Climatotherapy at the Dead Sea for psoriasis is a highly effective anti-inflammatory treatment in the short term: An immunohistochemical study

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Abstract
Climatotherapy is a well-described treatment of psoriasis. Dead Sea climatotherapy (DSC) in Israel consists of intensive sun and Dead Sea bathing and is very effective in improving clinical and patient-reported outcomes. However, the effect of DSC has not been widely studied. We aimed to investigate the effect of DSC on psoriasis skin using quantitative immunohistochemistry techniques and analysis of blood samples. Skin punch biopsies from 18 psoriasis patients from a previous cohort study were used. Biopsies were obtained from non-lesional skin and from a psoriasis target lesion at baseline. A biopsy was acquired from the target lesion after DSC. Among patients who achieved complete visual clearance, a biopsy was also obtained at relapse. Blood samples were obtained at the same time points. We performed haematoxylin and eosin staining and quantitative immunohistochemical analysis of CD3, CD4, CD8, CD11c, CD103, CD163, CD207, forkhead box P3, Ki67 and myeloperoxidase. We performed blood tests of cholesterol, c-reactive protein, glucose, haemoglobin A1c and triglycerides. All skin biomarkers except for CD207 were decreased after DSC. At relapse, none of the biomarkers were significantly different from the baseline lesional measurements. Total CD207 staining correlated with psoriasis area and severity index at baseline while CD163 staining correlated with psoriasis area and severity index at EOT. No changes were observed in selected blood tests during the study. Consistent with clinical results, DSC is highly effective in the short term almost normalising all investigated biomarkers. However, at relapse, biomarkers were upregulated to the baseline level.

KEYWORDS
heliotherapy, immunohistochemistry, inflammation, phototherapy, psoriasis

Abbreviations: CD, cluster of differentiation; CRP, c-reactive protein; DC, dendritic cell; DSC, Dead Sea climatotherapy; EOT, end of treatment; FOXP3, forkhead box P3; HBA1c, haemoglobin A1c; HE, haematoxylin and eosin; IL, interleukin; LC, Langerhans cell; LS, lesional; MPO, myeloperoxidase; NL, non-lesional; PASI, Psoriasis Area and Severity Index; TRM, tissue-resident memory T cell; UV, ultraviolet; UVA, ultraviolet A; UVB, ultraviolet B.

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1 | INTRODUCTION

Psoriasis is a common, chronic skin disease that has considerable impact on the health and quality of life of the people affected. Psoriasis is most often characterised by well-delineated dry and silvery-white scaly plaques. It is more than “skin deep” and is associated with several serious systemic manifestations such as cardiovascular disease, stress and depression. The pathogenesis of psoriasis is not fully elucidated. However, T cells and associated cytokines, such as interleukin (IL)-17 and IL-23, play a major role by recruiting a plethora of immune cells such as dendritic cells (DCs), Langerhans cells (LCs), neutrophils and macrophages to the skin. Furthermore, the inflammation results in keratinocyte hyperproliferation, dysfunction and production of cytokines, thus sustaining the inflammatory loop. Several treatment options exist for psoriasis; however, traditional systemic drugs have well-known clinical limitations and potential side effects. Ultraviolet (UV) irradiation with either artificial UVA or UVB light or with natural sunlight is another treatment option. This can be combined with salt water or alternatively as a combination with more favourable climate conditions termed climatotherapy. Despite the current myriad of treatment options, some patients decline all systemic therapies because of personal concerns or due to contraindications or side effects. A long tradition exists in the Nordic countries for offering climatotherapy treatment to patients with psoriasis at the Canary Islands, Gran Canaria and at the Dead Sea in Israel. In Denmark, climatotherapy is most commonly performed at Ein Gedi in Israel. The additive effect of sun and salt water and the unique location approximately 400 metres below sea level produces remarkable short-term response rates. The attenuation of the UV spectrum at the Dead Sea allows patients to stay for prolonged periods in the sun.

Since its inception in 1978, the Psoriasis Area and Severity Index (PASI) has become one of the most widely used clinical scores. PASI is often used to compare treatment outcomes in psoriasis research. Many psoriasis patients achieve PASI-100, that is, complete visual clearance from Dead Sea climatotherapy (DSC). However, visual disease-free remission is not long lasting and relapse occurs approximately 3–6 months after end of treatment (EOT). In brief, 18 patients with plaque-type psoriasis completed DSC at Ein Gedi in Israel. A total of 17 patients were examined after DSC of whom ten achieved PASI-100. Blood samples were acquired from ten patients at EOT and relapse. Biopsies were acquired from 15 patients at EOT and nine patients at relapse. Relapse was defined as first visible sign of psoriasis. The mean time from baseline to EOT was 46.5 days (standard deviation [SD]: 7.8, range: 32–57 days), and the mean time from EOT to relapse was 90.9 days (SD: 63.7, range: 21–216 days). The study was conducted in compliance with the Declaration of Helsinki, and signed informed consent was obtained from each patient before study inclusion.

2 | METHODS

2.1 | Study design

The study population and study design have been explained in detail elsewhere. Demographics and biopsy locations are seen in Table S1. In brief, 18 patients with plaque-type psoriasis completed DSC at Ein Gedi in Israel. A total of 17 patients were examined after DSC of whom ten achieved PASI-100. Blood samples were acquired from ten patients at EOT and relapse. Biopsies were acquired from 15 patients at EOT and nine patients at relapse. Relapse was defined as first visible sign of psoriasis. The mean time from baseline to EOT was 46.5 days (standard deviation [SD]: 7.8, range: 32–57 days), and the mean time from EOT to relapse was 90.9 days (SD: 63.7, range: 21–216 days). The study was conducted in compliance with the Declaration of Helsinki, and signed informed consent was obtained from each patient before study inclusion.

2.2 | Biopsy acquisition

At inclusion, a specific psoriasis lesion was designated as the target lesion, and biopsies were acquired from this lesion at baseline and at EOT. An additional biopsy was acquired from a visible plaque at relapse. Four-mm full-thickness punch biopsies were obtained from LS and NL skin at baseline and LS skin at EOT. Among PASI-100 responders, an additional biopsy was obtained from LS skin at relapse. NL biopsies were acquired at least five cm from the target lesion.

2.3 | Histology and quantitative immunohistochemistry

Four-µm thick sections of paraffin-embedded tissue samples were stained with haematoxylin and eosin (HE), as previously described. For immunohistochemical staining, sections were deparaffinised, rehydrated through graded ethanols and heated at a preboiling temperature in tris-ethylene glycol tetraacetic acid buffer (pH 9) for antigen unmasking. The antibodies used were CD3, CD4, CD8, CD11c, CD103, CD163, CD207, forkhead box P3 (FOXP3), Ki67 and myeloperoxidase (MPO). See Table S2 for vendor information, incubation time and clone information. For detection, the Quanto Detection System was used according to the manufacturer’s protocol (cat. no. TL-O60-QHD, Thermo Fisher Scientific) for single staining. For double staining, the MultiVision anti-mouse/HRP + anti-rabbit/AP
was used (cat. TL-012-MHRA, Epredia). As a negative control, sections were incubated without primary antibody. As isotype control, specific IgG was used instead of primary antibody. All slides were digitised for image analysis using a whole slide digital pathology scanner (NanoZoomer 2.0-HT, RRID:SCR_021658, Hamamatsu Photonics K.K) with a 20x objective. For all measurements, a region of interest excluding apparent artifacts and hair was defined. For quantitative image analysis, the pixel classification tool was used in the open-source software QuPath (QuPath, RRID:SCR_018257, version 0.2.3) and reported as epidermal, dermal or total stained area (epidermal + dermal area) normalised to epidermal length. Stratum corneum was not included in the epidermis definition. The dermal area was constrained to 400 μm below the ventral epidermal surface inspired by a previous method (see Figure S1A).

2.4 | Blood tests

Blood tests consisting of cholesterol, c-reactive protein (CRP), glucose, haemoglobin A1c (HBA1c) and triglycerides were acquired at baseline, at EOT and at relapse. All laboratory analyses were performed in an ISO 15189 and DANAK-accredited laboratory.

2.5 | Statistical analysis

Data are presented as mean ± standard deviation (SD) or median ± interquartile range (IQR). All figures were made in Graphpad Prism (RRID:SCR_002798, v9.0.0, GraphPad Software, Inc.) and compiled in Adobe Illustrator (RRID:SCR_010279, v2021, Adobe Inc.). All statistics were conducted in SigmaPlot (RRID:SCR_003210, v14.5, Systat Software). The Kruskal–Wallis one-way analysis of variance on ranks with post hoc Dunn’s test was performed. Spearman’s rank correlation coefficients were used to signify the correlation between PASI and individual cell densities. Missing data were not included in the statistical analysis. All p-value calculations were two-sided, and a p-value of <0.05 was considered significant.

3 | RESULTS

3.1 | Dead Sea climatotherapy had an immediate effect on epidermal thickness, proliferation and T-cell quantities; however, treatment effect was not long lasting

We first performed HE staining to measure the epidermal thickness (Figure 1, HE). DSC had a remarkable effect on epidermal thickness in the psoriasis plaques. However, epidermal thickness was not completely normalised to NL baseline levels. At relapse, epidermal thickness was not significantly different from LS baseline epidermal thickness.

Next, we assessed the cellular proliferation in the epidermis using Ki67 as a marker (Figure 1, Ki67). We found a significant effect on proliferation, which was normalised to baseline NL levels after DSC. However, at relapse, the proliferation had returned to baseline NL levels.

Psoriasis is considered a T-cell driven disease. We therefore also investigated the CD3+, CD4+ and CD8+ T-cell quantities in the skin (Figure 1, CD3, CD4, CD8). CD3+, CD4+ and CD8+ T-cell quantities were all significantly reduced at the EOT LS skin compared with baseline LS skin. However, at relapse, the quantity of CD3+, CD4+ and CD8+ T cells had returned to baseline LS levels. CD4+ T cells in LS skin at EOT were not completely reduced to baseline NL levels. DSC was more effective in eliminating CD3+, CD4+ and CD8+ T-cell presence from the epidermal compartment than from the dermal compartment (Figure S2B–G). Most CD8+ T cells were found located close to the basement membrane, whereas CD4+ T cells were present in the dermis and dermal papilla but also to some extent in the epidermis and lower part of the dermis in accordance with other studies (Figure 1, CD4/CD8, black arrows).

3.2 | DSC induced an immediate short-term reduction in dendritic cells, neutrophils, macrophages, resident memory cells, regulatory T cells but not Langerhans cells.

We next investigated other cell types known to play a role in psoriatic pathogenesis. DCs have been proposed to play a key role in sun-induced effects in the skin.33 We first stained with the DC marker CD11c (Figure 2, CD11c). The cell quantity was reduced significantly after treatment, although it was still significantly higher than baseline NL levels. The effect was more pronounced in the epidermal than dermal compartment (Figure S2A,G).

Neutrophils serve as a classic histopathologic hallmark of LS psoriasis skin while being almost non-existent in healthy and NL skin.34,35 To elucidate the presence of neutrophils before and after DSC, we stained for MPO, which is recognised as a marker of activated neutrophils. DSC produced a profound reduction in neutrophils. However, at relapse, the cell quantity had returned to baseline LS levels (Figure 2, MPO and Figure S2B,H).

CD3+CD103+ TRMs are believed to possess a sort of disease memory,25,37 and CD3+ T cells have been reported to colocalise with LCs in the epidermis.39 We sought to determine whether CD103+ cells remain in resolved psoriatic skin after DSC and whether any colocalisations with LCs could be found. We used CD103 as a marker of resident memory cells and CD207 as an LC marker. In the skin, CD103 is mostly expressed on T cells, but it can also be expressed on DCs and LCs.39,40 LCs are distinguished from other DCs by the markers CD1a and/or langerin/CD207.41

**Figure 1**

**Figure 2**
Our data revealed a significantly greater quantity of CD103+ cells at baseline in LS skin than in NL skin (Figure 2, CD103). Also, a significant reduction in the quantity of CD103+ cells was observed in LS skin after DSC compared with baseline LS skin. This effect was more pronounced in the epidermis (Figure S2D,J). Many CD103+ cells were found colocalising with CD207+ cells in both LS epidermal skin at baseline and at EOT, suggesting the presence of close antigen presentation in LS skin (Figure 2, CD103/CD207, black arrows).

We demonstrated no significant effect of DSC on the quantity of CD207+ cells between LS skin before DSC, LS skin at EOT and LS skin at relapse (Figure 2, CD207 and Figure S2C,I).

Lastly, we assessed CD163+ and FOXP3+ cells. CD163 has been shown to be a superior marker for macrophages in psoriasis, whereas FOXP3 is a marker of regulatory T cells. Objectively, both cell types localised mostly to the dermal papilla and dermis (Figure 2, CD163/FOXP3, black arrow), with few cells in the epidermis (Figure S2E,K). At relapse, CD163+ and FOXP3+ cell quantities were comparable to baseline LS levels in total and in the epidermal and dermal compartments (Figure 2, CD163/FOXP3 and Figure S2F,L).

3.3 | PASI correlated poorly with inflammatory cell quantities

To investigate the relationship between the clinical evaluation as measured with PASI and individual psoriasis biomarkers, we used Spearman’s rank order to calculate the correlation between tissue biomarkers and PASI (Figure S3). Total and epidermal staining values of CD207+ cells at baseline most negatively correlated with PASI, suggesting that this biomarker may possibly be used as a predictor of disease severity (Figure S3A,B). At EOT CD163+ cells correlated positively with PASI (Figure S3D+F). Using a Student’s t-test, no difference was found at baseline between PASI-100 responders and the rest of the cohort.

3.4 | DSC had no effect on blood markers

We also measured selected blood parameters including cholesterol, CRP, glucose, HBA1c and triglyceride at baseline, at EOT and at relapse. No significant difference between visits was observed (Figure S4A–E).
DISCUSSION

Dead Sea climatotherapy has been used for many years to treat psoriasis, and Denmark was one of the first countries to trial the treatment in psoriasis patients. In the present study, we showed that DSC is highly effective in the short term, neutralising a number of biomarkers in LS skin to NL levels after treatment. However, among PASI-100 responders, all investigated biomarkers had returned to baseline levels at relapse at a mean 3 months after EOT.

The beneficial, but also harmful, effects of phototherapy on inflammatory skin diseases are well known. However, the mode of action of phototherapy remains largely unknown. The two therapeutically relevant UV radiation spectra are UVA and UVB. These spectra are absorbed by endogenous chromophores, such as nuclear DNA. In psoriasis, this causes the formation of DNA photoproducts and suppression of DNA synthesis and subsequent apoptosis of keratinocytes. UV light also stimulates the synthesis of cytokines that play important roles in immune suppression. The end result is most likely apoptosis of leukocytes and induction of regulatory T cells, which is more pronounced among intraepidermal T cells. The transcription factor NF-κB plays a central role in psoriasis, and DSC has been shown to downregulate NF-κB activity.

A rapid decrease in all T-cell markers was observed in our study. DSC has been shown to reduce the number of CD3+ T cells in mycosis fungoides and the number of CD68+ and CD3+ T cells in psoriatic skin. In the study by Emmilia Hodak et al., DSC produced a 63% reduction in the Malpighian layer; it further caused a reduction of Ki67+ cells, keratin-16 staining and human leukocyte antigen expression; and an average 94% reduction of CD3+ T cells and an average 98% reduction of CD25+ T cells. Furthermore, 16 days of climatotherapy in Gran Canaria reduced CD1a+, CD3+, CD4+, CD8+ and FOXP3+ T cells in the dermis and epidermis. Thus, in agreement with previous studies, we found that DSC almost completely reversed the psoriatic features in the skin.

The role of DCs and LCs in the psoriatic pathogenesis is generally unknown. This is further complicated by conflicting results.
regarding whether the quantity of LCs is increased in LS skin and whether treatment affects the number of LCs in psoriatic skin.\textsuperscript{28,54–58} However, in agreement with a study on the effect of sun on macrophages and dendritic cells, we found a reduction in both cell types.\textsuperscript{31} The number of LCs was significantly increased in LS compared with NL skin at baseline. However, no difference was found when comparing baseline LS skin with LS skin at EOT and LS skin at relapse.

It is increasingly appreciated that the local cytokine microenvironment and epigenetic changes in inflamed tissues influence the plasticity of cells.\textsuperscript{59,60} Epigenetic changes have been shown to regulate DNA methylation, histone modifications and non-coding RNAs, which are associated with psoriasis.\textsuperscript{60} Because TRMs might be associated with the dysregulated cytokine environment in psoriatic skin,\textsuperscript{37} this may potentially explain the disease memory responsible for the recurrent localised plaques seen in psoriasis.\textsuperscript{25,31}

We found that CD103\textsuperscript{+} cell quantity during the study mimicked the picture seen for the other markers. Many CD103\textsuperscript{+} cells colocalised closely with LCs. This may suggest that the microenvironment and cell-to-cell interaction rather than the absolute number of resident memory cells is essential in dictating the disease memory in psoriasis.

We found CD207 and CD163 to be potential biomarkers that correlate well with PASI. Still, several basic flaws of the PASI have become clearer such as a lack of interobserver reliability, its non-linearity, unhandy arithmetic and its dependence on area assessment that clinicians are often poor at performing.\textsuperscript{65} Especially, PASI has low discrimination among patients with less than 10% skin involvement, which unfortunately describes most psoriasis patients.

With the approval of newer biologics such as IL-23 and IL-17 inhibitors, complete skin clearance is often attainable.\textsuperscript{62–64} Secukinumab is an IL-17A inhibitor and its use results in a reduction in LS epidermal thickness to NL baseline levels and a reduction in CD11c\textsuperscript{+} DCs and CD163\textsuperscript{+} cells after 12 weeks.\textsuperscript{65} A reduction of CD3\textsuperscript{+} T cells and proliferation (Ki67) was also observed after 6 weeks.\textsuperscript{66} Ustekinumab, a dual IL-12/IL-23 inhibitor, and risankizumab, an IL-23p19 inhibitor, are also effective biologics that halve epidermal thickness, CD3\textsuperscript{+} T cells and proliferation (Ki67) after 4 weeks of treatment.\textsuperscript{67} Our results suggest that the effects of DSC on psoriasis thus have an equal or earlier onset than biologics and are consistent with the clinical parameters.\textsuperscript{18} However, unlike biologics, persistent effects of DSC on skin are lacking.

Sunlight contains a wide range of wavelengths. Even though the attenuation of the UVB spectrum at the Dead Sea allows for extended sun exposure, it should be emphasised that prolonged sun exposure may lead to photoaging, lentigines, actinic keratoses and skin cancer.\textsuperscript{68} Unlike DSC, it has yet to be confirmed that narrow-band UVB phototherapy increases the risk of skin carcinomas.\textsuperscript{69}

We acknowledge several limitations of the present study. First, DSC precludes blinded and randomisation due to the intervention. Second, the sample size was based on feasibility. Thus, more patients might be needed to elucidate fully any correlation between PASI and disease severity as assessed by biomarkers.

In conclusion, treatment with DSC almost completely normalised biomarkers in psoriasis skin. However, among PASI-100 responders, biomarker levels had returned to baseline levels at relapse at mean 3 months after treatment. PASI negatively correlated with the total quantity of CD207\textsuperscript{+} LCs at baseline while CD163\textsuperscript{+} macrophages correlated positively with PASI at EOT. Lastly, DSC did not affect CRP, cholesterol, glucose, HBA1c and triglycerides. The results will contribute to further elucidating the effects of DSC on psoriasis and the role of DSC in the ever-expanding treatment palette for psoriasis.

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CONFLICT OF INTEREST

TE, AP, HH, AR, DL, TS, AB, LI and CJ declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

T.E., D.L., L.I. and C.J. involved in conceptualisation. T.E., D.L., T.S., A.B., L.I. and C.J. involved in methodology. T.E. involved in validation, data curation and visualisation. T.E., A.P., H.H. and A.R. involved in formal analysis. D.L., L.I., T.S. and C.J. involved in resources. T.E., A.P., L.I. and C.J. involved in writing/original draft preparation. T.E., A.P., H.H., A.R., D.L., T.S., A.B., L.I. and C.J. involved in writing/review and editing. T.S., A.B., C.J. and L.I. involved in supervision. T.E., D.L. and C.J. involved in project administration. T.E., T.S., L.I. and C.J. involved in funding acquisition. All authors have read and approved the final manuscript.

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SUPPORTING INFORMATION
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Fig S1. Segmentation and quantitative staining measurements from non-lesional (NL) and lesional (LS) skin before Dead Sea climatotherapy (DSC), LS skin at end of treatment (EOT), and LS skin at relapse. A. Example of the segmentation of epidermis (epi) and dermis and measurement of the epidermal (epi) length. The area 400 µm below the ventral part of the epidermis was automatically defined as the dermis. B–D, Cluster of differentiation (CD)3+, CD4+, and CD8+ T cell quantities in the epidermis. E–G, CD3+, CD4+, and CD8+ T cell quantities in the dermis. Median ± interquartile range are shown. Kruskal-Wallis one-way analysis of variance on ranks with post hoc Dunn’s. ***p < 0.001, **p < 0.01, *p < 0.05. Size bar = 100 µm. †, CD, cluster of differentiation; DSC, Dead Sea climatotherapy; EOT, end of treatment; Epi, epidermal; LS, lesional; NL, non-lesional.

Fig S2. Quantitative staining measurements from non-lesional (NL) and lesional (LS) skin from before Dead Sea climatotherapy (DSC), at end of treatment (EOT) and at relapse divided into the epidermal (epi) and dermal stained area. A–F, CD11c+, MPO+, CD103+, CD163+, and FOXP3+ cell quantities in the epidermis. G–L, CD11c+, MPO+, CD103+, CD207+, CD163+, and FOXP3+ cell quantities in the dermis. Median ± interquartile range is shown. Kruskal-Wallis one-way analysis of variance on ranks with post hoc Dunn’s showed no significant differences between the different visits.

Fig S3. Bar graph representing the Spearman’s rank correlation coefficient of total, epidermal and dermal cell quantities and psoriasis area and severity index (PASI). A–C, Total, epidermal, and dermal cell quantities and PASI at baseline. D–F, Total, epidermal, and dermal cell quantities and PASI at end of treatment (EOT). G–I, Total, epidermal, and dermal cell quantities and PASI at relapse. Only significant p-values are shown. †, CD, cluster of differentiation; EOT, end of treatment; FOXP3, forkhead box P3; MPO, myeloperoxidase.

Fig S4. Blood samples taken before Dead Sea climatotherapy (DSC), at end of treatment (EOT), and additionally at relapse. A, Cholesterol. B, C-reactive protein. C, Glucose. D, Haemoglobin A1c (HBA1c). E, Triglyceride. Mean ± standard deviation or median ± interquartile range is shown. Mixed model analyses with post hoc Tukey’s or Kruskal-Wallis one-way analysis of variance on ranks with post hoc Dunn’s showed no significant differences between the different visits.

Tab S1. Patient demographics and biopsy site locations. †, EOT, End of treatment; PASI, Psoriasis Area and Severity Index.

Tab S2. List of antibodies used for immunohistochemistry. †, CD, cluster of differentiation; FOXP3, forkhead box P3; MPO, myeloperoxidase; RRID, research resource identifier.

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