

The Role of Trace Elements in Psoriatic Patients Undergoing Balneotherapy with Dead Sea Bath Salt

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Abstract

Background: A beneficial effect was observed in patients with psoriasis vulgaris following balneotherapy with Dead Sea bath salt.

Objectives: To evaluate the possible role of trace elements in the effectiveness of balneotherapy.

Methods: Serum levels of 11 trace elements were analyzed in 23 patients with psoriasis vulgaris who participated in a double-blind controlled study of balneotherapy with either Dead Sea bath salt (12 patients) or common salt (11 patients). Thirteen healthy volunteers served as controls.

Results: The mean pre-treatment serum levels of boron, cadmium, lithium and rubidium were significantly lower in patients compared to controls, whereas the mean pre-treatment serum level of manganese was significantly higher in patients compared to controls. Balneotherapy with Dead Sea bath salt resulted in a significant decrease ($P = 0.0051$) in the mean serum level of manganese from 0.10 ± 0.05 mol/L to 0.05 ± 0.02 μ mol/L. The mean reduction in the serum level of manganese differed significantly ($P = 0.002$) between responders (% Psoriasis Area and Severity Index score reduction ≥ 25) and non-responders (% PASI score reduction < 25). Following balneotherapy with Dead Sea bath salt the mean serum level of lithium decreased in responders by 0.01 ± 0.02 μ mol/L, whereas its level in non-responders increased by 0.03 ± 0.03 μ mol/L. ($P = 0.015$).

Conclusions: Manganese and lithium may play a role in the effectiveness of balneotherapy with Dead Sea bath salt for psoriasis.

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Spa therapy modalities employed at the Dead Sea area include heliotherapy (sun exposure), thalassotherapy (bathing in the Dead Sea water), balneotherapy (immersion in baths and pools

of thermomineral water), pelotherapy (heated Dead Sea mud pack therapy) and climatotherapy (a type of treatment utilizing the atmosphere, temperature, humidity, barometric pressure, and light [1,2]). It has been shown that sun exposure was the main factor producing beneficial results for psoriasis (plaque-type) in Dead Sea spa therapy. [3]

A beneficial effect has been attributed to bathing in Dead Sea water (which has a high content of minerals) and to immersion in baths and pools of thermomineral water in dermatology [1,2] and rheumatology [4,5], although the mechanisms involved have not been fully elucidated. Such mechanisms probably incorporate mechanical, thermal, chemical and immunomodulatory effects [6–9]. Elution of pro-inflammatory mediators from the affected skin [10] may be induced by spa therapy as well.

The chemical effects of the Dead Sea spa therapy in psoriasis were demonstrated by Shani et al. [11–17] by *in vitro* and *in vivo* studies involving humans and animals, which revealed increased levels of minerals. The possibility that Dead Sea minerals penetrate psoriatic skin has been suggested in view of significant elevations of four ions, Br, Rb, Ca, and Zn, in the serum of psoriatic patients following daily bathing in the Dead Sea for 4 weeks [11]. It has been shown that Dead Sea minerals penetrate psoriatic skin more than healthy skin, and that this penetration may occur even if diluted Dead Sea water is used [11]. Psoriatic keratinocytes obtained from patients treated with Dead Sea salt solution and mud revealed elevated mineral content while retaining normal structure [14,15]. Furthermore, it has been shown that the Dead Sea minerals (magnesium and potassium ions) have a specific inhibitory capacity on the uncontrolled proliferation of psoriatic dermis grown in tissue culture [17]. These data suggest that the therapeutic effect observed in psoriatic patients following Dead Sea spa therapy may be attributable, at least in part, to Dead Sea minerals, which may play a role in cell proliferation and differentiation [18].

A recent study that we conducted in patients with psoriasis vulgaris revealed a beneficial effect of balneotherapy with Dead Sea bath salt as compared to common salt [19]. The percent

PASI = Psoriasis Area and Severity Index

reduction in the Psoriasis Area and Severity Index score following balneotherapy with Dead Sea bath salt at the end of treatment (3 weeks) and 1 month later (34.8% and 43.6%, respectively) was higher than that recorded following balneotherapy with common salt (27.5% and 24%, respectively). We suggested that balneotherapy with Dead Sea bath salt may serve as an adjuvant therapy in psoriasis vulgaris. The exact mechanism responsible for the therapeutic effect observed in this type of balneotherapy is unknown. It has been proposed that minerals and trace elements (i.e., bromine, magnesium, lithium and rubidium) in the Dead Sea bath salt may play a role [11,12,18].

The aim of the present study was to clarify the possible role of trace elements in balneotherapy with Dead Sea bath salt for psoriasis.

Materials and Methods

The study group comprised 23 of 25 patients (15 males and 8 females, age range 20–73 years, mean age 45.8 ± 14.7 years) who participated in the previously reported double-blind controlled clinical study of balneotherapy for psoriasis [19]. The patients suffered from psoriasis vulgaris involving more than 15% body area. None of the patients had ischemic heart disease, severe hypertension or any other disease that disqualified them from bathing in accordance with the treatment protocol. None of the patients was being treated with lithium, beta-blocking agents, anti-malarial drugs or non-steroidal anti-inflammatory drugs, all of which are known to aggravate psoriasis. The patients were allocated randomly to two treatment groups, with baths of either Dead Sea bath salt (12 patients) or common salt (11 patients). The two types of salts were supplied in identical packets (one packet per bath), and neither the physician nor the patients knew which bath salt was being administered.

Dead Sea bath salt was supplied in packets of 5 kg per bath, while common salt was supplied in packets of 3 kg per bath, in an attempt to achieve a similar osmolality of about 3% in both groups. The Dead Sea bath salt and the common salt were composed of minerals (of which $MgCl_2$, KCl, $CaCl_2$, NaCl, were the major ones), trace elements and water, in varying concentrations [19]. The content of trace elements in the Dead Sea bath salt and the common salt, measured by inductively coupled plasma mass spectrometer (ICP-MS), is presented in Table 1.

The treatment protocol involved once-daily immersion of 20 minutes duration over 3 weeks of the whole body (except for the head) in the salt baths that were heated to 35°C. Immediately after the salt baths the patients washed themselves with tap water and lubricated their skin twice daily with white soft paraffin. In order to assess the net effect of balneotherapy, the patients were instructed to stop topical and systemic anti-psoriatic therapy, 2 and 4 weeks prior to starting the treatment protocol, respectively. During the treatment period, the patients were advised to avoid sun exposure. All patients were assessed

Table 1. The content of trace elements in Dead Sea bath salt and common salt

Trace element	Dead Sea bath salt (ppm)	Common salt (ppm)
Aluminium (Al)	3.7	0.28
Barium (Ba)	0.59	0.4
Boron (B)	2.6	1.2
Bromine (Br)	3500	520
Cadmium (Cd)	0.030	0.011
Chromium (Cr)	0.047	0.039
Cobalt (Co)	ND	ND
Copper (Cu)	0.057	0.025
Iron (Fe)	20.3	1.6
Lead (Pb)	<0.15	0.24
Lithium (Li)	1.0	<0.2
Manganese (Mn)	2.3	38
Nickel (Ni)	0.16	0.067
Rubidium (Rb)	250	<1
Strontium (Sr)	15.3	4.7
Vanadium (V)	<0.03	0.029
Zinc (Zn)	0.5	0.04

ND = not detected

by one dermatologist (H.G.) before commencing treatment and at its conclusion (end of week 3). Clinical evaluation was based on the Psoriasis Area and Severity Index score. The percent reduction of the PASI score after treatment was calculated according to the formula:

$$\frac{(\text{PASI score before treatment} - \text{PASI score at the end of treatment}) \times 100}{\text{PASI score before treatment}}$$

In view of the results of the former clinical study [19] (34.8% and 27.5%, mean percentage reduction in the PASI score following balneotherapy with Dead Sea bath salt or common salt, respectively), the response to balneotherapy was defined as follows:

responders = % PASI reduction \geq 25; non-responders = % PASI reduction < 25.

Analysis of trace elements

Determination of serum trace element concentrations was performed in 23 psoriatic patients before and after balneotherapy, as well as in 13 healthy volunteers who served as controls (6 males and 7 females; age range 30–55 years, mean age 46.5 ± 7.1 years).

Seven milliliters of blood were drawn from the patients and the controls, after cleansing of the skin with distilled water followed by 70% ethanol. Blood samples were left to clot at room temperature and then centrifuged at 1,500 rpm for 10 minutes. The separated serum was collected and stored in sterile plastic tubes at -70°C until used. Determination of serum concentrations of 11 trace elements was performed using the inductively coupled plasma mass spectrometer (ICP-MS). The laboratory technician was blinded to the study group affiliation

for each serum sample. The trace elements tested for were: aluminium (Al), boron (B), bromine (Br), cadmium (Cd), cobalt (Co), copper (Cu), lithium (Li), manganese (Mn), rubidium (Rb), strontium (Sr) and zinc (Zn).

The main outcome measure was the serum levels of trace elements in the two treatment groups and their association with clinical response. Statistical analysis was done using parametric or non-parametric methods, as appropriate.

Results

The mean age did not differ significantly between the 23 psoriatic patients and the 13 controls (45.8 ± 14.7 and 46.5 ± 7.1 years, respectively). Furthermore, the mean age (42.7 ± 16.1 and 49.1 ± 13.1 years, respectively), or pre-treatment PASI score (18.9 ± 9.3 and 14.4 ± 6.0 , respectively) did not differ significantly between the two study groups (12 psoriatic patients treated with Dead Sea bath salt and 11 psoriatic patients treated with common salt). The number of responders (% PASI reduction ≥ 25) was higher in patients treated with Dead Sea bath salt (7/12, 58%) as compared to patients treated with common salt (4/11, 36%), although the difference was not statistically significant ($P > 0.05$). Similarly, the mean \pm SD

percentage reduction in the PASI score calculated for psoriatic patients treated with Dead Sea bath salt and common salt (25.6 ± 33.7 and 28.2 ± 9.1 , respectively) did not differ significantly ($P > 0.05$, Mann-Whitney test).

The mean serum levels of the 11 trace elements analyzed in psoriatic patients before and after balneotherapy with Dead Sea bath salt or common salt, and in healthy controls, are presented in Table 2. The mean pre-treatment serum levels of boron, cadmium, lithium and rubidium were significantly lower ($P = 0.012$, $P = 0.0049$, $P = 0.018$, and $P < 0.001$, respectively) in psoriatic patients compared to controls, whereas the mean serum level of manganese was significantly higher in psoriatic patients compared to controls (0.09 ± 0.05 vs. 0.01 ± 0.003 $\mu\text{mol/L}$, respectively, $P < 0.001$).

Following balneotherapy with Dead Sea bath salt, the mean serum level of manganese decreased significantly from 0.10 ± 0.05 mol/L to 0.05 ± 0.02 $\mu\text{mol/L}$ ($P = 0.0051$, Wilcoxon test). The mean reduction in the serum level of manganese in patients treated with Dead Sea bath salt differed significantly ($P = 0.002$) between responders (0.02 ± 0.02 $\mu\text{mol/L}$) and non-responders (0.08 ± 0.02 $\mu\text{mol/L}$). The mean serum level of manganese was not affected significantly by balneotherapy with common salt.

Table 2. Mean serum levels of trace elements in psoriatic patients before and after balneotherapy with Dead Sea bath salt or common salt and in controls

Trace element ($\mu\text{mol/L}$)	Psoriatic patients before and after treatment with Dead Sea bath salt			Psoriatic patients before and after treatment with common salt			Psoriatic patients before treatment	Controls	P**
	Patients	Before (mean \pm SD)	After (mean \pm SD)	Patients	Before (mean \pm SD)	After (mean \pm SD)	Mean \pm SD	Mean \pm SD	
Al	8	0.06 ± 0.05	0.03 ± 0.02	7	0.03 ± 0.04	0.02 ± 0.01	0.05 ± 0.05	0.07 ± 0.06	>0.05
B	12	1.72 ± 0.84	1.33 ± 0.86	11	1.81 ± 0.89	1.53 ± 0.27	1.77 ± 0.85	2.53 ± 0.80	0.012
Br	12	93.9 ± 23.8	88.9 ± 13.8	11	93.9 ± 16.3	97.6 ± 17.5	93.9 ± 20.0	91.4 ± 23.8	>0.05
Cd	12	0.0003 ± 0.0002	0.0002 ± 0.0002	11	0.0002 ± 0.0002	0.0003 ± 0.0002	0.0002 ± 0.0002	0.0007 ± 0.0005	0.0049
Co	12	0.006 ± 0.002	0.007 ± 0.002	11	0.006 ± 0.003	0.006 ± 0.001	0.006 ± 0.002	0.007 ± 0.002	>0.05
Cu	12	12.2 ± 3.7	11.7 ± 3.0	11	13.3 ± 4.5	13.0 ± 2.9	12.7 ± 4.0	12.6 ± 2.7	>0.05
Li	12	0.08 ± 0.03	0.09 ± 0.03	10	0.10 ± 0.03	0.10 ± 0.03	0.09 ± 0.03	0.13 ± 0.06	0.018
Mn	11	0.10* ± 0.05	0.05* ± 0.02	8	0.09 ± 0.06	0.07 ± 0.02	0.09 ± 0.05	0.010 ± 0.003	<0.001
Rb	12	1.27 ± 0.31	1.27 ± 0.36	11	1.25 ± 0.42	1.26 ± 0.23	1.26 ± 0.36	1.80 ± 0.26	<0.001
Sr	12	0.45 ± 0.11	0.46 ± 0.10	11	0.60 ± 0.24	0.58 ± 0.19	0.52 ± 0.20	0.56 ± 0.13	>0.05
Zn	12	7.66 ± 1.38	7.88 ± 0.89	11	9.11 ± 3.27	9.22 ± 2.78	8.35 ± 2.52	9.47 ± 1.10	>0.05

* The mean serum level of Mn before treatment with Dead Sea bath salt differed significantly from the mean serum level of Mn after treatment with Dead Sea bath salt ($P = 0.0051$, Wilcoxon test).

** Comparison between the mean pre-treatment serum levels of trace elements in psoriatic patients and in healthy controls, using the *t*-test or Mann-Whitney test, as appropriate.

Following balneotherapy with Dead Sea bath salt, the mean serum level of lithium in responders decreased by 0.01 ± 0.02 $\mu\text{mol/L}$ (from 0.09 ± 0.03 to 0.08 ± 0.03 $\mu\text{mol/L}$), whereas its level in non-responders increased by 0.03 ± 0.03 $\mu\text{mol/L}$ (from 0.07 ± 0.03 to 0.1 ± 0.03 $\mu\text{mol/L}$) ($P = 0.015$). The mean serum level of lithium was not affected significantly by balneotherapy with common salt.

The mean serum levels of the other nine trace elements were not affected significantly by balneotherapy with either Dead Sea bath salt or common salt.

Discussion

Analysis of Dead Sea spa therapy modalities for psoriasis revealed that the mean percentage reduction in the PASI score was 28.4% in patients who only bathed in the Dead Sea water, 72.8% in those only sunbathing, and 83.4% in those doing both, i.e., bathing in Dead Sea water enhanced the effect of solar radiation [3]. The mean percentage reduction in the PASI score observed by us in psoriatic patients following balneotherapy with Dead Sea bath salt [19] was similar to the improvement observed in psoriatic patients who only bathed in the Dead Sea water [3].

The present study aimed to evaluate the possible role of trace elements in the effectiveness of balneotherapy with Dead Sea bath salt for psoriasis. The mean serum levels of the 11 trace elements studied in healthy controls were similar to reported levels for the general adult population [20]. Decreased mean pre-treatment levels of boron, cadmium and rubidium were recorded in psoriatic patients compared to controls. The role of boron in psoriasis is obscure. Cadmium, a carcinogenic metal that is involved in gene regulation and cellular signaling pathways, may play a role in the pathogenesis of psoriasis. The decreased mean serum levels of rubidium recorded in patients suffering from psoriasis, a proliferative disorder of keratinocytes, may be analogous to decreased levels of rubidium recorded in the whole blood of 13 patients with colorectal cancer as compared to 10 normal controls [21].

The significant increase in the mean pre-treatment serum level of manganese, recorded by us in 23 psoriatic patients compared to 13 healthy controls, has been reported previously by Fidarov [22] in 30 psoriatic patients compared to 40 healthy controls. The mean serum level of manganese decreased in our psoriatic patients following balneotherapy with Dead Sea bath salt, but not following balneotherapy with common salt. Furthermore, the mean reduction in the serum level of manganese in patients treated with Dead Sea bath salt differed significantly between responders and non-responders. The mechanism responsible for the decreased serum manganese level in psoriatic patients following balneotherapy with Dead Sea bath salt is not clear. This trend is consistent with the low content of manganese in Dead Sea bath salt (2.3 parts per million) as compared to common salt (38 ppm). Previous

reports revealed decreased serum or blood manganese levels in psoriatic patients whose condition improved or achieved clinical remission following treatment [22]. Significantly diminished manganese levels were found also in psoriatic skin (involved and uninvolved) compared to normal skin [23]. Serum manganese levels in psoriatic patients may reflect the activity of manganese superoxide dismutase in psoriatic skin, an enzyme postulated to have a role in cell differentiation and proliferation. Accordingly, the decreased mean serum manganese levels recorded in psoriatic patients following balneotherapy with Dead Sea bath salt may merely represent an epiphenomenon, related to the enhanced clinical improvement induced by Dead Sea bath salt (58% responders) as compared to common salt (36% responders).

The trend towards increased serum levels of lithium in non-responders as compared to decreased serum levels of lithium in responders following balneotherapy with Dead Sea bath salt is consistent with the role of lithium in the induction of new-onset psoriasis or exacerbation of pre-existing psoriasis [24]. This role involves molecular mechanisms such as the adenylate cyclase system, the inositol pathway, and release of inflammatory cytokines. Increased serum levels of lithium following balneotherapy with Dead Sea bath salt may imply the possibility of transcutaneous absorption of lithium from the salt. This possibility is consistent with the high concentration of lithium in Dead Sea bath salt (1.0 ppm) compared to common salt (< 0.2 ppm). Yet, transcutaneous absorption of lithium ion from spa water containing lithium ion (40 ± 5 ppm) did not occur in healthy subjects [25]. Although the exact components of the Dead Sea bath salt, which are responsible for its therapeutic effects, are still obscure, the present study implies that elution of lithium from the salt may enhance its therapeutic properties. The low mean pre-treatment serum level of lithium recorded in psoriatic patients compared to healthy controls is not clear and may reflect homeostatic compensatory responses.

It may be argued that alterations in trace elements may merely reflect the influence of dietary intake [20], and that controlled dietary conditions are necessary. However, the average basal or normative requirements for manganese could not be established. Furthermore, the overall manganese balance was not significantly affected by differences in dietary fiber, which is believed to have the greatest negative effect on manganese bioavailability [20].

A major source of dietary intake of lithium ion is drinking water. Accordingly, dietary influences on the serum levels of lithium are not expected in patients included in our study who, being residents of the same area, were drinking from the same water sources [25].

In conclusion, alterations in manganese and lithium may play a role in the effectiveness of balneotherapy with Dead Sea bath salt for psoriasis. In view of the small sample size, further investigation is needed. Analysis of the concentrations of trace elements in the skin itself may further clarify the role of trace elements in the pathogenesis of psoriasis and in the effectiveness of Dead Sea spa therapy.

ppm = parts per million

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