Climatotherapy of Skin Diseases at the Dead Sea – an update

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Abstract
Introduction: The Dead Sea area attracts yearly thousands of patients suffering from chronic skin diseases and Climatotherapy protocols and treatments are now well developed and scientifically proven. Sun exposure is the most effective component for the treatment of skin diseases at the Dead Sea, and was recognized as such long ago. This region benefits from a specific reduction of ultraviolet (UV) radiation predominant for the UV-B rays with a wavelength shorter than 300 nm. Dead Sea baths exert an additional proven beneficial effect on Psoriasis and Psoriatic Arthritis, but also on Atopic Eczema and Vitiligo.
Material and Methods: The latest studies dealing with the influence of Dead Sea Climatotherapy on skin diseases were reviewed and analyzed.
Results: Numerous studies in vivo and in vitro demonstrated the success of this method, but it seems important to distinguish the beneficial effects of the natural balneo-phototherapy practiced in unique psychological ambiance and exceptional bioclimatic conditions from those obtained by artificial balneo-phototherapy.
Conclusion: More than 4 decades after being studied, Dead Sea Climatotherapy can be considered now as a natural and simple dermatological treatment, highly effective and free of side effects, that requires, in order to obtain optimal results, a medical and individualized follow-up for each patient.

Key words: Dead Sea, Climatotherapy, Psoriasis, Atopic Dermatitis, Vitiligo.

Climatoterapia de las enfermedades de la Piel en el Mar Muerto - una Actualización

Resumen
Introducción: La zona del Mar Muerto atrae cada año a miles de pacientes que sufren enfermedades crónicas de la piel y los protocolos de climatoterapia y tratamientos están bien desarrollados y probados científicamente. En el Mar Muerto la exposición al sol es el componente más efectivo para el tratamiento de las enfermedades de la piel, y fue reconocido como tal hace mucho tiempo. Esta región se beneficia de una reducción específica de la

radiación ultravioleta (UV), principalmente de los rayos UV-B con una longitud de onda más corta de 300 nm. Los Baños del Mar Muerto ejercen un efecto adicional probadamente beneficioso sobre la psoriasis y artritis psoriásica, y también sobre el eczema atópico y el Vitíligo.
Material y Métodos: Se han revisados y analizados los últimos estudios que se ocupan de la influencia de Climatoterapia del Mar Muerto en las enfermedades de la piel.
Resultados: Numerosos estudios in vivo e in vitro han demostrado el éxito de este método, pero parece importante distinguir entre los efectos beneficiosos de la balneo-fototerapia natural, practicada en un ambiente psicológicamente único y en excepcionales condiciones bioclimáticas, y los obtenidos por medio de la, balneo fototerapia artificial.
Conclusión: Más de 4 décadas después de haber sido estudiada, la Climatoterapia del Mar Muerto puede ser considerada ahora como un tratamiento dermatológico natural y sencillo, altamente eficaz y libre de efectos secundarios, que requiere, a fin de obtener resultados óptimos, un seguimiento médico e individualizado de cada paciente.

Palabras clave: Mar Muerto, Climatoterapia, Psoriasis, Dermatitis atópica, Vitíligo.

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INTRODUCTION

For over 40 years, the shores of the Dead Sea are home to many patients with skin diseases or rheumatic diseases, full of confidence and hope in this "miraculous" therapy, seeking relief for their chronic symptoms. Almost all of them indeed leave this area with a greatly improved quality of life, and often for a long remission of their disease[1-2]. This "natural" therapy has repeatedly been the subject of scientific and clinical studies, reporting and confirming its outstanding success.

Located less than 400 meters below sea level, the basin of the Dead Sea is known throughout the years of special geo-climatic conditions[3]. The dominant factors in this region are primarily weather, with high and stable temperatures, a low relative humidity and atmospheric pressure relatively higher than that of sea level Table 1. However, the therapeutic factors are mostly photo-biological, with the presence of a specific attenuation of the ultraviolet radiation (UV), predominant on smaller UVB wavelength, below 300 nm.

As a central element of the array, the Dead Sea is a hyper-saline terminal lake, with unique composition and concentration of salts Table 2. The presence of hot springs mineral waters highly enriched in magnesium, a sludge "marine" black accumulating deposition at the seabed, and an increased concentration of bromine in the atmosphere and selenium in waters complete the analytical description of this region and the list of the active principles of the therapy.

Table 1 - Climatic factors at the Dead Sea: monthly averages.

	Maximal Temperature Cº	Minimal Temperature Cº	Delta Cº	Relative Humidity %	Water Temperature Cº
Jan	*20*	*11*	9	43.5	20
Feb	22	13	9	**48.9**	*18*
Mar	25	16	9	40.9	21.5
Apr	29	20	9	39.5	24.5
May	34	24	10	*34.5*	33
Jun	37	27	10	38.5	34
Jul	**39**	28	11	37.2	**35**
Aug	38	**29**	9	40.3	**35**
Sep	36	27	9	42.6	33.5
Oct	32	24	8	45.8	32
Nov	27	18	99	42.1	25
Dec	22	13	9	46.2	22

PSORIASIS TREATMENT AT THE DEAD SEA

SUN EXPOSURE

Protocols

Sun exposure represents the most effective component of the treatment and was recognized as such for a long time. Standard protocols for psoriasis heliotherapy provided 6-7 hours of daily exposure (progressively reached), for a period of 28 days. These protocols also advocated the distribution of exposure time of 2 time slots of "work" morning and afternoon, avoiding the noon hours. However, later publications defined the optimal time to stay at the Dead Sea between 2 and 4 weeks[4-5]. Furthermore, a study published in 1996 demonstrated the effectiveness of three hours only of daily exposure during the months of July and August[6-7]. In fact,

Table 2 - Comparison of minerals concentrations (in mg/L).

	Dead Sea (1)	*Mediterranean Sea (2)*	*Ratio 1/2*	*Ocean (3)*	*Quotient 1/3*
Chloride	224,000	22,900	9.8	19,000	11.8
Magnesium	44,000	1,490	29.5	1,350	32.6
Sodium	40,100	12,700	3.1	10,500	3.8
Calcium	17,200	470	36.6	400	36.6
Potassium	7,650	470	16.3	390	19.6

this controversy was resolved through the work of Kudish et al.[3] in particular, showing the importance of calculating the dose of UVB produced by sun exposure, and not relying on the length of exposition.

Solar exposure protocols are now controlled by doctors and adapted to each patient depending on skin type and according to the prescribed amount of UVB. These regimens, similar to those used in phototherapy, advocate usually 0.7 MED (minimal erythema dose) for the first day and increase up to 3 or 4 MED per day. These doses are usually calculated using software that transforms raw data into MED intensities of UVB expressed in joules, depending on the type of patient's skin. These doses are not only varying with the months of the year but also depend on the chosen time for sun exposure. They were the subject of a recently published review[8].

Results

Retrospective studies have demonstrated the impressive positive results achieved by patients receiving several hours of exposure per day and by regularly bathing in the Dead Sea and reported long periods of remission after treatment[1].

Recently, a prospective study over a period of 1 year was conducted in cooperation between a German and an Israeli team, in order to quantify the short-and long-term treatment at the Dead Sea climate on plaque psoriasis[9]. The 64 German patients were followed for 4 weeks at the Dead Sea and then reviewed by their dermatologist to control their condition, in Germany. Their PASI (Psoriasis Assessment of Severity Index) has been greatly improved at the end of stay (mean baseline PASI 31.7 ± 7.1 and final 1.4 ± 1.9) and 75.9% of patients achieved an improvement over 75% (PASI 75) after 4 weeks of treatment. The average duration of remission (defined as PASI 50: state in which the severity of lesions of the patient is still half

of that which prevailed prior to treatment) was 33 weeks. The younger age of patients was significantly correlated with better outcomes and a longer remission. This study demonstrated short and long term efficacy after climatic treatment of 4 weeks at the Dead Sea in patients with plaque psoriasis. These results are - at least - comparable to those obtained by the various options currently available[9].

More recently, a new study confirmed again these results. The files of 605 patients who were suffering from plaque psoriasis and treated at the Dead Sea for 4 weeks were retrieved from the database of the Research Institute at the Dead Sea (RIDS) and divided in two groups, types I and II, according to whether the age at the onset of the disease was under or over 40 years, respectively. The primary outcome for the assessment of DSC was Psoriasis Assessment of Severity Index of 95 (PASI 95), which indicates that the PASI improvement percentage reached 95%. By the end of the study, 74% of the patients in group 1 reached PASI 95 in comparison to 62% in group 2. These efficacy rates are impressively high for plaque pso-riasis patients[10].

Theoretical side effects

Protocols using extended periods and cumulative sun exposure caused much criticism, especially regarding the possible increased risk of developing skin cancer or other actinic lesions. In a multicenter Israeli study including 460 patients; it was not found to significantly increase the risk for skin neoplasm[11]. However, the existence of lesions caused by sun, as elastosis, solar lentigo and wrinkles, was significantly increased in patients with psoriasis who received treatment at the Dead Sea climate.

Recently, a retrospective study of children with psoriasis demonstrated the efficacy and safety of the climatic treatment at the Dead Sea, using conventional protocols suitable for young patients[12].

IMMERSION IN THE DEAD SEA

The Dead Sea baths exert a beneficial effect on psoriasis and psoriatic arthritis. The standard protocol includes two daily baths, with duration of 5 minutes the first day, reaching 30 minutes at the end of treatment, in increments of 5 additional minutes every 3 days. Other authors recommend more frequent baths, but for a period not exceeding 20 minutes. It is important to calculate the time of therapy to assess correctly the UVB cumulative dose received by the patient at the end of treatment.

Since 1985, the chemical effects of Dead Sea salts have been demonstrated in vitro on healthy skin and psoriatic skin, by the team of Shani et al. and many others[13-16].

In vivo observations demonstrate the increased serum concentrations of bromine, rubidium, calcium and zinc in patients with psoriasis, after 4 weeks during which they had made a swim daily.

Thus, one could hypothesize epidermal absorption of minerals from the Dead Sea through intact skin or damage. However, some authors note that the absorption is lower in healthy skin and it is still possible with mineral concentrations lower than those found in the Dead Sea[14].

Another study[15] showed an increased concentration of minerals in the keratinocytes cells of psoriasis patients and normalization of cellular structures are maintained after exposure to Dead Sea salts in solution or after exposure to mineral slurries. Finally, inhibition of dermal cell proliferation was demonstrated in vitro by the presence of two minerals in the waters of the Dead Sea magnesium and potassium[16].

Clinical studies have also focused on the therapeutic properties of Dead Sea waters. A study published by Even Paz et al.[17] demonstrated the increased efficiency of climatotherapy with the addition of daily baths, in patients with plaque psoriasis. Three groups of patients were subjected for 4 weeks on a program consisting: 1) sea bathing only 2) sun exposure only and 3) sea and sun bathing. The percentage improvements in PASI were respectively 28.4% for the sea, 72.8 % for the sun and 83.4% for the combination of both methods. Thus, balneotherapy significantly improved the results obtained by the simple light therapy as demonstrated later by the Schempp team for artificial light therapy[14]. Finally, very recently, the simultaneous use of (artificial) Dead Sea salts has been shown to be able to improve very significantly (more than 49%) the results of UVB treatment[18].

A prospective multi-stage, double-blind study against placebo published by Halevy[19] has focused on the clinical and biochemical changes caused by Dead Sea salt bath. Performed outside of the Dead Sea, this work helped define the consequences of repeated daily immersion in hypertonic saline in patients with plaque psoriasis. The 25 patients were randomized and divided in 2 groups, at a spa using Dead Sea salt or table salt, for the control group, during 3 weeks. Local and systemic treatments were suspended before the start of the study and throughout its duration. PASI values in the treated group were improved modestly, giving further evidence of the beneficial effect of balneotherapy using Dead Sea salts for plaque psoriasis.

In another hand, four years after the publication of Léauté-Labrèze[20], Dawe et al. published in 2005 a randomized, comparative, double-blind study, demonstrating no significant difference between the results obtained after UVB narrowband phototherapy with or without prior immersion of psoriasis patients in saline[21]. In their comments on this work, Gambichler et al. admit that there is no need to use the spatherapy as an alternative to conventional phototherapy. However, they justify its use in major sites for its realization, close to natural resources, despite the lack of statistical evidence for such therapy[22]. However, another German randomized, compara-

tive, double-blind study, came to contradict these conclusions, clearly demonstrating the superiority of the spa-therapy in routine dermatological practice[23].

One should note that these studies are based on immersion in saline solutions at different concentrations, usually lower than those present in the Dead Sea Lake and still very different from those used during natural balneotherapy. Moreover, it seems essential to distinguish the beneficial effects of natural-spa-therapy from those obtained by artificial climatotherapy, practiced in quite different psychological and bioclimatic conditions. Therefore, we should remember that the complexity of potential therapeutic mechanisms involved during Dead Sea Climatotherapy does not allow us to conclude definitively on their intrinsic properties.

Recent research and progress

In the study by Halevy et al. cited above[19], plasma concentrations trace elements have been controlled before and after therapy, in both patients and 13 healthy volunteers. The manganese concentration, higher in patients before therapy, has decreased after treatment in patients, especially since they had a better therapeutic response clinic. The concentration of lithium had decreased after treatment by patients which improved while it increased in those who had no good clinical outcome finding[24].

What could be the meaning of these changes? An early answer lies in the results studies showing correlations between the fall in serum manganese levels and the clinical improvement of patients with psoriasis. The low concentrations of manganese in the dermal and epidermal cells of affected or healthy skin of patients with psoriasis compared to those described in healthy subjects was also demonstrated. It thus appears that the serum concentration of manganese may reflect the proliferative activity or differentiation psoriatic cells.

Lithium, meanwhile, is recognized long as a factor initiating, maintaining or exacerbating psoriasis, through various molecular processes. Its presence in the Dead Sea salts could be of particular interest in the treatment of this disease, although a possible mechanism action is not yet very clear.

The affected skin biopsies, performed during this same study, have showed after treatment slight histological and immune-histochemical changes in the dermis, more pronounced when the improvement clinic was more evident.

The conclusions of this important study emphasize the possible intervention of Dead Sea salts in the chemical signals responsible for the proliferation and cell inflammation present in the skin of patients with plaque psoriasis.

In a study conducted by another Israeli team[25], the influence of the Dead Sea climate treatment could be demonstrated by 27 patients with psoriasis vulgaris, treated for 28 consecutive days by solar exposure and sea bathing. Clinical improvement, demonstrated by lower PASI scores, was accompanied by normalization

of epidermal pathologic parameters (differentiation and expression of cell keratin 16) and in a decreased T lymphocyte activity.

The latest studies carried out at the Dead Sea on the treatment of psoriasis introduce a new dimension in research on the therapeutic possibilities of climatotherapy. They demonstrate the beneficial influence but also the specificity and uniqueness of this treatment on the expression of many genes. In a study recently published[26], epidermal genetic profiles of patients with psoriasis were analyzed before and after phototherapy and Climatotherapy in order to identify cellular mechanisms involved in these two similar therapies. Three patients followed a standard protocol of 3 weeks at the Dead Sea and three other were treated with 20 to 27 sessions of narrow-band UVB phototherapy. Biopsies of epidermis, analyzed by micro-array, allowed identifying 248 genes whose expression was influenced by heliotherapy at the Dead Sea while only in 116 the expression was changed after artificial phototherapy. In addition, a specific gene, the IGFBP7 (Insulin-Like Growth Factor-Binding Protein-7), has been identified as under-expressed in patients compared with healthy subjects, and significantly normalized after treatment.

A confirmation of this work was recently published by the team of Sprecher[27]. His study conclusions allow positioning the IGFBP7 as a specific proliferation and differentiation regulatory gene of keratinocytes, suggesting a therapeutic potential for this protein in papulo-squamous diseases such as psoriasis.

TREATMENT OF ATOPIC ECZEMA (ATOPIC DERMATITIS, AD) AT THE DEAD SEA

Several publications report the beneficial effects of climatic treatment at the Dead Sea in this indication. In a clinical retrospective study unpublished on 1408 cases, excellent results were observed after 4 to 6 weeks of treatment in the vast majority of cases. The improvement in clinical signs and itch occurred within the first week.

In another study[28], 56 patients (Including 18 children) followed the standard heliotherapy and spa protocol, with diluted seawater associated with topical therapy based on emollients. The clinical evaluation through SCORAD evaluation was clearly demonstrated.

In a retrospective study of 1718 cases[29], the clinical results were correlated with demographic parameters of the population. An improvement of over 95% could thus be positively associated with the presence of a climatic treatment anterior and a treatment time longer than 4 weeks. Daily sun exposure mean did not exceeded five hours in this series, and the degree of skin involvement had no influence on the results. This study did not show evidence of notable side effects and the authors conclude on the very interesting cost-effectiveness profile of this method, when all economic factors are taken into account[29].

Immersion in a solution containing Dead Sea salts normalizes the functions of absorption of the skin in patients with atopic eczema. In a comparative study, using tap water, saline solution has been shown to efficiently improve hydration of the skin and decrease its redness and roughness. The authors designate magnesium as responsible these changes, reminding its hydrophilic properties but also anti-proliferative and beneficial effects on the epidermal barrier[30].

Recently, the combination of balneotherapy and artificial phototherapy has been proven more effective than phototherapy alone. In a study conducted by a German team[31], the difference between the results reached by the two methods was over 26% in favor of immersion prior in a solution of sea salt Dead. Further clinical studies, based on data collected at the Dead Sea and confirming these results have been recently published, showing clearly that Dead Sea Climatotherapy is a particularly effective treatment method for the sub-population of adults with severe AD[32].

The files of 78 European patients (37 male, 41 female, mean age 37.8 years) with AD undergoing DSC were included in this retrospective study. Demographic and clinical parameters as well as treatment characteristics - maximal and cumulative sun exposure doses - were recorded. SCORAD 75 was defined as ≥75% decrease in SCORAD values following therapy. After an average of 30 days of treatment, mean SCORAD values dropped from 50.5 to 11 (76.7%, $P < 0.001$). 64.1% of all patients, regardless of sub-group, reached SCORAD 75, whereas 78.9% of patients with severe disease achieved this result. In a multivariate logistic regression, factors associated with achieving SCORAD 75 were maximal sun exposure, family history of AD and age at disease onset ($P = 0.002$, $P = 0.009$ and $P = 0.040$ respectively).

CLIMATIC TREATMENT FOR VITILIGO AT THE DEAD SEA

To date, only few publications report the beneficial effects of treatment in this indication, discovered fortuitously twenty years ago, by means of a patient suffering simultaneously from psoriasis and vitiligo, returning regularly at the Dead Sea for clearing its psoriasis lesions. The positive effects on the white patches were identified and controlled by his doctor in Germany.

The first clinical study was published in 1994 and involved 102 patients treated and followed for a period of 4 to 6 weeks: 11% of patients have been completely improved, 82% of them showed a clear re-pigmentation at the end of treatment and only 6% presented a modest result while ten patients did not show any change on any of their lesions[33].

The presence of low concentrations of catalase in the epidermis of patients with vitiligo has been considered as major factor of the disease. In presence of an oxidative stress, especially related to high concentrations of hydrogen peroxide, catalase is considered as a potent stress controller. The simultaneous use of a cream contain-

ning a pseudocatalase during climate treatment of 21 days at the Dead Sea allowed a fast re-pigmentation[34]. However, the therapeutic effect in the climatotherapy "alone" on Vitiligo patients could also be identified in this study.

A retrospective study of 436 patients treated at the Dead Sea has definitely set this method to its place in the very limited options available for dermatologists[35]. After treatment of 4 weeks, 3.9% of patients showed already significant re-pigmentation (defined by more than 50% pigmented surface in more than half of total lesions count), 81.4% good response (defined by start of the process of re-pigmentation), 13.1% simple sustainable redness in their lesions and finally 1.6% had no change. These results have been evaluated immediately after the end of stay at the Dead Sea and do not account for possible delayed and long-term therapy effects. They show however a clear difference compared to conventional methods.

In a prospective, nonrandomized and with healthy controls, Schallreuter and colleagues report the benefits in climatotherapy group at the Dead Sea based criteria defining quality of life patients[36]. Improvements scores were observed after 20 days and 1 year after treatment allowing the authors to advise strongly this type of treatment.

There are undoubtedly inherent disadvantages in this treatment modality, as a result of having to stay at the Dead Sea 3 to 4 weeks, to allow at least three consecutive treatments and often forego any refund from medical insurance. However, doing a "natural" treatment with the hope to see this aesthetic disgrace (so often associated with chronic depression and mood disorders) finally defeated drive more and more patients to consider this medical destination.

CONCLUSION

The effectiveness of the climatic treatment at the Dead Sea is clearly demonstrated by clinical and laboratory studies in two major dermatological indications: Psoriasis and Atopic Eczema. It is necessary to conduct further studies for Vitiligo and other disorders treated at the Dead Sea, before including them into the list of proven indications. Balneo-phototherapy at the Dead Sea is a classical and well known treatment, natural, simple, effective and without side effects. However, this therapeutic option still requires careful monitoring by an experienced medical team, for each patient.

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