The Effect of the Dead Sea Environment on Uveitis

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Abstract

Background: Uveitis is an acute or chronic inflammatory process of the uvea caused by a number of etiologies. In many patients the etiology is unknown.

Objective: To investigate the effect of the Dead Sea environment (climatotherapy) on the signs, symptoms and clinical course of chronic uveitis.

Methods: Fifty-five patients with chronic uveitis were examined at the beginning and end of a 3–4 week stay at the Dead Sea region and on repeat visits to the region. Study data included demographic information, medical history, etiology, diagnosis, medication, and a complete ophthalmic examination.

Results: Statistically significant improvements were seen between the two examinations within each visit in four parameters (negative values indicate improvement): a) visual acuity for near and far: Jaeger (-0.98 $\pm$ 0.18, $P \leqslant 0.001$) and best corrected visual acuity (-0.22 $\pm$ 0.04, $P \leqslant 0.0001$); b) anterior chamber flare (-0.18 $\pm$ 0.06, $P \leqslant 0.01$); c) anterior chamber cells (-0.12 $\pm$ 0.03, $P \leqslant 0.0001$); and d) vitreous cells (-0.17 $\pm$ 0.05, $P \leqslant 0.001$). There was a significant mean improvement during visits to the Dead Sea area and a slight dissipation of the effect during the intervals between visits. Sixty-four percent of the patients reported that they required less medication and had fewer and milder attacks of uveitis following the visits.

Conclusions: The results of this study provide evidence of short- and possibly long-term improvement in the signs and symptoms of uveitis following exposure to the Dead Sea environment.

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Uveitis is a general term used to describe an inflammation of the uvea. Although the specific etiology of uveitis is unknown in many cases, etiologic causes in known cases include infection, trauma, neoplasia, and autoimmune conditions [1]. Uveitis is usually defined by the anatomic section of the affected eye in accordance with the classification system of the International Uveitis Study Group: a) anterior (iritis and iridocyclitis), b) intermediate (cyclitis), c) posterior uveitis (choroiditis), and d) panuveitis [2]. Uveitis is characterized further by the mode of onset (insidious/sudden), duration (short/long/chronic), and degree of activity (mild/moderate/severe) [3]. It can affect visual acuity and in severe cases may cause blindness [4]. The treatment of idiopathic uveitis may include topical and systemic steroids, and severe persistent cases may even require cytotoxic drugs. The purpose of the present study was to investigate the potential beneficial effect of the Dead Sea environment on the clinical course of uveitis, including the need for medication.

The Dead Sea region, which at 400 meters below sea level is the lowest place on earth, has unique climatic qualities such as a low level of ultraviolet radiation, particularly UVB [5]. The ratio of UVA to UVB is higher than in other areas. The relative oxygen pressure (PO_2) is also higher. Similarly, the level of minerals, such as magnesium, bromides and sulfur compounds, is much higher in Dead Sea water, spas, mud and air. One or more of these factors, as well as other regional characteristics, may have a positive effect on disease-associated mechanisms.

The medical literature contains many references to the positive influence of the Dead Sea region on autoimmune diseases, particularly psoriasis, atopic dermatitis and vitiligo [6–9]. A beneficial effect has also been observed in rheumatoid arthritis, osteoarthritis and psoriatic arthritis [8,10–12], which have an etiologic relationship to uveitis [13]. The results of preliminary studies have shown that the environment of the Dead Sea has a positive effect on uveitis [14–17]. Manthey et al. [15,16] conducted a comprehensive study of 45 patients with chronic iridocyclitis and intermediate uveitis. Three months after a 3 week stay at the Dead Sea region 39% of the patients showed an improvement in visual acuity of one or two lines on Snellen charts. Six months later 43.9% of the patients had an improvement in near visual acuity. There was also a significant decrease in the incidence of uveitis attacks – from 2.9/patient/year before the Dead Sea visit to 1.0 patient/year in the first year after the visit.

We present the results of a study on the effect of the Dead Sea environment on the severity of uveitis symptoms and the clinical course of the disease among patients who came for one or more climatotherapy visits of 3–4 weeks.

Patients and Methods

Patients

Fifty-five foreign patients suffering from chronic uveitis were recruited to participate in this prospective study. Upon recommendation by their ophthalmologist the patients visited the Dead Sea for climatotherapy from 1993 to 2000 for periods of about 3-4 weeks. These patients were examined upon arrival and then at the end of the visit by the same senior ophthalmologist (R.Y.). All examinations included a thorough eye examination and a detailed medical history. Some patients visited the Dead Sea area repeatedly. In all, 55 patients underwent 201 examinations (55 first exams and 146 follow-up exams). Patients were asked not to make any changes in their medication during their stay at the Dead Sea. They were encouraged to take advantage of the spa, mud baths and the sea itself. Otherwise no other treatment was applied.

UV = ultraviolet

Study design

In this study each patient served as his or her own control and changes in each patient's condition were compared for both the same visit and for the time interval between the last examination of one visit to the first examination of the subsequent visit. Patients were requested not to change their medication as prescribed by their doctor abroad. Since medications remained unchanged, the only therapeutic variable was exposure to the Dead Sea environment.

Clinical data collection

Study data included demographic information (age at first visit, gender), etiology of uveitis, systemic and ophthalmic diagnoses, systemic and topical medication, and the results of the ophthalmic examinations.

Outcome variables

The study focused on changes in VA, indicators of eye inflammation, and frequency and severity of uveitis attacks. Only eyes with active uveitis during the visit were included in the statistical analyses.

The outcome variables, near and far visual acuity (Jaeger and best corrected visual acuity), anterior chamber flare and cells, and vitreous cells, showed statistically significant changes both within visits (from the first examination at the beginning of a visit to the final examination at the end of the same visit), and between visits (from the last examination of one visit to the first examination of the subsequent visit) with the time interval spent at home in the country of origin. These variables were used for all subsequent analyses. However, the direction of the statistically significant change in these variables was opposite, reflecting improvement in the uveitis in the within-visit analyses, and dissipation of that improvement in the between-visit analyses (see Results).

Statistical analysis

An analysis of variance (ANOVA) was performed for demographic and temporal data. Within-visit and between-visit differences were tested by unpaired *t*-tests. Statistical significance was set at $P < 0.05$ throughout. To test for independence between the two eyes of each patient, pair-wise correlation coefficients were calculated for the selected variables (visual acuity and inflammation). The two eyes were found to be statistically independent for BCVA and only moderately dependent for the Jaeger (coefficient = 0.3034). The coefficients between the two eyes for inflammation variables (anterior chamber, flare and cells, vitreous cells – 0.57, 0.48, and 0.61, respectively) were significant, indicating dependence. When the two eyes were statistically analyzed separately for all three inflammation variables, the results showed minor differences between the two eyes in the power of effect and were parallel to those data treating the two eyes as independent; in all comparisons the trend was the same. Thus, for simplicity all selected variables for both eyes, including the inflammation variables, were treated statistically as independent.

Results

Demographic characteristics and data

Demographic and temporal factors for the total study population, and by uveitis classification, are presented in Table 1. Data are presented as means and medians because of the wide range of data in some of the uveitis subgroups. Women comprised 75% of the study population. The mean age at the first visit was 33.2 ± 2.31 years (SEM, standard error of means), the median age was 32 and the range was 4–70 years. Forty percent of the subjects were between the ages of 20 and 39.

Twenty-two patients (40%) had anterior uveitis, 18 (32.7%) had panuveitis, 10 (18.2%) had posterior uveitis, and 5 (9.1%) had intermediate uveitis. The etiology of the uveitis for our patients was as follows: 36 cases (65%) were idiopathic; rheumatologic diseases (including rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis) were reported in 18 cases (33%), and thyroid-associated disorders in 5 (9%).

Almost 60% (n=33) of the patients came for one visit, about 15% (n=8) for two visits, 22% for three to four visits, and 4% for five to seven visits. The mean number of visits was 1.85 ± 1.8 (range 1–7). The length of stay at the Dead Sea ranged from 19 to 38 days. A paired *t*-test was performed between the various diagnostic subgroups for all demographic variables. There were no statistically significant differences between the diagnostic subgroups for demographic and temporal variables.

Table 1. Sociodemographic and clinical data for total sample and by uveitis subtype (means are ± SEM)

	All n=55 (100%)	Panuveitis n=18 (32.7%)	Posterior n=10 (18.2%)	Anterior n=22 (40.0%)	Intermediate n=5 (9.1%)
Age (yrs)					
Mean	33.2 ± 2.31	38.1 ± 4.76	37.5 ± 5.80	29.2 ± 3.04	29.4 4.37
Median	32	38.5	42	29	33
Range	4–70	8–70	13–58	4–49	15–38
Gender (M/F)	14/41	3/15	2/8	9/13	0/5
No. of visits					
Mean	1.85 ± 0.18	2.1 ± 0.38	1.3 ± 0.21	2.0 ± 0.28	1.4 ± 0.4
Median	1	1	1	1.5	1
Range	1–7	1–7	1–3	1–5	1–3
Days per visit					
Mean	26.7 ± 0.31	27.3 ± 0.38	26.4 ± 0.85	26.4 ± 0.54	25.7 ± 1.30
Median	28	28	28	28	28
Range	19–38	21–30	21–28	19–38	21–29
Total days					
Mean	49.5 ± 5.0	56.2 ± 10.66	34.3 ± 5.66	54.04 ± 8.03	36.0 ± 11.38
Median	28	28	28	35	28
Range	21–198	21–198	21–77	21–131	21–81
No. of examinations					
Mean	3.38 ± 0.13	2.15 ± 0.25	2.5 ± 0.40	4.32 ± 0.63	2.8 ± 0.8
Median	2	3	2	3.5	2
Range	1–11	1–11	2–6	1–10	1–6

VA = visual acuity
BCVA = best corrected visual acuity

In Table 2, medication as prescribed by the attending ophthalmologist abroad is detailed for each visit. Thirty-three patients were taking topical and/or systemic treatment during the first visit; only one patient on his fourth visit was prescribed systemic treatment from abroad, and the two patients who had five to seven visits had not been prescribed systemic treatment by their attending ophthalmologist abroad. According to the study design, the medical treatment during the Dead Sea visit remained unchanged.

Effect of the Dead Sea environment: objective variables

An ANOVA test performed between the subtypes of uveitis for the four outcome variables showed no significant differences between the various diagnosis groups.

Table 2. Ongoing medicinal treatment as prescribed for the patients by their ophthalmologists abroad during each visit*

Visit number	1	2	3	4	5	6	7
No. of patients	55	22	14	7	2	1	1
No. of patients receiving medication	33	13	10	5	2	–	1
Topical treatment							
Steroid treatment	30	13	10	5	2	–	1
NSAIT **	12	7	3	3	2	–	1
Cycloplegia	5	2	–	1	–	–	–
Systemic treatment							
Steroids	9	4	6	–	–	–	–
Non-steroidal anti-inflammatory drugs	2	–	–	1	–	–	–
Cytotoxics	4	2	1	–	–	–	–

* Some patients took more than one type of medication; therefore the sum total is not equal to the number of patients.

The data were analyzed for within-visit and between-visit changes The data obtained at the examination at the end of the visit reflected changes in uveitis during the course of that visit (within visits). The interval between visits was one year or more, so the data obtained at the first examination of each return visit reflected changes in the patient's condition over the year since the previous visit at the Dead Sea visit (between visits).

Table 3 compares the changes within visits and between visits. All the differences were statistically significant except for the difference between visits for vitreous cells. The results indicate a slight mean improvement during visits (negative values) and dissipation of part of the effect (positive values) during the interval between visits. Most of the significant differences were seen in patients with panuveitis and anterior uveitis.

In Table 4 the differences within visits and between visits are shown for each visit. The results for the first visit are all statistically significant. The trend of the differences indicates that there was improvement during visits and a deterioration or dissipation of the effect between visits.

Effect of the Dead Sea environment: medical history

At each follow-up examination at the Dead Sea, patients were asked if they noticed any change in their general condition, in the frequency of uveitis attacks, and in their use of medications since the last examination. Standardized questions were asked as follows: number of attacks before, during and after visits; and the duration and severity of attacks as reflected by the use of medication during and between attacks. Changes in medication were analyzed by the quality (potency) and the dosage prescribed**.**

We obtained 104 histories from 154 follow-up examinations. Sixty-four percent of the patients reported that they felt better, had fewer and milder attacks and required less medication. Obviously,

Table 3. Analysis of changes in selected variables (within and between visits) for total sample and by uveitis diagnosis (unpaired *t*-test, mean $\pm$ SEM)[a]

	Total	Panuveitis	Posterior	Anterior	Intermediate
No. of patients (%)	55 (100%)	18 (32.7%)	10 (18.2%)	22 (40%)	5 (9.1%)
No. of eyes (%)[b]	101 (100%)	34 (33.7%)	18 (17.8%)	41 (40.6%)	8 (7.9%)
Visual acuity, Jaeger					
Within visits	-0.98 $\pm$ 0.18 (n=132)****	-1.48 $\pm$ 0.41 (n=39)***	-1.5 $\pm$ 0.52 (n=20)**	-0.5 $\pm$ 0.17 (n=62)**	-1 $\pm$ 0.76 (n=11)
Between Visits	0.80 $\pm$ 0.30 (n=51)**	1.36 $\pm$ 0.68 (n=14)	1.75 $\pm$ 0.63 (n=4)	0.41 $\pm$ 0.38 (n=29)	0.75 $\pm$ 1.11 (n=4)
BCVA					
Within visits	-0.08 $\pm$ 0.02 (n=168)****	-0.08 $\pm$ 0.04 (n=31)	-0.10 $\pm$ 0.04 (n=16)*	-0.07 $\pm$ 0.02 (n=48)**	-0.08 $\pm$ 0.08 (n=10)
Between visits	0.07 $\pm$ 0.03 (n=55)**	0.05 $\pm$ 0.05 (n=17)	0.14 $\pm$ 0.08 (n=6)	0.09 $\pm$ 0.03 (n=28)*	0.08 $\pm$ 0.08 (n=4)
Anterior chamber, flare[c]					
Within visits	-0.22 $\pm$ 0.04 (n=168)****	-0.27 $\pm$ 0.06 (n=59)****	0.05 $\pm$ 0.05 (n=22)	-0.21 $\pm$ 0.05 (n=75)****	-0.33 $\pm$ 0.19 (n=12)*
Between visits	0.25 $\pm$ 0.06 (n=83)****	0.32 $\pm$ 0.11 (n=34)**	0 (n=6)	0.25 $\pm$ 0.09 (n=39)**	0 (n=4)
Anterior chamber, cells[c]					
Within visits	-0.12 $\pm$ 0.03 (n=168)****	-0.10 $\pm$ 0.04 (n=59)****	0 $\pm$ (n=22)	-0.12 $\pm$ 0.05 (n=75)**	-0.41 $\pm$ 0.19 (n=12)
Between visits	0.11 $\pm$ 0.04 (n=83)**	0.12 $\pm$ 0.06 (n=34)	0 (n=6)	0.10 $\pm$ 0.06 (n=39)	0.25 $\pm$ 0.25 (n=4)
Vitreous cells[c]					
Within visits	-0.17 $\pm$ 0.05 (n=93)***	-0.28 $\pm$ 0.09 (n=36)**	0.06 $\pm$ 0.06 (n=16)	-0.10 $\pm$ 0.08 (n=29)	-0.33 $\pm$ 0.14 (n=12)
Between visits	0.05 $\pm$ 0.09 (n=44)	-0.09 $\pm$ 0.09 (n=22)	0.25 $\pm$ 0.25 (n=4)	0 $\pm$ 0.18 (n=14)	0.75 $\pm$ 0.48 (n=4)

*$P \leqslant 0.05$, **$P \leqslant 0.01$, ***$P \leqslant 0.001$, ****$P \leqslant 0.0001$

[a] Negative values indicate improvement.

[b] Sick eyes only.

[c] Data ranged from 0 to +4.

Table 4. Analysis of changes in selected variables according to within visits (unpaired *t*-test, mean ± SEM)[a]

	Visit 1	Between visits 1-2	Visit 2	Between visits 2-3 & 3-4	Visit 3-4	Between visits 4-5, 5-6 & 6-7	Visits 5-7
No. of patients	55 (100%)	22 (40%)	22 (40%)	14 (25%)	14 (25%)	2 (4%)	2 (4%)
No. of eyes (%)[b]	101 (100%)	41 (40.6%)	41 (40.6%)	25 (25%)	25 (25%)	4 (4%)	4 (4%)
Visual acuity Jaeger	-0.51 (±0.11)***	0.11 (±0.39)	-0.52 (±0.21)**	0.89 (±0.51)*	-0.40 (±0.15)**	1 (±0.58)	-0.67 (±0.49)
BCVA	-0.05 (±0.01)****	0.06 (±0.04)*	-0.02 (±0.02)	0.06 (±0.06)	-0.05 (±0.02)*	0.05 (±0.003)**	0.03 (±0.03)
Anterior chamber, flare [b]	-0.09 (±0.03)***	0.18 (±0.08)*	-0.06 (±0.03)*	0.43 (±0.12)***	-0.19 (±0.07)**	0.5 (±0.29)	-0.13 (±0.13)
Anterior chamber, cells [b]	-0.09 (±0.02)***	0.10 (±0.06)	-0.04 (±0.03)	0.17 (±0.08)*	-0.09 (±0.04)*	0	0
Vitreous cells [b]	-0.06 (±0.02)**	-0.05 (±0.11)	-0.1 (±0.06)*	0.31 (±0.24)	-0.15 (±0.09)	0	0

*$P \leqslant 0.05$, **$P \leqslant 0.01$; ***$P \leqslant 0.001$; ****$P \leqslant 0.0001$

[a] Negative values indicate improvement.

[b] Data ranged from 0 to +4.

this is a subjective report reflecting the patient's assessment of his own medical condition. As previously described, a mild attack was defined as being shorter in duration and having to use less medication during the attack. Fewer attacks were defined as lower frequency of attacks than before their visit to the Dead Sea. Less medication was determined by both the quality and quantity of the medicine.

Discussion

This study included 55 chronic uveitis patients who came for climatotherapy at the Dead Sea. The distribution of etiologies indicates, as expected, the relationship between rheumatologic diseases, especially rheumatoid arthritis and juvenile rheumatoid arthritis, and anterior uveitis. The fact that two of our patients with rheumatoid arthritis had panuveitis, rather than anterior uveitis, does not necessarily infer that the two diseases in these patients are mutually dependent. As for the prevalence of thyroid disorders, all those suffering from thyroid disorders were women. Since thyroid malfunction or imbalance is very common within the adult female population, the prevalence of thyroid-associated disorders in this sample of patients is not surprising.

The results of the study demonstrate significant improvement in four parameters: VA for near and far (Jaeger and BCVA) and reduction of inflammation in the anterior chamber (cells and flare) and the vitreous (cells). Significant improvement was found in both short- and long-term analyses, but the mean short-term effect (within each visit) was more pronounced than the long-term effect. This difference can be explained by the dissipation in the effect over the course of the interval between visits of one or more years to the Dead Sea area.

The beneficial effect of UVB light on chronic ocular inflammation is most probably related to its effect on the immune system. UVB light affects both DNA synthesis and the immune effector apparatus [18]. Immunosuppression is maintained by inhibition of both type 1 and 2 helper T cell-mediated immune responses [18]. The development of most autoimmune inflammatory diseases depends on the cytokines interleukin-2 and interferon-gamma produced by Th-1 cells [19]. Th-1 and Th-2 cells have a reciprocal effect. Narrow-band UVB phototherapy can shut down or suppress unwanted inflammatory processes by affecting Th-1 activity [20].

The present study and that of Manthey [15] comprised only chronic uveitis patients. However, our study included patients with different types of chronic uveitis, while Manthey [15] included only those with iridocyclitis and intermediate uveitis. Both studies reported reduced inflammation after a 3–4 week visit at the Dead Sea and an improvement in VA. Also, patients reported fewer attacks and an improved feeling of general welfare following the visit. Both found improvement in VA. Manthey reported improvement in far VA (Snellen) and we demonstrated improvement in both far vision (BCVA) and near vision (Jaeger). In both studies patients had fewer attacks during the 6 month period following exposure to the Dead Sea environment.

Although the patients reported improvement as long as 6 months after their visit to the Dead Sea, we could not verify this long-term effect since our follow-up examinations took place only after an interval of a year or more. Also, since the patients came from abroad and we had no contact with the patient or his/her ophthalmologist abroad, follow-up examinations between visits could not be included in the study. Even though the improvement our patients reported in vision and uveitis attacks during their visit to the Dead Sea were subjective accounts, these reports tend to correspond to the actual improvement in vision and the decrease in inflammation measured during the visit. It is also possible that rest and elimination of stress were factors that may have influenced the uveitis in addition to the local factors. In further studies these variables should be investigated.

In conclusion, this pilot study indicates that there could be a significant short-term and possibly a long-term improvement in uveitis symptoms and activity following exposure to the Dead Sea environment. The subjective feeling of improvement was confirmed by objective measurements indicating improvement in near and far VA and a decrease in inflammation of the anterior chamber and the vitreous cells. These findings lend further credence to the beneficial effect of climatotherapy on different types of chronic uveitis. Further studies with larger patient groups and more data regarding patients' condition between visits is required in order to further investigate the effect of the Dead Sea environment on uveitis.

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Th-1 = type 1 helper T

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Capsule

Anti-angiogenics fortify first, then destroy

In clinical trials, "anti-angiogenic" drugs, which are designed to destroy the blood vessels that feed tumors, have limited efficacy when administered as single agents. However, when provided as a combination therapy, they enhance the efficacy of conventional cytotoxic drugs targeting tumor cells, even though the destruction of the tumor vasculature might be expected to impede drug delivery to the tumor. Jain reviews evidence supporting the counterintuitive notion that anti-angiogenic drugs initially fortify, rather than destroy, the tumor vasculature, thereby improving delivery of cytotoxic drugs to the tumor. If further substantiated, this hypothesis could have important implications for the optimal dose and scheduling of combination cancer therapies.

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E. Israeli

Capsule

Brain repair mechanism

The transcription factors Olig1 and Olig2 are closely related in sequence, but affect their key targets, oligodendrocyte cells, in different ways. Oligodendrocytes are responsible for wrapping neurons of the central nervous system in an insulating myelin sheath. Olig2 is important for developmental specification of oligodendrocyte cells. Arnett et al. show that Olig1 does not play a role in brain development but in repair. Mice lacking Olig1 are deficient in their ability to repair demyelinated brain lesions, the kind of lesions that occur in multiple sclerosis.

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E. Israeli