/l), calcium (16.86 g/l), potassium (7.26 g/l), bromide (5.12 g/l), sulfate (0.47 g/l), and bicarbonate (0.22 g/l) are notable (1,2,4,5). The bituminous Dead Sea mud, which is found in the Dead Sea and its springs, is rich in inorganic materials (mainly salts) and contains also a lower amount of organic materials (mainly from plants and animals) (3).

Since ancient times several therapeutic properties have been attributed to the Dead Sea, in the Bible and in the Talmud (the writings of the Jewish sages). Aristotle (384-322 BCE) was the first to inform the outer world about the medicinal properties of the Dead Sea. Modern medical research on the therapeutic properties of the Dead Sea was pioneered by Dostrovsky et al. in 1959 (8).

Dead Sea climatotherapy refers to being exposed to the local environmental conditions of the Dead Sea (among them high temperature, low humidity). Balneotherapy in the Dead Sea refers to Dead Sea water immersions or Dead Sea springs' water immersions or sulfur baths. Dead Sea phototherapy (or heliotherapy) refers to sun exposure in the Dead Sea. Artificial Dead Sea water balneotherapy (with reconstituted Dead Sea salts) and artificial phototherapy [with device-administered ultraviolet (UV) radiation] have been used as a substitute to these natural Dead Sea resources.

The aim of this systematic review was to present critically the level of evidence for the claims of therapeutic effects of Dead Sea treatments in rheumatologic diseases and psoriasis as well as to review these treatments' safety.

MATERIALS AND METHODS

Abstracts of articles cited in MEDLINE under the query "Dead Sea" were initially retrieved (360 articles). All the abstracts were reviewed and clinical articles in which Dead Sea balneotherapy, phototherapy, or mud therapy were investigated for rheumatologic diseases (31 articles), psoriasis (50 articles), or safety assessment (25 articles) were retrieved and included. Individual case reports or opinions were excluded (42 articles). The available evidence and strength of recommendation was graded using a published system (9) (Table 1) and is presented in the discussion. Data from small studies that contribute interesting information has been included in this review, although their findings are not considered in the final conclusions regarding the evidence of the benefit of Dead Sea balneotherapy, phototherapy, and mud therapy for each medical condition. The molecular mechanisms by which the Dead Sea treatments exert their therapeutic effect are beyond the scope of this article but are discussed in other publications (10).

Table 1 Evidence and Strength of Recommendation

Level of Evidence
A: More than one RCT/meta-analysis
B: A single RCT or well-designed nonrandomized trial like prospective observational registries (case-controls, cohorts)
C: Expert consensus: this includes case reports and retrospective series, here the expert decides based on his experience
Strength of recommendation
Class I: conditions for which there is evidence or general agreement that a given procedure/therapy is useful and effective
Class II: conditions for which there is conflicting evidence or divergence of opinion about the usefulness/efficacy of performing the procedure/therapy
Class IIa: weight of evidence/opinion is in favor of usefulness/efficacy
Class IIb: usefulness/efficacy is less well established by evidence/opinion
Class III: conditions for which there is evidence or general agreement that a procedure/therapy is not useful/effective and in some cases may be harmful

RESULTS

Psoriasis—Dermatologic Manifestations

Dead Sea water balneotherapy and phototherapy have been used to treat dermatologic and rheumatologic involvement in psoriasis. Although several new therapeutic approaches have emerged in the last decade for psoriasis, resistant forms of the disease, cases in which only partial remission is achieved with medications and cases in which medications have unacceptable toxicity, may benefit from complementary treatments like Dead Sea water balneotherapy and phototherapy (11,12).

In a large retrospective study involving the records of 1448 consecutive patients treated with Dead Sea water balneotherapy and phototherapy, Abels et al. reported that clearing of 80% to 100% of the lesions was seen in 88% of the patients and in 58% there was almost complete clearance of psoriatic lesions (13). In another retrospective series of 192 patients spanning 18 years, Knudsen and Worm (14) reported that Dead Sea water balneotherapy and phototherapy at the Dead Sea resulted in total or almost total remission in 73% of the patients. In addition, 55% of the remissions lasted for 1 to 3 months.

Klein and colleagues (15) published the results of a prospective randomized trial in which 367 patients with moderate to severe psoriasis were treated either with device administered phototherapy alone (PT) or with a combination of device-administered phototherapy and bathing in 10% Dead Sea salt solution (synchronous BalneoPhotoTherapy, sBPT). The treatment was provided for a length of 35 sessions or until clearance of dermatologic manifestations. Improvement was assessed using the Psoriasis Assessment of Severity Index (PASI).

Both treatments were clinically effective but treatment with sBPT was statistically superior to PT alone both at the end of the treatment and at follow-up of up to 6 months.

However Dawe and colleagues found no additional benefit for Dead Sea salt solution soaks in a prospective randomized comparison of narrowband ultraviolet B (UVB) phototherapy in chronic plaque psoriatic patients, in which some of the patients were randomly assigned Dead Sea salt solution soaks as an addition to phototherapy treatment (16).

In another publication, a prospective nonrandomized multicenter study by Schiffner et al. found that sBPT for psoriasis vulgaris patients had a 71.4% improvement in the PASI score when assessed according to the protocol and 61% on an intention-to-treat basis (17).

It has been published also that this same protocol of sBPT led to improvements of different types of psoriasis as assessed by the PASI score in a retrospective study: small-plaque psoriasis had a PASI decrease of 76.1%, guttate type 73.7%, large-plaque type 67.1%, and confluating type 62% (18).

Using retrospective data, David et al. (4) reported that the types of psoriasis most likely to benefit from Dead Sea water balneotherapy are guttate and chronic plaque type. Moderate improvement can be seen in flexural psoriasis and palmoplantar psoriasis. Scalp and erythrodermic type psoriasis are usually unresponsive and in generalized pustular psoriasis Dead Sea water balneotherapy is contraindicated (4).

A meta-analysis comparing the effectiveness of artificial Dead Sea water balneotherapy and phototherapy and natural Dead Sea water balneotherapy and phototherapy was performed using the published literature during the past two decades (19). Both treatments were effective for psoriasis and their results were comparable.

In a prospective nonrandomized study, Harari et al. (20) reported on complete clearance after 4 weeks of natural Dead Sea water balneotherapy and phototherapy in 70% of the patients in a cohort of 740 psoriatic patients.

Also Harari et al. (21) performed a retrospective study in which they divided 605 patients treated in the Dead Sea with Dead Sea water balneotherapy and phototherapy (mean treatment length was 4.1 weeks) for dermatologic manifestations of psoriasis (plaque psoriasis) into two groups: age of disease onset under 40 years old (type 1) and age of disease onset over 40 years old (type 2). The Psoriasis Assessment of Severity Index of 95 (PASI 95) was reached in 74% of the former in comparison with 62% of the latter, indicating that those that developed dermatologic manifestations of psoriasis (plaque psoriasis) at an earlier age (type 1) respond better to Dead Sea water balneotherapy and phototherapy.

Cohen et al. (22) reported on shorter term (2 weeks) Dead Sea water balneotherapy and phototherapy in 85 patients with psoriasis vulgaris. In this prospective nonrandomized study, 55% of the patients achieved PASI 75, which is lower than the remission rates achieved in longer treatments of 1-month duration. For example, in another prospective nonrandomized study, Harari et al. (23) reported that, after a similar treatment of 1-month duration, 75.9% of the patients reached PASI 75. The median time of remission was 23.1 weeks.

Also Abels and colleagues (13) have reported (retrospective data) on partial response in Dead Sea water balneotherapy and phototherapy shorter than 1 month.

Trying to understand the individual contribution of Dead Sea water balneotherapy and phototherapy, David et al. prospectively compared 3 treatments: only Dead Sea phototherapy, only Dead Sea water balneotherapy, or both. The improvement as assessed by PASI score was 79%, 22.1%, and 87%, clearly pointing to the phototherapy as the most important factor but demonstrating a specific contribution of Dead Sea water balneotherapy (4). In line with these findings, it has been demonstrated that skin soaking in sodium chloride solutions sensitizes the skin to UVB (24). In another investigation, Boer and colleagues concluded that simultaneous UVB phototherapy and bathing have better effects than UVB phototherapy alone (25).

The addition of acitretin in a small number of severe psoriatic patients has been reported by Shiri et al. (26) to further enhance the results of Dead Sea water balneotherapy and phototherapy, leading to doubling the remission time.

Ben-Amitai et al. (27) observed in a prospective nonrandomized study that 17 children (10 to 18 years old) with plaque-type psoriasis vulgaris had also a clear and long-lasting improvement (in many cases more than 6 months) after Dead Sea water balneotherapy and phototherapy. More than 75% improvement in the PASI score was noted in 35.3%; 50% to 75% improvement occurred in 29.4% of the patients.

Studying skin biopsies of psoriatic patients before and after undergoing Dead Sea water balneotherapy and phototherapy-induced psoriasis remission, Hodak and colleagues (28) described a significant reduction in the number of activated T-lymphocytes in the epidermis (depletion of more than 90% of $CD3^+$ and $CD25^+$ cells) and in the dermis (depletion of 69.4% of $CD3^+$ and of 77.4% $CD25^+$ cells). There was also a marked reduction in HLA-DR expression in keratinocytes.

Bt studying biopsies of patients undergoing artificial Dead Sea water balneotherapy with Dead Sea salts and artificial UVB phototherapy, it was shown that after treatment there was a reduction in the number of Langerhans' cells in the epidermis (29).

It has also been reported that the mean serum levels of manganese and lithium decreased in psoriatic patients that responded to Dead Sea water balneotherapy (30).

Dead Sea salts have also demonstrated in vitro antiproliferative effects, something that can help in psoriasis (31), possibly through the effects of magnesium bromide or magnesium chloride (4,32).

Interestingly, methionine-encephalin levels, known to be increased in psoriatic lesions, were not substantially modified after Dead Sea water balneotherapy and phototherapy, while nonlesional methionine-encephalin levels increased after Dead Sea water balneotherapy and phototherapy, together with the lesions' healing (33).

In psoriatic patients a significant increase in selenium-dependent glutathione peroxidase activity was reported after a period of 4-week Dead Sea water balneotherapy and phototherapy. Drinking water at the Dead Sea has high selenium content. In fact healthy persons drinking only low-selenium water had significantly lower levels of selenium-dependent glutathione peroxidase activity than those drinking local water (34). Also serum bromine levels increased 2- to 3-fold in Danish patients after 4-week Dead Sea water balneotherapy and phototherapy. Bromine levels are also increased in the healthy population living at the Dead Sea. High bromine levels are found in the Dead Sea water and air (as an aerosol) (35).

A selective therapeutic pattern of the sun's radiation at the Dead Sea has been pointed out by Abels et al. (36). It is known that UV radiation [especially UVB but also in a lower degree ultraviolet A (UVA)] is attenuated when traversing the extra 420 m of atmosphere of the Dead Sea, which also has a particular composition because of Dead Sea vapors and aerosols overhanging the lake. This modifies the natural phototherapy spectrum at the Dead Sea. It is however mistaken to say that no UVB radiation is present in the Dead Sea, a popular belief that seems to have resulted from the selective attenuation of the erythematous wavelengths of the UVB radiation, which allows for longer exposures to the sun radiation than in other places ("less burns") (2). Kudish and Kushelevsky (5,37) studied the characteristics of sun radiation in the Dead Sea (420 m below sea level) comparing them to those in Be'er Sheva (315 m above sea level). They found that in the Dead Sea there is a significant attenuation of the shorter, more deleterious erythematous UVB (280 to 300 nm) and a mild attenuation of the larger therapeutic wavelengths (300 to 320 nm), resulting in an enhancement of the therapeutic/damaging ratio. Even-Paz et al. (38) determined that phototherapy in the Dead Sea can be shortened to 3 h/d (instead of the accepted 6 h/d schedule) during the months of March to November; thus, diminishing the actinic damage of the skin and the theoretic risk of skin neoplasia.

Using the data obtained from the study of sun radiation at the Dead Sea, enhanced protocols of phototherapy are being designed (39).

Dead Sea water balneotherapy and phototherapy for psoriasis have been demonstrated to be one of the most cost-effective treatments (40). It has been calculated that the annual cost of Dead Sea water balneotherapy and phototherapy is US$2300.

In another publication, Weinrauch (41) calculated that for the mean North American patient, including the treatment itself, round trip costs and the loss of working days, a 4-week treatment at the Dead Sea costs between US$4000 and US$5000 (prices estimated in 1996). Artificial Dead Sea water balneotherapy cost has been calculated in US$950 including medical consultation and 27 treatments (as in the German model). It can be further reduced by maintenance therapy once to twice weekly for 6 months (price around US$750). The additional benefit of artificial Dead Sea water balneotherapy is that it allows for the patients to continue being productive during their treatment (42). Table 2 summarizes the aforementioned investigations.

Rheumatological Diseases

Dead Sea water balneotherapy, Dead Sea springs' water balneotherapy-sulfur balneotherapy, and Dead Sea mud have been used extensively for rheumatic diseases, both inflammatory and noninflammatory.

Rheumatoid Arthritis

Sukenik and colleagues (43) treated 36 patients for 12 days at the Ein Gedi Dead Sea spa; the patients were divided into the 4 following groups: Dead Sea water balneotherapy ($n = 9$), sulfur baths ($n = 9$), Dead Sea water balneotherapy and sulfur baths ($n = 10$), no treatment ($n = 8$). The researcher was blind to the treatments given to the patients. There was a statistically significant improvement in clinical parameters in all 3 treatment groups that lasted for up to 3 months.

In another investigation by Sukenik and colleagues (44) Dead Sea mud was used to treat rheumatoid arthritis patients. The investigation took place in Be'er Sheva (315 m above sea level); for 14 days patients were treated in a double-blinded fashion with 40°C heated unaltered Dead Sea mud packs applied over the extremities, neck, and back for 20 minutes a day ($n = 14$) or with washed-out Dead Sea mud packs devoid of most minerals ($n = 14$). Statistically significant clinical improvement lasting 1 to 3 months was seen in the unaltered Dead Sea mud packs group.

In yet another investigation by Sukenik and colleagues (45), Dead Sea water treatment was tested to treat rheumatoid arthritis patients. This trial took place also in Be'er Sheva: for 14 days patients were treated in a double-blinded fashion with 35°C heated Dead Sea water baths for 20 minutes daily ($n = 15$) or with sodium chloride baths ($n = 15$). Statistically significant clinical improvement in most parameters and for up to 1 month was observed only in patients treated with Dead Sea water baths.

In a randomized prospective double-blinded investigation, Codish and colleagues (46) tested the therapeutic properties of microwave-heated unaltered Dead Sea mud compresses ($n = 22$) or washed-out and mineral-poor Dead Sea mud compresses ($n = 23$). The compresses were applied at the patients' home 5 times a week for 3 weeks (the patients lived in the Be'er Sheva area). In the unal-

Table 2 Publications Considered for the Evidence and Strength of Recommendation Analysis Regarding Psoriasis

Disease	Ref.	Study Design	Intervention/Design	Number of Patients	Results/Response
Psoriasis—dermatologic manifestations	(13)	Retrospective analysis	Dead Sea water balneotherapy and phototherapy	1448	Lesion clearing of 80%-100% seen in 88% of the patients
	(14)	Retrospective analysis	Dead Sea water balneotherapy and phototherapy	192	Total or almost total remission of psoriatic lesions in 73% of patients
	(20)	Prospective nonrandomized study	Dead Sea water balneotherapy and phototherapy	740	Total remission of psoriatic lesions in 70% of patients
	(23)	Prospective nonrandomized study	Dead Sea water balneotherapy and phototherapy	64	75.9% of the patients reached PASI 75
	(22)	Prospective nonrandomized study	Shorter term Dead Sea water balneotherapy and phototherapy: 2 wk instead of normal 4-wk treatment	85	55% of the patients achieved PASI 75 (lower than the remission rates achieved in 1-mo treatments)
	(21)	Retrospective analysis	Dead Sea water balneotherapy and phototherapy, 2 groups: patients with psoriasis onset under or over 40 years old	605	PASI 95 in 74% of the patients with psoriasis onset under 40 yr old, and in 62% of patients with psoriasis onset over 40 yr old
	(17)	Prospective nonrandomized multicenter study	Synchronous BalneoPhotoTherapy, according to protocol vs intention-to-treat basis	280 (according to protocol) 692 (intention-to-treat)	Psoriasis vulgaris patients had 71.4% improvement in the PASI score when assessed according to the protocol and 61% in an intention-to-treat basis
	(15)	Prospective randomized trial	Either device administered phototherapy alone (PT) or synchronous BalneoPhotoTherapy, sBPT: 35 sessions	367	Both treatments were effective but treatment with sBPT was statistically superior to PT both at the end of the treatment and at follow-up of up to 6 mo
	(4)	Prospective trial	Comparison of 3 treatments: only Dead Sea phototherapy, only Dead Sea water balneotherapy or combined therapy	81	The improvement as assessed by PASI score was 79% for only Dead Sea phototherapy, 22.1% for only Dead Sea water balneotherapy and 87% for the combined therapy
	(16)	Prospective randomized comparison	Patients treated with phototherapy and randomized to addition of Dead Sea salt solution soaks or no additional treatment	60	No added benefit of Dead Sea salt solution soaks
	(18)	Retrospective study	Synchronous BalneoPhotoTherapy in different types of psoriasis	373	Small-plaque psoriasis had a PASI decrease of 76.1%, guttate type 73.7%, large-plaque type 67.1%, and confluating type 62%
	(19)	Meta-analysis	Synchronous BalneoPhotoTherapy vs natural Dead Sea water balneotherapy and phototherapy	NA	Both treatments were effective for psoriasis and their results were comparable

tered Dead Sea mud compresses group, there was a significant reduction in the number of swollen and tender joints and patients' global assessment of pain lasting up to 1 month after the end of the therapy. In the washed-out and mineral-poor Dead Sea mud compresses group, the only improvement was a significant reduction in patient global assessment of joint pain.

Sukenik et al. (47) randomized 40 rheumatoid arthritis patients to be treated for 14 days with 1 of the following (single-blinded): Dead Sea mud packs ($n = 10$), sulfur baths ($n = 10$), Dead Sea mud packs and sulfur baths ($n = 10$), or no treatment ($n = 10$). Statistically significant improvement for up to 3 months was observed in the treatment groups in most clinical indexes but not in the erythrocyte sedimentation rates, levels of rheumatoid factor, or serum amyloid A.

Psoriatic Arthritis

In a noncontrolled prospective trial, Sukenik et al. (48) treated 166 psoriatic arthritis patients with Dead Sea water balneotherapy and phototherapy. One hundred forty-six patients received additional mud packs and sulfur baths treatment, whereas 20 received no additional treatment. After 3 weeks of treatment, significant improvement in clinical parameters was seen in both groups. However there was a significant reduction in spinal pain as well as an improvement in the range of movement of the lumbar spine seen only in the group that received additional mud packs and sulfur baths treatment.

Elkayam et al. (49) treated 42 psoriatic arthritis patients with daily Dead Sea water balneotherapy and phototherapy. Twenty-three patients were additionally treated with mud packs and sulfur baths. Nineteen patients did not receive additional therapy. In both groups there was a similar and significant improvement in morning stiffness, patient self-assessment, right and left grip, and axial skeleton movements. Improvement over time was better in the group with the addition of mud packs and sulfur baths.

In another noncontrolled prospective trial Sukenik et al. (50) treated 28 patients suffering from both psoriatic arthritis and fibromyalgia for 3.5 weeks with a combination of Dead Sea mudpacks, sulfur baths, Dead Sea water balneotherapy, and phototherapy. There was a significant reduction in morning stiffness, the number of inflamed joints, as well as tender points. No correlation was found between the improvement in the number of inflamed joints and the reduction in the number of tender fibromyalgia points.

Fibromyalgia

Buskila and colleagues (51) investigated the effect of sulfur baths in fibromyalgia patients. A randomized prospective trial of 10 days' treatment included 48 patients randomized to sulfur baths ($n = 24$) or no treatment ($n = 24$). There was a significant clinical improvement in the sulfur baths group. Pain, fatigue, stiffness, and anxiety improved in both groups but lasted longer in the sulfur baths group.

Neumann et al. (52) published a randomized prospective trial of treatment at a Dead Sea spa for 10 days in which 48 fibromyalgia patients were divided into 2 groups: sulfur baths treatment ($n = 24$) or no treatment ($n = 24$). Overall there was an improvement in the physical aspects of quality of life, which lasted around 3 months. However the psychological aspects of quality of life had a shorter improvement. Patients in the sulfur balneotherapy group reported higher and longer lasting improvement than patients in the no treatment group. Supporting these findings, Avriel and colleagues (53) found that the quality of life is better in communities in the Dead Sea region as compared to a similar community near the Dead Sea but situated at 600 m above sea level.

Ankylosing Spondylitis

Codish et al. (54) treated 28 ankylosing spondylitis patients in the Dead Sea in a randomized prospective researcher-blinded trial: 14 patients were treated with mud packs and sulfur pools, 14 patients used the fresh water pools. There was a significant improvement in the disease activity index and visual analog scale for pain and for spinal movement. Quality of life improved because of pain reduction in the mud packs and sulfur pool group.

Osteoarthritis

Sukenik et al. (55) investigated some Dead Sea spa treatments in knee osteoarthritis patients: 40 patients were randomized to 4 treatment groups, while the researcher remained blinded. The treatments were administered for 14 days. The patients were randomized to either sulfur baths ($n = 10$), Dead Sea water balneotherapy ($n = 10$), Dead Sea water balneotherapy and sulfur baths ($n = 10$), or no treatment ($n = 10$). A significant clinical improvement was seen in all 3 treatment groups.

In a prospective double-blinded trial that also took place in Beer Sheva, Flusser and colleagues (56) randomized knee osteoarthritis patients for a 3-week treatment with one of the following: unaltered Dead Sea mud compresses ($n = 40$) or washed-out and mineral-poor Dead Sea mud compresses ($n = 18$). A significant reduction in knee pain was observed in the unaltered Dead Sea mud group only. A reduction in the Lequesne index was seen at the end of therapy and a month after therapy in the unaltered Dead Sea mud group, while in the washed-out and mineral-poor Dead Sea mud group a reduction in the Lequesne index was only apparent at 1 and 3 months after therapy ended.

In yet another investigation by Sukenik and collaborators (57) knee osteoarthritis patients were randomized in a double-blind fashion to be treated for 14 days with either Dead Sea water baths ($n = 13$) or sodium chloride solution baths ($n = 13$). This investigation took place in

Be'er Sheva. At the end of the treatment period self-assessment of improvement was apparent only in the Dead Sea water baths group. In both groups there was a significant improvement of the index of severity of osteoarthritis at the end of treatment as well as 1 month later.

Sherman and collaborators (58) investigated the value of intermittent sulfur balneotherapy by randomizing 44 patients with knee osteoarthritis to be treated twice weekly for 6 consecutive weeks with balneotherapy at 35 to 36°C of either sulfur baths ($n = 24$) or tap water baths ($n = 20$). A statistically significant improvement of up to 6 months was seen in the sulfur treatment group for most of the clinical parameters. In the tap water group the only improvements were in the Short Form-36 bodily pain scale at 6 months, the Lequesne index at 1 month, and the WOMAC pain score at the end of the treatment period. It is interesting to note the importance of the intermittent therapy, which was able to produce significant clinical improvement while avoiding the costs of prolonged stay in the Dead Sea area (as usual treatment schedules call for) and allowing the patients to continue to perform their normal daily activities, which has added value from an economic point of view as well as because of improved compliance.

It should be noted that a number of the aforementioned trials, in rheumatic arthritis patients (44-46) as well as in osteoarthritis patients (56,57), were performed not at a Dead Sea location but in Be'er Sheva, which, although being the Dead Sea's closest large city, stands 315 m above the sea level and lacks the unique climatic environment of the Dead Sea. This was made with the intention of evaluating the therapeutic properties of the Dead Sea water and mud without the confounding factor of the other environmental features of a prolonged Dead Sea stay, among them its unique climate, higher barometric pressure, low humidity, and physical and psychological relaxation (3).

Possible explanations for the beneficial effects of Dead Sea water, sulfur baths, and Dead Sea mud have been proposed: an increased diuresis that may shrink inflamed tissues partially, increased production of ACTH and cortisol that may reduce inflammation, increased production of endorphins that may lead to a decrease in pain, increased vitamin D serum levels, transdermal absorption of magnesium and selenium that can replete their relative lack in the tissues, which has been reported in some inflammatory diseases (59-61), and, in addition, the benefit of the benign climate, rest, and lack of stress in the Dead Sea environment (3,62). Table 3 summarizes the aforementioned investigations.

Safety

Several factors inherent to the special environment of the Dead Sea have raised concerns of toxicity and safety, among them the possibility of actinic damage of the skin and its potential to induce neoplastic diseases. There are also concerns of toxicity from environmental and water salts (63) as well as concerns of hazardous hemodynamic changes and deleterious effects of the high barometric pressure. Investigations that have addressed these concerns are discussed in the next section.

Differences in the quantity and quality of UVB radiation in the Dead Sea compared with places above sea level have been reported for many years (64). The UVB radiation at the Dead Sea has a better safety profile because of the relative attenuation of the more damaging erythematous wavelengths (2,5,37). As a whole, UVB radiation is proportionally more attenuated than UVA radiation. Kushelevsky and colleagues (65) determined the UVB radiation absorbed by psoriatic patients during a 4-week stay at the Dead Sea and compared it to the UVB dose received by psoriatic patients also treated with climatotherapy in Sweden and Switzerland as well as in radiation cabins at 7 university clinics in several countries (Israel, USA, Germany, Sweden, Bulgaria, New Zealand, Switzerland). It was determined that the mean UVB exposure dose at the Dead Sea is one of the lowest reported for clearance of psoriatic plaques.

David et al. (66) published the results of a multicenter controlled cross-sectional study comparing 460 Israeli outpatient psoriatic patients with 738 control patients. Data about sun exposure habits including exposure in the Dead Sea were obtained. It was concluded that Dead Sea treatments in psoriatic patients were not associated with an increase in melanoma or nonmelanoma skin tumors. However, other actinic damage of the skin including elastosis, solar lentigines, poikiloderma, and facial wrinkles were significantly more common among patients with psoriasis. The severity of some of these actinic skin damages was even associated with the length of sun exposure. Further evidence to actinic skin damage was provided by Avriel and colleagues (53), who found that benign actinic skin damage was more prevalent in communities in the Dead Sea region as compared to similar communities around the Dead Sea. Interestingly there were no other differences in morbidity between these 2 populations. In a related investigation (67) the authors claim that actinic keratoses prevalence was even lower in psoriatic patients.

On the other hand Danish psoriatic patients treated in the Dead Sea had a higher risk for nonmelanoma skin cancer than the general population (68) in a large (1738 psoriatic patients) retrospective investigation.

Klein and colleagues (15) treated 367 patients with moderate to severe psoriasis with either device-administered PT or a combination of device-administered phototherapy and bathing in 10% Dead Sea salt solution (sBPT). The treatment was provided for a length of 35 sessions or until clearance of dermatologic manifestations. Three hundred fifty-nine patients underwent a safety analysis: skin erythema was present in 2.1% of patients who underwent sBPT and in 1.1% of those with PT, light dermatoses in 6.1% of sBPT and in 1.8% of PT. No

patient showed an increase in the number of melanocytic nevi during the follow-up of 6 months.

Concern about raising blood pressure during prolonged immersion in Dead Sea water as opposed to in fresh water (69) led to the suspicion that treatments in the Dead Sea could be contraindicated in hypertensives. Paradoxically, it has been observed for many years that hypertensive patients tend to lower their blood pressures during their stay in the Dead Sea (70).

In a prospective nonrandomized study, Gabizon et al. (71) followed 19 patients with congestive heart failure with New York Heart Association functional class II-III, after cardioverter defibrillator implantation. The patients traveled to the Dead Sea, stayed in a hotel environment as does every tourist, and returned home after a 4-day uneventful stay. Several parameters were assessed before, during, and after the Dead Sea stay. The quality-of-life score improved, and the 6-minute walk significantly increased by 63 m. B-type natriuretic peptide levels increased slightly with no statistical significance, and the heart rate variability significantly decreased. There were no significant changes in blood pressure, weight, blood oxygen saturation, or ejection fraction.

Paran and colleagues (72) studied blood pressure changes in 72 patients (both hypertensive and normotensive) that were treated in the Dead Sea during a 2-week stay because of rheumatic diseases. The patients were divided into 4 groups: balneotherapy in thermomineral pool ($n = 18$, sulfur pools at 35°C), balneotherapy in Dead Sea water ($n = 16$), a combination of the aforementioned balneotherapies ($n = 19$), and no balneotherapy as control ($n = 19$). In all the groups both hypertensive and normotensive patients demonstrated a decrease in blood pressure during their stay in the Dead Sea area. The exception was the hypertensive patients treated in the thermomineral pools, who showed a mild but significant increase in blood pressure.

Kushelevsky et al. and also Shani et al. observed reductions in blood pressure in groups of 1142 and 1366 hypertensive psoriatic patients (73,74).

All these studies concluded that hypertension is not a contraindication to Dead Sea treatments.

Bromide salt toxicity has been reported after months of deliberate ingestion of Dead Sea salts, leading to mental impairment, labile mood, and disorganized, slurred speech (75).

Abdel-Fattah and Pingitore investigated the composition of Dead Sea mud samples (from 3 spots in the Jordanian side of the Dead Sea) and found that minerals known to have toxic potential are present in concentrations below concern levels. In the same investigation, 16 commercial (and undisclosed) Dead Sea mud-based and mud-enhanced cosmetic products, which were purchased in Jordan and in the USA, were analyzed. In general, minerals were significantly diluted in these cosmetic products, with the exception of cadmium, which was found to have levels exceeding those in the plain Dead Sea mud samples in several of the commercial muds and in one facial mask. Overall, the authors conclude that there is no reason for concern regarding mineral toxicity from Dead Sea mud or Dead Sea mud-based products (76).

Dead Sea exposure has also been associated with thyrotoxicosis as claimed in a case report by Mueller et al. (77). The author suggests that Dead Sea environmental iodine was the cause of the thyrotoxicosis.

Dead Sea near-drowning was reported in 37 patients in whom swallowing of Dead Sea water led to hypercalcemia and hypermagnesemia with the corresponding electrocardiographic changes (78). In fact the accompanying hypercalcemia has been regarded as partially protective for the potentially fatal arrhythmic effects of severe hypermagnesemia (79).

Dead Sea water poisoning has been described in a series of 48 adult patients, leading to hypercalcemia and hypermagnesemia, cardiac rhythm disturbances, disturbed sensorium, and adult respiratory distress-like syndrome among other disorders. The mortality rate was 19% (80).

Addressing the potential oxidative stress of the higher oxygen pressure in the Dead Sea, Karadsheh et al. compared levels of antioxidant enzymes between residents of the Dead Sea (420 m below sea level, 794.7 mm Hg) and Amman (766 m above sea level, 697.5 mm Hg). Apart from catalase levels, which were equal in both populations, all other antioxidant enzymes (glutathione, superoxide dismutase, G6PD, 6-phosphogluconate dehydrogenase) were found to be lower in Dead Sea residents (81). Table 4 summarizes the aforementioned investigations.

DISCUSSION

Several investigations have been published on the benefits of the Dead Sea treatments in a large host of rheumatologic diseases and psoriasis.

In psoriasis, topical therapy of skin manifestations is based on glucocorticoid preparations and calcineurin inhibitors (82). UV light and psoralens are also used to treat psoriasis (4,83). Systemic therapies with methotrexate and retinoids combined with UV light are used for more extensive disease (84). Biologic agents like alefacept, efalizumab, etanercept, and infliximab are also used for extensive or unresponsive disease as well as for combined skin and joint disease (85). There is evidence (level B, class I) that Dead Sea water balneotherapy together with Dead Sea phototherapy is an effective treatment for several types of psoriasis. There is also evidence (level B, class IIa) that Dead Sea water balneotherapy has an additive benefit over the better known benefits of phototherapy. Similar benefits have been obtained using artificial Dead Sea water balneotherapy together with artificial phototherapy when compared to natural Dead Sea water balneotherapy and phototherapy (level B, class I). Shorter than 4-week Dead Sea water balneotherapy and phototherapy achieves only partial benefit when compared with standard 4-week therapy (level B, class I). Dead Sea water balneotherapy

Table 3 Publications Considered for the Evidence and Strength of Recommendation Analysis Regarding Arthritis

Disease	Ref.	Study Design	Intervention/Design	Number of Patients	Results/Response
Rheumatoid Arthritis	(43)	Randomized prospective single-blinded (researcher)	During 12-d patients treated with one of the following: Dead Sea water balneotherapy ($n = 9$) Sulfur baths ($n = 9$) Dead Sea water balneotherapy and sulfur baths ($n = 10$) No treatment ($n = 8$)	36	Statistically significant clinical improvement lasting up to 3 mo in all treatment groups
	(44)	Randomized prospective double-blinded	During 14-d patients treated with 40°C heated: Unaltered Dead Sea mud packs ($n = 14$) Or Washed-out and mineral-poor Dead Sea mud packs ($n = 14$)	28	Statistically significant clinical improvement lasting for 1-3 mo only in patients treated with unaltered Dead Sea mud packs
	(45)	Randomized prospective double-blinded	During 14-d patients treated with 35°C heated: Dead Sea water baths ($n = 15$) Or NaCl solution baths ($n = 15$)	30	Statistically significant clinical improvement in most parameters was observed only in patients treated with Dead Sea water baths for up to 1 mo
	(46)	Randomized prospective double-blinded	During 21-d patients treated with 30-35°C heated: Unaltered Dead sea mud compresses ($n = 22$) Or Washed-out and mineral-poor Dead Sea mud compresses ($n = 23$)	45	Significant reduction in the number of swollen and tender joints and patients' global assessment of pain in the unaltered Dead Sea mud compresses group, in the washed-out and mineral-poor Dead Sea Mud compresses group. There was only a significant reduction in patient global assessment of joint pain.
	(47)	Randomized prospective single-blinded (researcher)	During 14-d patients treated with one of: Dead Sea mud packs ($n = 10$) Sulfur Baths ($n = 10$) Dead Sea mud packs and sulfur baths ($n = 10$) No treatment ($n = 10$)	40	Statistically significant improvement for up to 3 mo was observed in the treatment groups in most clinical indexes
Psoriatic arthritis	(48)	Prospective trial	During 21 d all patients treated Dead Sea water balneotherapy and phototherapy. 20 patients received no additional therapy 146 patients received additional mud packs and sulfur baths treatment	166	Significant improvement in clinical parameters was seen in both groups. However there was also a significant reduction in spinal pain and range of movement of the lumbar spine seen only in the group that received additional mud packs and sulfur baths treatment
	(50)	Prospective trial	Patients suffering from both psoriatic arthritis and fibromyalgia were treated for 3.5 wk with Dead Sea mudpacks, sulfur baths, Dead Sea water balneotherapy, and phototherapy	28	There was a significant reduction in morning stiffness, in the number of inflamed joints, as well as in tender points

Table 3 Continued

Disease	Ref.	Study Design	Intervention/Design	Number of Patients	Results/Response
	(49)	Prospective trial	42 psoriatic arthritis patients were treated with daily Dead Sea water balneotherapy and phototherapy. 23 patients were additionally treated with mud packs and sulfur baths. 19 patients do not receive additional therapy	42	In both groups there was a similar and significant improvement in morning stiffness, patient self-assessment, right and left grip, and axial skeleton movements. Improvement over time was better in the group with the addition of mud packs and sulfur baths
Fibromyalgia	(50)		See same article in psoriatic arthritis section		
	(51)	Randomized prospective	Treatment at Dead Sea Spa for 10 d: Sulfur baths ($n = 24$) Or No treatment ($n = 24$)	48	There was a significant clinical improvement in sulfur baths group. Pain, fatigue, stiffness, and anxiety improved in both groups but lasted longer in the sulfur baths group
	(52)	Randomized prospective	Treatment at Dead Sea Spa for 10 d: sulfur baths ($n = 24$) Or no treatment ($n = 24$)	48	Overall improvement in physical aspects of quality of life for 3 mo. Psychological aspects of quality of life had a shorter improvement. Patients in the sulfur balneotherapy group reported higher and longer lasting improvement
Ankylosing spondylitis	(54)	Randomized prospective single-blinded (researcher)	14 patients treated with mud packs and sulfur pool in the Dead Sea, 14 patients used the fresh water pool in the Dead Sea.	28	Significant improvement in disease activity index, in visual analog scale for pain, and for spinal movement. Quality of life improved due to pain reduction in the mud packs and sulfur pool group
Osteoarthritis	(55)	Randomized prospective single-blinded (researcher)	During 14-d patients treated with one of the following: Sulphur Baths ($n = 10$) Dead Sea water balneotherapy ($n = 10$) Dead Sea water Balneotherapy and Sulphur baths ($n = 10$) No treatment ($n = 10$)	40	Significant clinical improvement in all treatment groups
	(56)	Randomized prospective double-blinded	For 3 wk knee osteoarthritis patients treated with one of the following: Unaltered Dead Sea mud compresses ($n = 40$) or Washed-out and mineral poor Dead Sea mud compresses ($n = 18$)	58	A significant reduction in knee pain was observed in the unaltered Dead Sea mud group only. A reduction in the Lequesne index was seen at the end of therapy and a month after therapy in the unaltered Dead Sea mud group, while in the washed-out and mineral poor Dead Sea mud group this was only patent at 1 and 3 mo after therapy ended
	(58)	Randomized prospective single-blinded (researcher)	Knee osteoarthritis patients treated intermittently twice weekly for 6 consecutive weeks with 35–36°C balneotherapy of: Sulfur baths ($n = 24$) or, Tap water ($n = 20$)	44	Significant improvement of up to 6 mo in the sulfur treatment group for most of the clinical parameters

Table 3 Continued

Disease	Ref.	Study Design	Intervention/Design	Number of Patients	Results/Response
	(57)	Randomized prospective double-blinded	During 14-d patients treated with 35°C heated: Dead Sea water baths (n = 13) Or NaCl solution baths (n = 13)	26	At the end of the treatment period self-assessment of improvement was patent only in the Dead Sea water baths group. In both groups there was significant improvement of the index of severity of osteoarthritis both at the end of treatment as well as 1 mo later

and phototherapy should be considered as a treatment for psoriasis due not only to its effectiveness but also to its safety profile, high patient satisfaction, and relatively low cost.

The treatment of rheumatoid arthritis may include disease-modifying antirheumatic drugs like methotrexate, leflunamide, and sulfasalazine (86). Several anti-tumor necrosis factor (TNF) drugs like infliximab, etanercept, and adalimumab as well as other biologic drugs like rituximab are used for progressive disease and increasingly early in the disease (87). Nonsteroidal anti-inflammatory drugs (NSAIDs) and systemic glucocorticoids are frequently used for flare-ups and as add-on medications, but their side effects severely counterbalance their usefulness. We found evidence that Dead Sea water balneotherapy (level B, class I), sulfur balneotherapy (level B, class I), and Dead Sea mud (level A, class I) are beneficial in rheumatoid arthritis.

Psoriatic arthritis is treated with disease-modifying antirheumatic drugs like methotrexate as well as with biologic anti-TNF drugs similarly as used in rheumatoid arthritis. The control of both skin and joint manifestations of psoriasis may be achieved with biologic drugs (88). As in rheumatoid arthritis, the use of NSAIDs and systemic glucocorticoids is common and also leads to limiting side effects. It has also been proven (level B, class I) that Dead Sea water balneotherapy, sulfur balneotherapy, and Dead Sea mud are beneficial in psoriatic arthritis.

Fibromyalgia treatment is based on thermal therapy, physiotherapy, behavioral changes, as well antidepressants like amitriptyline. The use of duloxetine (89) and pregabalin (90) has expanded the therapeutic options in this difficult-to-treat syndrome. However limited symptom improvement and side effects severely limit disease control. In fibromyalgia patients it has been demonstrated that Dead Sea sulfur balneotherapy can reduce symptoms (level B, class I).

The anti-TNF drugs adalimumab, etanercept, and infliximab are the cornerstone of ankylosing spondylitis treatment (91). However NSAIDs and glucocorticoids are used as add-on medications with their respective side effects limiting its use. In ankylosing spondylitis patients mud packs and Dead Sea sulfur balneotherapy demonstrated benefit (level B, class I).

Osteoarthritis is treated with analgesics, among them acetaminophen, NSAIDs (92), and intra-articular glucocorticoids. Nonpharmacologic therapy includes weight reduction, orthopedic devices, and surgical procedures including joint replacement. Regarding knee osteoarthritis, there is evidence that Dead Sea water balneotherapy (level B, class I), Dead Sea sulfur balneotherapy (level B, class I), and Dead Sea Mud (level B, class I) are beneficial.

These treatments should be considered complementary treatments for the aforementioned rheumatic diseases, with particular emphasis for those cases in which drug toxicity limits therapy, for incomplete responders, and for orphan diseases like fibromyalgia.

Table 4 Publications Considered for the Evidence and Strength of Recommendation Analysis Regarding Safety

Disease	Ref.	Study Design	Intervention/Design	Number of Patients	Results/Response
Skin neoplasia	(66)	Multicenter cross-sectional controlled study	Israeli outpatient psoriatic patients treated in the Dead Sea compared with control patients	460 psoriatic patients and 738 control patients	Dead Sea treatments in psoriatic patients were not associated with an increase in melanoma or nonmelanoma skin tumors
	(68)	Retrospective study	The registries of Danish psoriatic patients treated in the Dead Sea were searched for diagnosis of skin neoplasia	1738 psoriatic patients	Psoriatic patients who were treated among other treatments in the Dead Sea had a higher risk for nonmelanoma skin cancer than the general population
	(15)	Prospective study	Patients with moderate to severe psoriasis were treated during 35 sessions with either device administered phototherapy alone (PT) or a combination of device administered phototherapy and bathing in 10% Dead Sea salt solution	367 patients	No patient showed an increase in the number of melanocytic nevi during the follow-up of 6 mo
Skin actinic damage	(66)	Multicenter cross-sectional controlled study	Israeli outpatient psoriatic patients treated in the Dead Sea compared with control patients	460 psoriatic patients and 738 control patients	Nonneoplastic actinic damage of the skin including elastosis, solar lentigines, poikiloderma, and facial wrinkles were significantly more common among patients with psoriasis that underwent Dead Sea treatments
Hypertension	(71)	Prospective nonrandomized	Patients with congestive heart failure with New York Heart Association functional class 2-3, after cardioverter defibrillator implantation traveled to the Dead Sea for a 4-d stay and returned home	19 patients	Uneventful stay and journey with no significant changes in blood pressure
	(72)	Randomized prospective single-blinded (researcher)	Rheumatic patients (both hypertensive and normotensive) treated in the Dead Sea for 2 wks. Randomized to 4 groups: balneotherapy in thermomineral pool ($n = 18$, sulfur pools at 35°C), balneotherapy in Dead Sea water ($n = 16$), a combination of the aforementioned balneotherapies ($n = 19$) and no balneotherapy as control ($n = 19$)	72 patients	Decrease in blood pressure in all the groups with the exception of the hypertensive patients treated in the thermomineral pools who showed a mild but significant increase in blood pressure

Safety concerns have been raised in the past about the possibility of actinic and neoplastic damage of the skin in patients treated with phototherapy in the Dead Sea, as well as toxicity elicited by Dead Sea minerals because of Dead Sea balneotherapy or Dead Sea mud therapy.

We have reviewed evidence that Dead Sea phototherapy does not increase melanocytic nevi in the short term (6 months) (level B, Class I). Regarding an increase in the risk of nonmelanoma skin neoplasia in the long term in patients treated in the Dead Sea, a clear conclusion cannot be drawn from the current evidence (level C, class IIa). It seems that melanoma skin neoplasia in the long term is not increased in patients treated in the Dead Sea (level C, class I). Nonneoplastic skin actinic damage seems to be increased in patients treated in the Dead Sea (level C, class I).

It is clear that Dead Sea treatments do not lead to worsening of blood pressure, and there is evidence that there is even an improvement of blood pressure in patients treated in the Dead Sea (level B, class I).

From observational studies and case reports, we know that substantial ingestion of Dead Sea water (generally in near-drowning cases) is toxic and can result in hypercalcemia, hypermagnesemia, and rhythm disturbances. Use of Dead Sea salts for cooking is also contraindicated and may result in bromide toxicity. On the other hand, laboratory analysis of Dead Sea mud did not reveal mineral concentrations that could be a health concern for their intended use.

ACKNOWLEDGMENTS

Many thanks to Dr. Miriam Vered for the English proofreading.

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