

Balneotherapy, a Complementary Non-pharmacological Approach for Non-Inflammatory Complaints in Systemic Lupus Erythematosus: A Pilot Study

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Abstract. *Background/Aim: Despite remission or low disease activity non-inflammatory complaints like exhaustion, fatigue, and pain persist in a significant proportion of patients with systemic lupus erythematosus (SLE) and have a considerable impact on health-related quality of life. This study evaluated the effects of balneotherapy on non-inflammatory complaints, quality of life, and work productivity of patients with SLE. Patients and Methods: SLE patients in remission/low disease activity in three rheumatology centers were included in this randomized, controlled, follow-up study. In addition to the standard of care (SOC), sixteen out of the thirty patients with SLE received balneotherapy (3-week period, 15 times, for 30 min) and fourteen patients received the SOC only. Pre-validated survey instruments including Lupus Quality of Life (LupusQoL), Short-Form Health Survey (SF-36), Work Productivity, and Activity Impairment-Lupus (WPAI-Lupus) questionnaires were used. Results: Based on the SF-36 questionnaires, several subdomains of physical condition improved significantly after the course; the improvement remained durable ($p=0.019$). General health improved significantly by the end of the course ($p=0.001$). According*

to the LupusQoL questionnaire, physical health and pain showed a tendency of improvement shortly after the spa treatment. Changes in the WPAI-lupus questionnaire indicated a short-term improvement of the daily activity by the end of the observation period. No adverse reactions were observed. Conclusion: Thermal water therapy may be an effective, well-tolerated, complementary non-pharmacological approach for non-inflammatory complaints of patients with SLE. Physical condition improved in the short-term, whereas fatigue worsened despite treatment.

Systemic lupus erythematosus (SLE) is a chronic, heterogeneous systemic autoimmune disease, with a prevalence in Hungary of 70.5 per 100,000 people, depending on both sex (women are affected nine to ten times more often than men) and age (onset of SLE peaks from the second to the fourth decade of life) (1). It is characterized by the production of antinuclear autoantibodies and clinical involvement in multiple organ systems (2). In addition to various organ manifestations, pain and fatigue are common symptoms of the disease. The treatment of SLE primarily targets remission or, if this state cannot be achieved, low disease activity (3). According to the treat-to-target approach, prevention of organ damage is essential and the improvement of quality of life is also necessary. Despite remission or low disease activity, fatigue, pain, mood disorders, and fibromyalgia-like symptoms may frequently persist and highly influence the quality of life of patients with SLE (4).

Balneotherapy is a medical remedy, which uses medically and legally recognized mineral waters, muds, and natural gases from natural springs for therapeutic and rehabilitation purposes. Unlike in hydrotherapy, in balneotherapy, in addition to the physical properties of water, its chemical properties also prevail. The absorption of minerals dissolved

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Key Words: Fatigue, pain, balneotherapy, SLE, quality of life.



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in water through the skin may play a role in the mechanisms of action. In the past decades, several studies have confirmed that balneotherapy has a beneficial effect on the treatment of chronic musculoskeletal disorders (5-7). Hungary is extremely rich in medicinal waters, therefore balneotherapy is a popular treatment in rheumatology and rehabilitation (8).

Considering that residual pain, fatigue, and musculoskeletal symptoms are common in SLE patients with low disease activity/remission, and in most of the cases anti-inflammatory treatment is not effective for these non-inflammatory complaints, balneotherapy, as a complementary non-pharmacological treatment, may have a beneficial effect. As there have been no previous reports, we conducted a prospective study to investigate the effect of thermal water on the quality of life and work productivity of patients with SLE. Our secondary goal was to determine whether balneotherapy is safe for patients with SLE.

Patients and Methods

Study design. This study was a randomized, controlled, follow-up, pilot study, performed in accordance with the ethical principles of the Declaration of Helsinki, the International Conference on Harmonization and Good Clinical Practice with the permission of the Regional Research Ethics Committee (number: 31959-2/2017/EKU). All patients provided written informed consent. The study was performed between December 2017 and January 2020. The ClinicalTrials.gov registration No. is: NCT04392791.

Study population. A total of 32 patients with SLE from three medical centers (Polyclinic of Hospitaller Brothers of St. John of God, Budapest; Division of Rheumatology, Faculty of Medicine, University of Debrecen; Department of Rheumatology and Immunology, Faculty of Medicine, University of Szeged) were enrolled. Two subjects declined to participate; therefore, we evaluated 30 patients (Figure 1). All patients underwent regular follow-ups at these institutions. Balneotherapy was carried out at the Széchenyi (Budapest, Cation and Anion concentrations 1,390 mg/l), Nagyerdei (Debrecen, Cation and Anion concentrations 4,021 mg/l) and Anna Baths (Szeged, Cation and Anion concentration 1,244 mg/l).

The inclusion criteria for the study were as follow: men and women aged 18-79 years; diagnosis of SLE according to SLICC/ACR, 2012 criteria (9); remission or low disease activity as determined by SLEDAI-2K <6 (10).

The exclusion criteria included psychiatric disease and the general contraindications to balneotherapy (unstable angina pectoris, poorly controlled hypertension, congestive heart failure, respiratory insufficiency, unbalanced endocrinological disease, acute febrile condition, infection, or extensive inflammation of the skin, severe genitourinary or other diseases, fecal or urinary incontinence, lack of compliance).

The main characteristics of the patients are presented in Table I. The generation of initial homogeneous patient groups was followed by simple randomization, using a computer program. The computer randomly assigned the patients into each group. According to the randomization list, 16 of 30 participants received thermal water

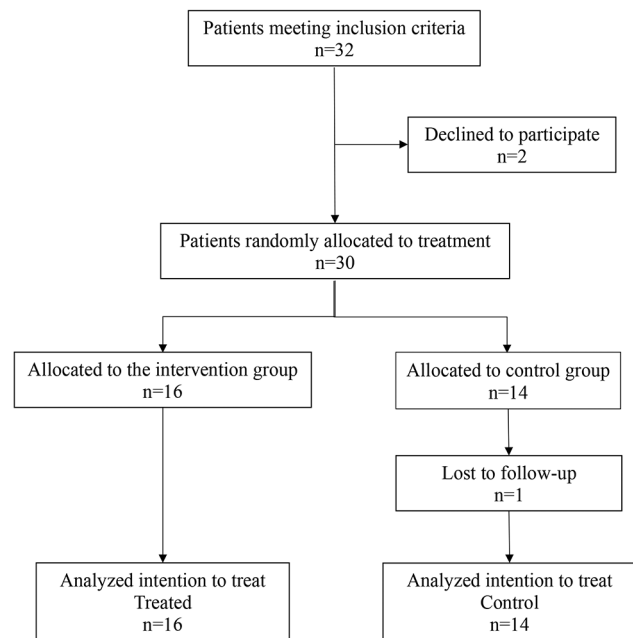


Figure 1. Distribution of patients.

therapy. The two groups were thus homogenous in terms of disease activity, disease duration, and mean age. Patients were examined by independent examiners at each visit. The questionnaires were self-administered. The statistical processing of the data was carried out by an expert statistician.

During the study, all participants underwent outpatient care and received the usual medications. In addition to the usual medications, the study group received 3 weeks of balneotherapy in outpatient care. They were treated 15 times in 3 weeks, from Monday to Friday, at the same time, with thermal mineral water for 30 min. The water temperature was 33-35°C. In the pool, the participants could sit or move freely; swimming and physical therapy were not allowed. The possible side effects of the balneotherapy were evaluated by an independent physician and finally by the rheumatologists supervising the treatments. The control group did not receive balneotherapy, but the usual medications.

Outcome parameters. For efficacy measurements, SLEDAI-2K was applied to objectively evaluate disease activity. It is a global index consisting of 24 weighted clinical and laboratory variables of nine organ systems assessing the preceding 10 days (10). As disease activity may not always correlate with the general health status of the patient, various standardized self-reported questionnaires, including SF-36 and LupusQoL, were used to determine the quality of life.

SF-36 is the most widely used in both medicine and research. It measures general aspects of health, contains a total of 36 questions in 8 categories (physical activity, role limitation due to physical problems, physical pain, general health, vitality, social activity, role limitation due to emotional problems, and general mental health) and is recognized as a relevant indicator to assess the quality of life in Caucasian patients with SLE (11). The Cronbach's alpha indicating the reliability of the test was 0.955.

Table I. Patient characteristics.

Group	Sex	Age (mean±SD) (years)	Disease duration (mean±SD) (years)	Disease activity SLEDAI-2K	
Treated	2 males 14 females	54.93±11.53	11.60±8.26	2.125±0.947	
Control	14 females	53.58±10.50	11.50±7.72	2.4286±1.437	
Patient	SLEDAI-2K	Medication	ds-DNA (IU/ml)	C3 (g/l)	C4 (g/l)
Patient 1	2	AZA, CQ, MPred	31.85	0.875	0.271
Patient 2	4	MTX, CQ	16.15	1.098	0.414
Patient 3	2	AZA, CQ	330	1.272	0.200
Patient 4	0	CQ	15.84	1.686	0.344
Patient 5	2	MTX, MPred	80.77	1.105	0.211
Patient 6	4	CQ	57.46	0.962	0.254
Patient 7	0	AZA	17.61	1.428	0.242
Patient 8	2	CQ, MPred	34.38	1.006	0.155
Patient 9	2	AZA, CQ, MPred	66.67	1.118	0.187
Patient 10	0	CQ, MPred	11.47	1.118	0.187
Patient 11	4	AZA, MPred	6.29	1.241	0.223
Patient 12	0	-	2	1.18	0.334
Patient 13	6	AZA, CQ, MPred	505	0.970	0.116
Patient 14	6	-	31	1.08	0.216
Patient 15	0	AZA, MPred	10	1.13	0.13
Patient 16	4	AZA, CQ, MPred	124	0.738	0.065
Patient 17	0	AZA, CQ, MPred	14.82	1.462	0.290
Patient 18	8	HCQ, MPred	68.62	0.212	0.023
Patient 19	6	MPred	93	0.908	0.088
Patient 20	2	MPred	32.25	0.128	0.315
Patient 21	0	AZA	19	1.328	0.211
Patient 22	2	-	45.3	1.27	0.24
Patient 23	0	CQ	7.7	0.967	0.11
Patient 24	0	CQ	89.4	0.120	0.128
Patient 25	0	CQ	6.2	0.102	0.261
Patient 26	4	CQ, MTX	34	0.982	0.176
Patient 27	0	CQ, MPred	10.4	1.73	0.261
Patient 28	2	-	34	1.54	0.31
Patient 29	4	CQ	16	0.96	0.23
Patient 30	0	MPred, MMF, RTX	6.3	1.243	0.253

AZA: Azathyoprin; CQ: chloroquin; HCQ: hydroxychloroquin; MMF: mycophenolat mofetil; MPred: methylprednisolon; MTX: methotrexate; RTX: rituximab. Reference range C3: 0.9-1.8 g/l, C4: 0.1-0.4 g/l, ds-DNA <20 IU/ml.

LupusQoL is a disease-specific health-related quality of life index. Considering the previous 4-week period, 34 items comprising eight domains evaluate physical health, emotional health, body image, pain, planning, fatigue, intimate relationships, and burden to others (12). The Cronbach's alpha indicating the reliability of the test was 0.977.

WPAI-Lupus is a disease-specific questionnaire developed to measure work capacity and daily activity. Six questions, covering four topics record the prior 7 days impairment: absenteeism, presenteeism, overall work impairment, and activity impairment (13).

The treated subjects completed questionnaires regarding quality of life and work productivity three times: before treatment (baseline: week 0), as well as 6 and 10 weeks after the initiation of treatment. The control group did not undergo balneotherapy and they completed the same questionnaires twice, at weeks 0 and 6. The

measurement instruments used for quality of life were SF-36 and LupusQoL, whereas for the work productivity WPAI-Lupus was used. Only patients completing at least 80% of the treatments were included in the analysis.

Statistical analysis. Statistical analysis was performed by using IBM SPSS Statistics v.26 (New York, NY, USA). Some of the missing data were added according to the "last observation carried forward" (LOCF) method. The parameters of the treated and control group were compared with the Mann-Whitney test, the changes between evaluations with the Wilcoxon test and the data of the treated group with the Friedman test. The distribution of continuous data was analyzed by the Kolmogorov-Smirnov test and the reliability of questionnaires with Cronbach's alpha. The level of statistical significance was $p < 0.05$.

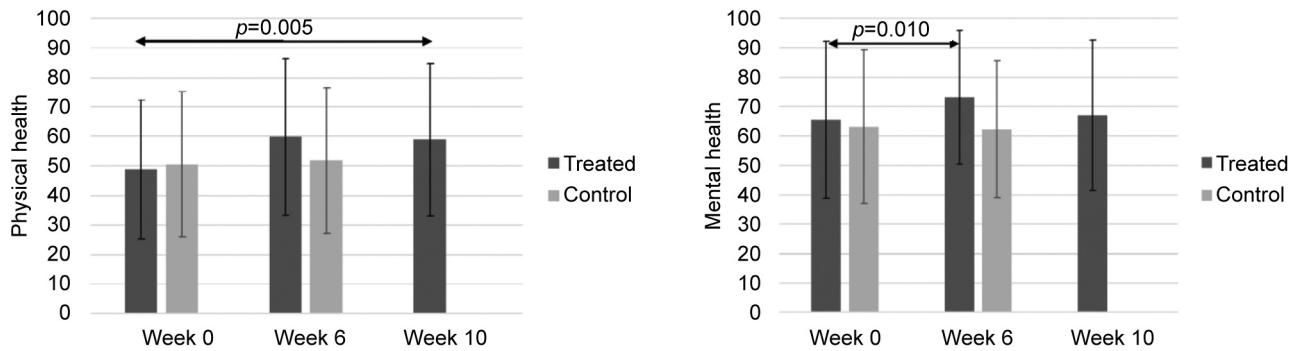


Figure 2. SF-36 questionnaire, physical component (PCS) (A) and mental component (MCS) (B).

The General Health data of the 6th week SF36-questionnaire were examined using G-power 3.1.9.7 program. At power 0.8 the required sample size was 19 patients in both groups. Unfortunately, the targeted number of cases was not reached. Regarding the calculations performed with the total number of cases, for a significant change in the General Health domain between weeks 0 and 6, power of 0.77 was applied.

Results

A total of 32 patients with SLE met the inclusion criteria, of whom two subjects declined to participate; therefore, we randomized 30 patients. One patient of the control group dropped out of the study. His data and the missing data of the other patients were replaced according to the last observation carried forward (LOCF) rules. Patients participated in at least 80% of the treatment sessions. No side effects were observed during the treatment period or the follow-up period. All patient data were analyzed according to the intent-to-treat principle (Figure 1). The mean age in the treated group was 54.93±11.53 years (range=38-78 years) and that of the control group 53.58±10.50 years (range=36-72 years). Patients were also equally distributed in terms of disease activity and disease duration. The mean SLEDAI was 2.125±0.947 in the active treatment group, 2.4286±1.437 in the control group, mainly based on the laboratory results (dsDNA, serum complement levels as C3 and C4) and in four cases on arthritis. There was no organic systems involvement behind higher SLEDAI indexes in any of the cases. The disease duration was 11.60±8.26 in the treated group and 11.50±7.72 in the control group. The sex distribution in the study population was 27 females and 3 males (Table I). Sixteen patients received balneotherapy, while 14 were assigned to the control group. At baseline, there were no significant differences between the parameters of the two groups.

Concerning the SF-36 questionnaire, both main components, physical component summary (PCS) and mental component summary (MCS) (Figure 2) improved significantly by the end

of the treatment (PCS, $p=0.003$; MCS, $p=0.01$). PCS was sustained until week 10. Subdomains of the physical component like physical activity ($p=0.05$), role limitation due to physical condition ($p=0.036$), social activity ($p=0.011$), and general health ($p=0.001$) improved significantly after the treatment -Week 6 -, but only the improvement of the role limitation due to the physical condition was sustained till week 10 ($p=0.019$). The Mann-Whitney test comparing treated (9.69 ± 8.84) vs. control (1.79 ± 8.23) showed significant improvement ($p=0.001$) in general health. There were no significant changes in any parameters of the SF-36 questionnaire in the control group (Table II).

By the end of the balneotherapy, the components of the LupusQoL questionnaire, pain, and physical health, showed a tendency of improvement (not significant), but no longer than the 3rd measurement on week 10. A reverse tendency was observed regarding the fatigue component, which deteriorated significantly ($p=0.035$) after the treatment. No significant changes in the LupusQoL parameters were observed (Table III).

According to the WPAI-Lupus questionnaire completed by 8 treated and 8 control patients there was no significant improvement of the work capacity in those receiving balneotherapy compared to controls. The daily activity of the active group improved significantly short term, week 0 vs. 6 ($p=0.036$) (Table IV). No adverse reactions were observed in the participants throughout the study.

Discussion

Systemic lupus erythematosus is a complex autoimmune disease with a chronic relapsing-remitting course and variable clinical manifestations. Fatigue and pain are common symptoms in addition to joint, skin, nervous system, kidney, and hematological disorders. Over the past years, there has been significant progress regarding the understanding of disease pathophysiology, optimal outcome

Table II. Results of SF36 questionnaire.

Domains	Week 0		Week 6		Week 10	<i>p</i> -Value	<i>p</i> -Value	<i>p</i> -Value	<i>p</i> -Value
	Mean±SD	<i>p</i> -Value	Mean±SD	<i>p</i> -Value	Mean±SD	(week 0 vs. 6)	(week 0 vs. 10)	(week 6 vs. 10)	(week 0 vs. 6 vs. 10)
Physical activity									
Treated	60.31±27.84	0.822	66.56±23.36		65.00±29.50	0.053	0.192	0.639	0.225
Control	63.57±22.31		63.93±25.21			0.786			
Role limitation due to physical condition									
Treated	40.62±41.71	0.984	60.94±42.79	0.224	62.50±40.82	0.036	0.019	1.000	0.053
Control	39.29±40.09		41.07±39.96			0.705			
Role limitation due to emotional problems									
Treated	66.67±47.14	0.637	81.25±32.13	0.193	72.92±34.89	0.167	0.380	0.157	0.233
Control	59.52±41.71		59.52±43.71			1.000			
Vitality									
Treated	53.12±23.23	0.951	56.56±30.40	0.377	52.19±29.32	0.326	0.824	0.179	0.140
Control	50.00±23.70		48.57±23.49			0.819			
Mental health									
Treated	72.25±19.40	0.918	74.25±21.36	0.580	71.50±25.46	0.547	0.972	0.260	0.867
Control	72.00±21.28		70.57±20.13			0.670			
Social activity									
Treated	70.31±33.19	0.951	80.47±24.14	0.240	71.88±26.42	0.011	0.810	0.035	0.094
Control	71.43±31.94		70.54±23.82			0.832			
Physical pain									
Treated	56.25±19.26	0.822	64.22±28.07	0.951	63.59±26.63	0.108	0.172	0.943	0.153
Control	59.46±26.28		64.64±27.17			0.160			
General health									
Treated	38.13±21.67	0.918	47.81±20.16	0.334	44.69±21.64	0.001	0.099	0.355	0.004
Control	40.00±22.10		38.21±21.89			0.478			

measures, and effective treatment strategies (3). It is widely accepted that the main therapeutic target is clinical remission, with low disease activity as the best possible alternative (14) and a treat-to-target strategy should be applied (3, 14). Even though remission or low disease activity is achievable in a significant proportion of patients, non-inflammatory complaints like exhaustion, fatigue and pain persist. These residual symptoms have a considerable impact on health-related quality of life, and over time may lead the patient to overestimate the disease activity, which in turn leads to dissatisfaction with the care process and could potentially impact adherence to treatment or care (15). It is therefore crucial, in the context of a modern approach to the management of SLE, to combine the control of the disease activity with an adequate improvement in the quality of life. Balneotherapy, as an adjunct to non-pharmacological treatment, may have a beneficial effect on non-inflammatory pain and fatigue, and therefore on the quality of life in SLE patients in remission or low disease activity.

Furthermore, during the last decades, balneotherapy has become a relevant part of the public health systems of many countries not only in Europe but in other countries like Japan or Israel. It is widely accepted as an effective, well-tolerated,

complementary approach in the treatment of several diseases, including cardiovascular, respiratory, gastrointestinal, endocrine, and neurological or rheumatic conditions (6-8, 16, 17). A great number of publications demonstrated its effectiveness in the treatment of osteoarthritis (18). Regarding balneotherapy for inflammatory musculoskeletal disorders, data are contradictory. In rheumatoid arthritis (RA), several studies demonstrated a positive effect of thermal water (19). In contrast, the 2015 Cochrane review found no evidence of balneotherapy efficacy in RA (20). In spondyloarthritis (SpA), clinical studies showed a good effect, moreover, balneotherapy may be used in addition to TNF inhibitors (21). In systemic sclerosis, mud therapy was effective to treat hand involvement (22). Regarding non-pharmacological treatments in SLE, most data have been published on exercise. A systematic review and meta-analysis found that exercise had no deleterious effect on disease activity; it may even improve cardiorespiratory capacity, reduce fatigue, and positively influence depression (23). Twelve weeks of progressive treadmill aerobic exercise increases cardiorespiratory fitness without exacerbating arterial stiffness, inflammation, or oxidative stress in women with SLE (24). Although most studies report positive effects of exercise (26), a Turkish

Table III. Results of Lupus quality of life questionnaire.

Domains	Week 0		Week 6		Week 10	p-Value	p-Value	p-Value	p-Value
	Mean±SD	p-Value	Mean±SD	p-Value	Mean±SD	(week 0 vs. 6)	(week 0 vs. 10)	(week 6 vs. 10)	(week 0 vs. 6 vs. 10)
Physical health									
Treated	76.09±18.66	0.728	77.19±18.75	0.637	75.76±20.95	0.128	0.648	0.566	0.066
Control	73.21±19.10		75.89±19.55			0.292			
Pain									
Treated	77.50±15.94	0.984	80.83±13.96	0.377	76.25±18.05	0.235	0.677	0.057	0.097
Control	77.14±16.48		76.67±15.64			0.832			
Planning									
Treated	82.08±20.18	0.854	79.58±26.38	0.854	78.75±25.90	0.932	0.799	0.317	0.707
Control	79.05±23.07		79.05±21.86			0.854			
Intimate relationships									
Treated	74.44±32.83	0.862	72.22±32.32	0.972	70.00±33.91	0.157	0.180	0.655	0.264
Control	76.67±23.48		76.67±23.87			1.000			
Burden to others									
Treated	86.25±14.03	0.637	84.79±21.77	0.473	81.25±22.07	0.619	0.124	0.061	0.184
Control	81.42±20.78		82.38±18.41			0.465			
Emotional health									
Treated	82.08±20.76	0.498	82.29±19.46	0.637	78.75±21.08	0.878	0.106	0.010	0.115
Control	77.38±21.21		81.67±4.78			0.116			
Body image									
Treated	83.94±20.15	0.790	80.04±18.71	0.886	80.71±23.42	0.248	0.233	0.790	0.223
Control	80.52±24.09		79.72±19.40			0.721			
Fatigue									
Treated	75.62±23.66	0.448	72.81±24.76	0.637	71.25±24.87	0.227	0.035	0.386	0.174
Control	71.79±22.31		71.43±18.23			0.739			

Each domain is derived from a 100-point value normalized to the average of the question groups; the higher the value, the better. Bold values represent significant differences.

Table IV. Results of the WPAI-Lupus questionnaire.

Domains	Week 0		Week 6		Week 10	p-Value	p-Value	p-Value	p-Value
	Mean±SD	p-Value	Mean±SD	p-Value	Mean±SD	(week 0 vs. 6)	(week 0 vs. 10)	(week 6 vs. 10)	(week 0 vs. 6 vs. 10)
Absence from work due to SLE									
Treated	1.75±3.88	0.645	1.50±4.24	0.442	2.25±4.20	0.655	1.000	0.655	0.905
Control	5.50±8.73		7.25±13.85			1.000			
Absence from work for other reasons									
Treated	2.88±4.64	0.798	0.50±1.41	0.645	3.25±6.23	0.102	0.715	0.180	0.146
Control	11.00±18.11		6.00±14.02			0.414			
Working hours									
Treated	31.63±8.84	0.721	33.25±11.17	0.959	33.50±11.11	0.596	0.588	1.00	0.705
Control	24.75±18.76		31.88±16.15			0.273			
Impact of SLE on work (1-10)									
Treated	2.00±1.77	0.279	1.88±1.73	0.080	1.88±1.36	0.317	0.705	0.480	0.247
Control	3.50±2.67		3.88±2.30			0.480			
Impact of SLE on other activities (1-10)									
Treated	3.50±2.61	0.697	2.75±2.02	0.294	2.94±2.64	0.036	0.244	0.546	0.264
Control	4.07±3.15		3.79±2.69			0.763			

Eight treated and eight control patients were employed. They completed questions 2 to 5. Question 6 was for everyone. Bold values represent significant differences.

study demonstrated that the majority of studied patients with SLE had high levels of kinesiophobia, the fear that physiotherapy may increase fatigue (26).

Since the reduction of fatigue is an unmet need in the treatment of SLE patients, and Hungary is one of the richest countries in the world in mineral and thermal water resources, we performed this pilot study. As this is the very first study on balneotherapy in patients with SLE, we were unable to compare our results with those of other studies. In our SLE cohort, fatigue was not negligible and even worsened after balneotherapy. However, the disease-specific health-related quality of life index (LupusQoL) components assessing pain, physical health, and to a lesser extent emotional health improved shortly after treatment. This tendency was not present at the 3rd measurement. Some SF-36 components as physical activity, role limitation due to physical condition, social activity and general health showed significant improvement. Increased work disability has been demonstrated in SLE (27). Among our patients, only 16 out of 30 were employed full-time at baseline, and there was no significant improvement in the work capacity in those receiving balneotherapy. The daily activity improved significantly in the short term. In terms of the water composition of the three baths, the water of the Budapest Széchenyi Bath is rich in calcium-magnesium bicarbonate, Debrecen Nagyerdei Bath and Szeged Anna Bath have similar sodium bicarbonate content, with the Anna Bath having lower sodium concentration. According to our best knowledge, there is no comparative data available regarding the influence of waters with different mineral content on musculoskeletal diseases. Therefore, the moderate difference between the mineral waters is not expected to influence our results. Due to the relatively low number of patients, subgroup analysis was not possible.

Our study has strengths and limitations. The main strength is that this is the very first study that assessed the effects of balneotherapy on SLE. Limitations include the relatively low number of patients and the short follow-up time. Longer follow-up studies with a larger number of patients should be carried out in the future.

Conclusion

In summary, although our results have shown only short-term effects, balneotherapy proved to be beneficial for patients with SLE. It had no deleterious effects on disease activity; therefore, it may be used as a complementary, non-pharmaceutical therapeutic remedy for SLE patients in remission or with low disease activity.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

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