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Nonpharmaceutical treatment of distal sensorimotor polyneuropathy in diabetic patients: an unblinded randomized clinical trial

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Abstract

Background For Diabetic polyneuropathy, the most prevalent form of polyneuropathy, there is a lack of evidence-based treatment options. Current approaches include pain management, alpha-lipoic acid, and antidepressants. Physical interventions, such as electrical stimulation (four-chamber galvanic bath) have been suggested but have limited supporting evidence. Heated granular stone therapy is another option to consider.

Methods An unblinded randomized controlled trials was conducted in 68 diabetic patients with distal sensorimotor polyneuropathy undergoing rehabilitation for diabetes mellitus as a primary or secondary diagnosis in the Paracelsus-Harz-Clinic (Quedlinburg, Germany). Patients were randomized into either the intervention group receiving heated granulated stone footbaths, or the control group receiving four-chamber galvanic baths. The primary endpoint was the assessment of any change in polyneuropathy using a vibration sensation test (Rydel-Seiffer scale, 8/8) from admission to discharge, analyzed by t-test and multivariable regression. Additionally, serum TNF-α and IL-6 as potential markers for polyneuropathy were compared over time using paired t-test.

Results The mean age of the patients was 66.8 ± 7.8 years; 63.2% were male and mean BMI was 32.2 ± 6.4 kg/m^2. Of the patients, 98.5% suffered from type 2 diabetes (one patient with type I diabetes); 82.4% were receiving oral antidiabetic medication; and 58.8% were insulin dependent. Distal sensorimotor polyneuropathy improved in both groups. The sum score increased from 16.7 to 22.6 in the study group and from 20.3 to 23.6 in the control group. A t-test showed a non-significant difference in the change of sum score between the treatment groups (2.6 points, $p = 0.092$), but adjusting for potential risk factors favors the intervention group ($p = 0.043$). Both analyzed markers decreased over time in each treatment group with IL-6 showing a clinical and significant reduction in the control group ($p = 0.03$).

Conclusion Diabetic patients with distal sensorimotor polyneuropathy benefit from physical treatment with administration of electrical stimulation (four-chamber galvanic bath) or a therapy with heated granulated stones three times a week. Our results indicate that heated stone therapy may be a potential treatment option. However, further research is required to understand the underlying biological processes.

Trial registration The study was registered in clinical trials.gov (identifier: NCT05622630, registration date: 18/11/2022).

Keywords Diabetes mellitus, Distal sensorimotor polyneuropathy, Physical treatment

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Background

Diabetic neuropathy comprises various diseases with different forms of manifestation that can affect both the peripheral and the autonomic nervous system. The most common form is sensorimotor polyneuropathy [1]. The frequency of this condition varies in the literature, but up to 50% of patients have been reported to be affected [2]. Risk factors are numerous and include not only disease-specific factors such as the duration of diabetes or the setting of diabetes (hyperglycemia), but also comorbidities such as arterial hypertension, peripheral arterial disease (PAD), dyslipoproteinemia, and obesity and underlying lifestyle habits such as exercise, diet, alcohol consumption, and nicotine use [1].

Diagnosis of diabetic neuropathy is initially provided by anamnestic and clinical evidence, including the use of a 128-Hz tuning fork according to Rydel-Seiffer in sensorimotor polyneuropathy, but diagnosis should be expanded by other diagnostic procedures [3].

Studies have suggest that inflammatory processes are also involved in the pathogenesis of distal sensorimotor polyneuropathy. This has been further confirmed by studies of inflammatory biomarkers such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) as markers for the onset and progression of this disease [4].

Therapeutic options include tricyclic or other antidepressants, anticonvulsants such as pregabalin, and analgesics like metamizole or opioids are recommended [5]. There is little evidence on the effect of physical treatments [6], such as massages, alternating baths, or hydroelectric baths (four-cell bath), which are commonly used in German rehabilitation clinics. However, some studies have shown that external electrical muscle stimulation (EMS) and transcutaneous electrical nerve stimulation (TENS) are effective in treating symptomatic neuropathy in patients with type 2 diabetes [7–9]. Therefore, we aimed to analyze the effect of footbaths with heated granulated stones in comparison to four-cell baths in diabetic patients regarding the improvement in distal polyneuropathy.

Methods

Trial design

The study was registered in ClinicalTrials.gov (identifier and registration date: NCT05622630, 18/11/2022). For presenting the results, we used CONSORT reporting guidelines [10]. After receiving approval from the ethics committee of the Saxony-Anhalt Medical Association (Nr. 51/15) and written consent from participants, patients were 1:1- randomized to a study group or control group (parallel group design).

Participants

The study population consisted of diabetic patients with distal sensorimotor polyneuropathy who were in rehabilitation in the Paracelsus Harz Clinic due to cardiovascular diseases and/or diabetes mellitus and at least 18 years old. Exclusion criteria involved lack of consent, infection or skin damages on the extremities to be bathed, patients who had pacemaker or ICD implantations or metal in parts of the body to be bathed.

Interventions

In the study group, the patients were given a footbath with heated granulated stones of different sizes for a period of 20 min, during which time patients were encouraged to move their feet evenly (Fig. 1). The effectiveness and safety of this treatment was prospectively examined for the first time in a small pilot study with 10 patients, in which nearly all patients reported improvement of their symptoms. In addition, distal polyneuropathy as measured by the Rydel-Seiffer tuning fork improved in 9 patients. In the control group, therapy with a four-cell bath was carried out for a period of 20 min each. A four-cell bath is a hydroelectric partial bath. During treatment in the four-cell bath, the patient's extremities are in two arm and leg tubs. Two electrodes are installed in each of the four tubs, which can be switched on individually or used together. This makes the large-scale effect of galvanic current possible (Fig. 2). The prerequisite for receiving either of the therapies was intact skin with regards to wounds and infections (fungal diseases, etc.). It was necessary to disinfect the hands and feet prior to use.

Outcomes

The primary outcome was change in distal polyneuropathy, assessed by a vibration sensation test using a tuning fork (8/8 scale) according to Rydel-Seiffer. The

Fig. 1 Footbath treatment with heated stones (granules)

Fig. 2 Four-chamber galvanic bath

test was carried out on the meta-tarso-phalangeal joint of the great toe, the inner malleolus, and the tibial tuberosity. By summing up the scale values for 8 measurements, a total score (from 0 to 64) was calculated for each patient at admission and discharge.

Secondary outcomes, such as medical parameters (for example, blood pressure, weight, BMI, waist-hip ratio, blood glucose, HbA1c, and LDL-C) were determined. Furthermore, the patients received a questionnaire in which they were asked to describe their symptoms, how long they have existed, and how intense they are. The intensity was assessed using a Likert scale from 1 = minor symptoms to 6 = severe symptoms.

To further measure the effect of treatment, serum TNF-α and IL-6 as markers for polyneuropathy were measured. For this, whole blood samples were collected; sera were separated and then stored at −80˚C for assessment of IL-6 and TNF-α. The cytokines were quantified by flow cytometry (BD FACSCelesta™ Flow Cytometer, BD Biosciences, San Jose, CA, USA) using BD Cytometric Bead Array Human Flex Set for IL-6 and TNF-α (BD Biosciences) according to the manufacturer's instructions. FCAP Array, v. 3.0, software (Becton Dickinson, Franklin Lakes, NJ, USA) was used for data analysis. Results were expressed as pg/mL, based on standard concentration curves. Quality of life was measured using the SF-12 questionnaire and anxiety and depression using the HADS-D questionnaire. All secondary endpoints were measured at admission and discharge.

Sample size

The sample size calculation was based on the data from a pilot study of the primary outcome change in polyneuropathy (sum score, see above). By planning a two-sided t-test with 80% power, a significance level $\alpha = 0.05$, a mean change in the total score by 4 points in the footbath group and a mean zero change in the four-cell bath group, and a common standard deviation of 5.2 points in both groups, this calculation resulted in a sample size of $n = 28$ subjects per group. We assumed a drop-out rate of 20% over the course of the study at time T1 (after completion of the rehabilitation measure), which results in a sample size of $n = 34$ subjects per group.

Randomization and blinding

The patients were identified through our in-house hospital information system, then recruited and informed by the study doctors (Volha Laputsina and Axel Schlitt) and randomized in the chief physician's office. An external randomization list was created for randomization, with the randomization algorithm assigning patient IDs to the two treatment groups. Randomization was carried out using previously sealed, opaque, and consecutively numbered envelopes. Investigators and patients were not blinded to the treatment.

Statistics

For statistical analysis SPSS software was used. The primary outcome, change in vibration sum score, was analyzed using a t-test to compare the treatment groups. Furthermore, a multivariable linear regression model was constructed, taking into account the clinical important variables [11]: treatment group, gender, alcohol consumption, insulin usage, PAD, smoking and the intake of antidepressants. In addition, the development of potential markers for polyneuropathy, such as serum TNF-α or IL-6, was examined over time. We compared secondary endpoints at discharge using t-tests for independent samples. Furthermore, to compare the symptoms and markers over time, we used a paired t-test. The result of the primary analysis was deemed significant for a p-value lower than 0.05. All statistical statements regarding the secondary endpoints should be considered exploratory in nature.

Results

From 13.08.2019 to 24.08.2021, 34 patients per group (68 in total) were recruited in the study. Specifically, of 85 consecutive patients who met the inclusion criteria and were invited to participate in the study, 68 participated. Especially, no drop-out occurred during the intervention time. Patients had an average follow-up time of 3 weeks, and the study ended when the last patient measurement

was taken. The mean age was 66.8 ± 7.8 years; 63.2% were male, mean BMI was 32.2 ± 6.4 kg/m^2, and 14.7% were active smokers, with no clinically relevant differences in comparing the two treatment groups for these and other baseline variables (see Table 1). Among the patients, 98.5% suffered from type 2 diabetes (one patient with type 1 diabetes). Of these, 82.4% had received oral antidiabetics and 58.8% required insulin treatment, again with no clinically relevant differences in these and other diabetes variables when comparing the two treatment groups (see Table 1). One major clinical difference between the groups was the higher proportion of patients in the four-chamber galvanic bath group who had been treated with insulin (64.7%) in comparison to the study group (52.9%) as insulin treatment is known to be a risk factor for distal polyneuropathy [1]. Laboratory data showed that patients had not been optimally treated for diabetes, as shown by a mean HbA1c of 7.7 ± 1.2 mg/dl and a fasting serum glucose of 8.3 ± 2.4 mmol/l at admission (see Table 1).

We compared the subjective perception of the intensity of the symptoms using a Likert scale as presented in the methods section. Overall, the subjective symptoms improvement was 0.3 points for the complete sample. Precisely, a total improvement of 0.4 in the study group (3.7 at admission vs. 3.3 at discharge, $p=0.08$) and 0.3 in the control group (3.4 at admission vs 3.1 at discharge, $p=0.23$) was observed. Importantly, distal sensorimotor polyneuropathy improved in both groups as measured by vibration sensation with the tuning fork. The sum score increased from 16.7 to 22.6 in the study group and 20.3 to 23.6 in the control group (Fig. 3). The t-test showed a non-significant mean difference of 2.6 in the sum score change between the two groups ($p=0.092$). However, after adjusting for clinical important and skewed risk factors in the multivariable linear regression, the improvement difference favored the study group with a significant mean difference of 3.2 ($p=0.043$), see Table 2.

Daily capillary blood glucose profiles had improved according to the comparison of first to last daily profiles in both groups, however no statistical difference was observed between the groups at discharge (see Table 3).

Anxiety, depression and both SF-12 summation scales trend towards improvement in both groups without showing statistical difference between the treatments. Importantly, the improvement in the physical summation scale was more pronounced in the study group in comparison to the four-chamber galvanic bath (3.9 points vs. 1.0 points, $p=0.27$), see Table 4. As shown in Fig. 4a TNF-α decreased non-significantly in both treatment groups over time. To be concrete, a decrease in the study group from 89.3 ± 27.7 to 88.2 ± 25.4 pg/ml was observed ($p=0.84$), compared to the control group with a decrease from 76.9 ± 21.5 to 71.7 ± 12.3 pg/ml ($p=0.11$). IL-6 also decreased numerically in both treatment groups, namely from 14.8 ± 18.2 to 10.3 ± 7.6 pg/ml ($p=0.20$) in the study group and from 14.1 ± 20.5 to 6.1 ± 3.7 pg/ml ($p=0.03$) in the control group (Fig. 4b).

Discussion

In this open, prospective, randomized study, we showed that diabetic sensorimotor polyneuropathy improves with physical treatment methods including therapy with heated granulated stones or a four-cell bath as part of an inpatient rehabilitation program. More precise, a mean increase of 5.9 points was achieved by patients of the intervention group, while the controls group showed a mean increase of 3.3 points. Hence, both physical treatments were slightly more effective than originally expected by the sample size calculation and these results indicate that the therapy with heated granulated stones might be more efficient. Moreover, the effects of therapy with heated granulated stones vs. a four-cell bath in the parameters SF-12-physical summation scale and subjective pain sensation tended to be better according to a Likert scale. The inflammatory markers IL-6 and TNF-α, which have been found to be related to symptoms and progression of distal polyneuropathy [4], decreased only moderately during the study in both groups without showing any relevant differences in the intergroup comparison. However, regarding intragroup comparison, IL-6 decreased significantly in the control group from 14.1 ± 20.5 to 6.1 ± 3.7 pg/ml ($p=0.03$, Fig. 4b). The reason for this is unclear. Important factors increasing inflammatory markers in diabetes are ageing, insulin treatment, smoking, male sex, and obesity [12–14]. Additionally, it is known, that antidiabetic treatment decreases inflammatory markers in type 2 diabetes [15, 16]. Since patients were sufficiently treated during inpatient rehabilitation (see Table 3), we hypothesize that this might be a possible explanation for the decrease of inflammatory markers in both groups. Due to the diabetes pandemic, diabetic neuropathy represents the most common form of polyneuropathy worldwide [17, 18]. According to the national German care guideline for diabetes in adulthood, the prevalence of diabetic sensorimotor polyneuropathy is as high as 8–54% in type 1 and 13–46% in type 2 diabetes, respectively [18, 19]. The pathophysiological process in diabetic sensorimotor polyneuropathy might be explained by multiple factors such as microcirculation disorders, activation of alternative metabolic pathways, inflammation, formation of neurotoxic glycated proteins, and others [17, 18].

The most common form of distal polyneuropathy is the distally symmetrical form associated with sensory

Table 1 Baseline characteristics

Variable	All patients (*n* = 68)	Heated granulated stones (*n* = 34)	Galvanic four-cell bath (*n* = 34)
Sociodemographic factors			
Age (years)	66.8 ± 7.8	66.9 ± 7.5	66.8 ± 8.2
Male (%)	63.2	64.7	61.8
Body mass index (kg/m^2)	32.2 ± 6.4	31.5 ± 5.3	33.1 ± 7.3
Waist circumference (cm)	114 ± 14	114 ± 14	114 ± 14
Systolic blood pressure (mmHg),	144 ± 21	143 ± 21	146 ± 21
Diastolic blood pressure (mmHg)	81 ± 10	79 ± 11	84 ± 9
Heart rate (beats per minute)	80 ± 12	80 ± 12	80 ± 12
Active smoking (%)	14.7	11.8	17.6
Alcohol consumption (%)	36.8	35.3	38.2
Medical history			
Diabetes mellitus type I (%)	1.5	0	3
Diabetes mellitus type II (%)	98.5	100	97
Diabetes mellitus, only managed by diet (%)	7.4	11.8	2.9
Diabetes mellitus, oral antidiabetics (%)	82.4	85	79
Diabetes mellitus, insulin (%)	58.8	53	65
Diabetic retinopathy (%)	4.4	6	3
Diabetic nephropathy (%)	19.1	21	18
Arterial hypertension (%)	98.5	97	100
Dyslipoproteinemia (%)	70.6	71	71
Peripheral artery disease (%)	5.9	2.9	8.8
Coronary heart disease (%)	47.1	53	41
Drug therapy			
Insulin (%)	58.8	52.9	64.7
Biguanides (%)	60.3	61.8	58.8
Sulfonylurea (%)	5.9	0	11.8
DPP4 antagonists (%)	23.5	26.5	20.6
GLP1 agonists (%)	23.5	26.5	20.6
SGLT2 inhibitors (%)	32.4	32.4	32.4
Calcium channel blockers (%)	35.3	32.4	38.2
Diuretics (%)	60.3	70.6	50
ACE inhibitors (%)	36.8	29.4	44.1
Beta-blocker (%)	73.5	73.5	73.5
Angiotensin receptor blocker (%)	55.9	61.8	50
Oral anticoagulation (%)	17.6	14.7	20.6
Aspirin (%)	54.4	58.8	50
P2Y12 inhibitors (%)	27.9	29.4	26.5
Antidepressants (%)	16.2	23.5	8.8
Statins (%)	67.6	64.7	70.6
Antiepileptics (%)	20.6	20.6	20.6
Analgetics (%)	7.4	8.8	5.9
Laboratory data			
Creatinine, µmol/l	94 ± 27	92 ± 24	96 ± 31
Estimated Glomerular filtration rate, ml/min	62.5 ± 16.8	63.2 ± 15.5	61.8 ± 18.2
CRP, mg/l	5.8 ± 8.7	5.5 ± 6.0	6.2 ± 10.9
Leukocytes, gpt/l	8.2 ± 2.4	7.9 ± 2.8	8.4 ± 1.9
Hemoglobin, mmol/l	8.5 ± 0.9	8.4 ± 0.9	8.6 ± 0.9

Table 1 (continued)

Variable	All patients (*n* = 68)	Heated granulated stones (*n* = 34)	Galvanic four-cell bath (*n* = 34)
HbA1c, mg/dl	7.7 ± 1.2	7.5 ± 1.3	7.8 ± 1.1
Fasting serum glucose, mmol/l	8.3 ± 2.4	8.2 ± 2.7	8.4 ± 2.0
Total cholesterol, mmol/l	4.1 ± 1.1	4.4 ± 1.3	3.7 ± 0.5
LDL cholesterol, mmol/l	2.3 ± 0.9	2.4 ± 1.0	2.3 ± 0.8
Albumin, urine, mg/dl	34.0 ± 56.1	33.9 ± 30.9	34.1 ± 71.2

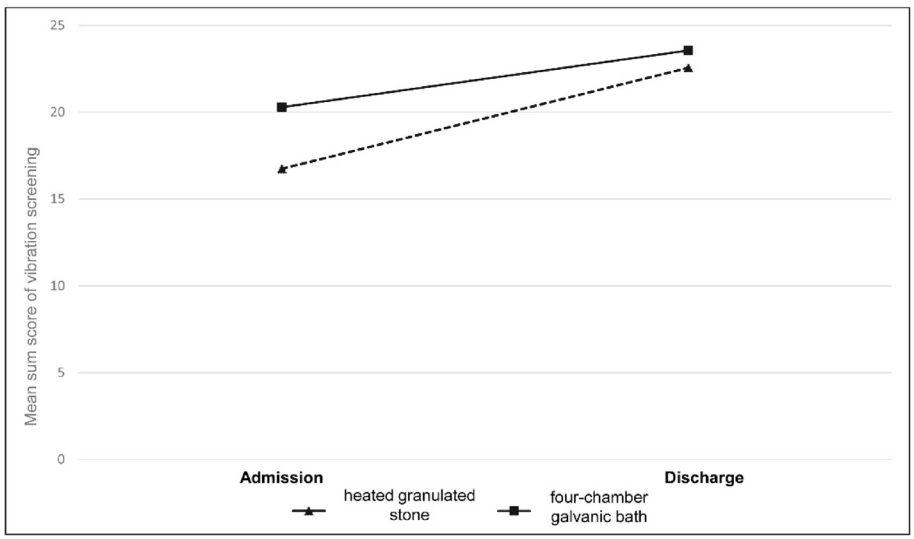

Fig. 3 Sum Score of vibration sensation in comparing the treatment groups (means). Patients treated with heated granulated stones changed from 16.7 to 22.6 (difference of 6.1), while patients treated with four-chamber galvanic bath changed from 20.3 to 23.6 (difference of 3.6). Difference in change of the sum score was non-significant (difference of 2.6, $p = 0.092$). $N = 68$

Table 2 Results of multivariable linear regression ($R^2 = 0.496$; $R^2_{adj} = 0.312, n = 68$)

	β	Standard deviation	*p*-value	95%-Confidence intervals
Treatment groups (Reference Heated stones) Four-chamber galvanic bath	-3.221	1.559	**0.043**	(-6.344; -0.098)
Gender (Reference: Male sex) Female	-0.951	1.806	0.601	(-2.667; 4.569)
Alcohol consumption (Reference: No) Yes	-0.177	1.620	0.913	(-3.068; 3.422)
Insulin treatment (Reference: No) Yes	4.697	1.591	**0.005**	(1.510; 7.885)
Smoking (Reference: No) Yes	1.809	0.940	0.060	(-0.075; 3.692)
Peripheral artery disease (Reference: No) Yes	2.721	3.229	0.403	(-3.747; 9.188)
Antidepressants (Reference: No) Yes	-1.838	2.155	0.397	(-6.154; 2.478)

Table 3 Capillary blood glucose, daily profile

Variable	All patients ($n=68$)	Heated granulated stones ($n=34$)	Four-chamber galvanic bath ($n=34$)	p-value[1]
07:00 am (mmol/l) Mean ± Standard deviation				
Admission	8.2 ± 2.5	8.0 ± 3.1	8.4 ± 1.9	0.73
Discharge	7.9 ± 1.9	7.8 ± 2.1	8.0 ± 1.7	
11:30 am (mmol/l) Mean ± Standard deviation				
Admission	8.7 ± 3.5	8.5 ± 3.2	8.9 ± 3.9	0.64
Discharge	7.9 ± 2.4	7.7 ± 2.5	8.1 ± 2.5	
2:30 pm (mmol/l) Mean ± Standard deviation				
Admission	8.7 ± 2.8	8.4 ± 2.7	8.9 ± 2.9	0.22
Discharge	8.2 ± 2.0	8.5 ± 2.3	8.0 ± 1.8	
7:00 pm (mmol/l) Mean ± Standard deviation				
Admission	9.0 ± 3.2	9.1 ± 3.5	9.0 ± 2.9	0.90
Discharge	8.1 ± 2.1	8.2 ± 2.2	8.1 ± 2.2	
2:00 am (mmol/l) Mean ± Standard deviation				
Admission	7.1 ± 2.5	7.1 ± 2.1	7.2 ± 2.8	0.95
Discharge	7.1 ± 1.9	7.1 ± 1.4	7.1 ± 2.3	

[1] p-value compares values between groups at discharge

Table 4 Results for HADS-D and SF-12 at admission and discharge

	All patients ($n=68$)	Heated granulated stones ($n=34$)	Four-chamber galvanic bath ($n=34$)	p-value[1]
HADS-D, anxiety score Mean ± Standard deviation				
Admission	6.1 ± 4.3	5.4 ± 4.2	6.8 ± 4.3	0.52
Discharge	5.2 ± 4.2	4.8 ± 4.3	5.5 ± 4.1	
HADS-D, depression score Mean ± Standard deviation				
Admission	5.8 ± 3.9	5.8 ± 4.0	5.7 ± 3.8	0.46
Discharge	5.3 ± 3.9	4.9 ± 4.0	5.6 ± 3.7	
SF-12 Physical summation scale Mean ± Standard deviation				
Admission	34.0 ± 9	34.1 ± 10.3	33.9 ± 7.8	0.27
Discharge	36.3 ± 10.3	38.0 ± 9.8	34.9 ± 10.6	
SF-12 Mental component summation scale Mean ± Standard deviation				
Admission	47.0 ± 10	48.1 ± 9.5	46.0 ± 10.6	0.49
Discharge	49.7 ± 9.9	50.6 ± 9.2	48.8 ± 10.5	

[1] p-value compares values between groups at discharge

symptoms such as numbness and paresthesia or also as small fiber neuropathy with typical symptoms of pain and loss of temperature sensitivity [17–20].

After diabetic sensorimotor polyneuropathy develops, symptom-based treatment, especially pain therapy, and optimal treatment of diabetic foot syndrome are recommended [17–20]; however, the effect of these therapies has not been proven in prospective, randomized studies. Other authors formulate this even more sharply. Ardeleanu V et al. state as a conclusion of their narrative review that "*although multiple therapies are available, the guidelines and recommendations regarding the treatment of diabetic neuropathy have failed to offer a unitary consensus, which often hinders the therapeutic options in clinical practice.*" [21]. Typically of and reflecting of the effect of inpatient rehabilitation in diabetes patients, general care of the patients was likely better during the time in the clinic than before, since e. g. glucose profiles improved. This may also play a role in symptom improvement. In the current study, a substantial part of the study population received antiepileptics, mostly pregabalin, and antidepressants, mostly duloxetine, as pain treatment (see Table 1). Surprisingly, only a small proportion of patients (7.4% in total) in the current study received analgesics as long-term medication, although almost all patients received them as rescue medication, most commonly metamizole.

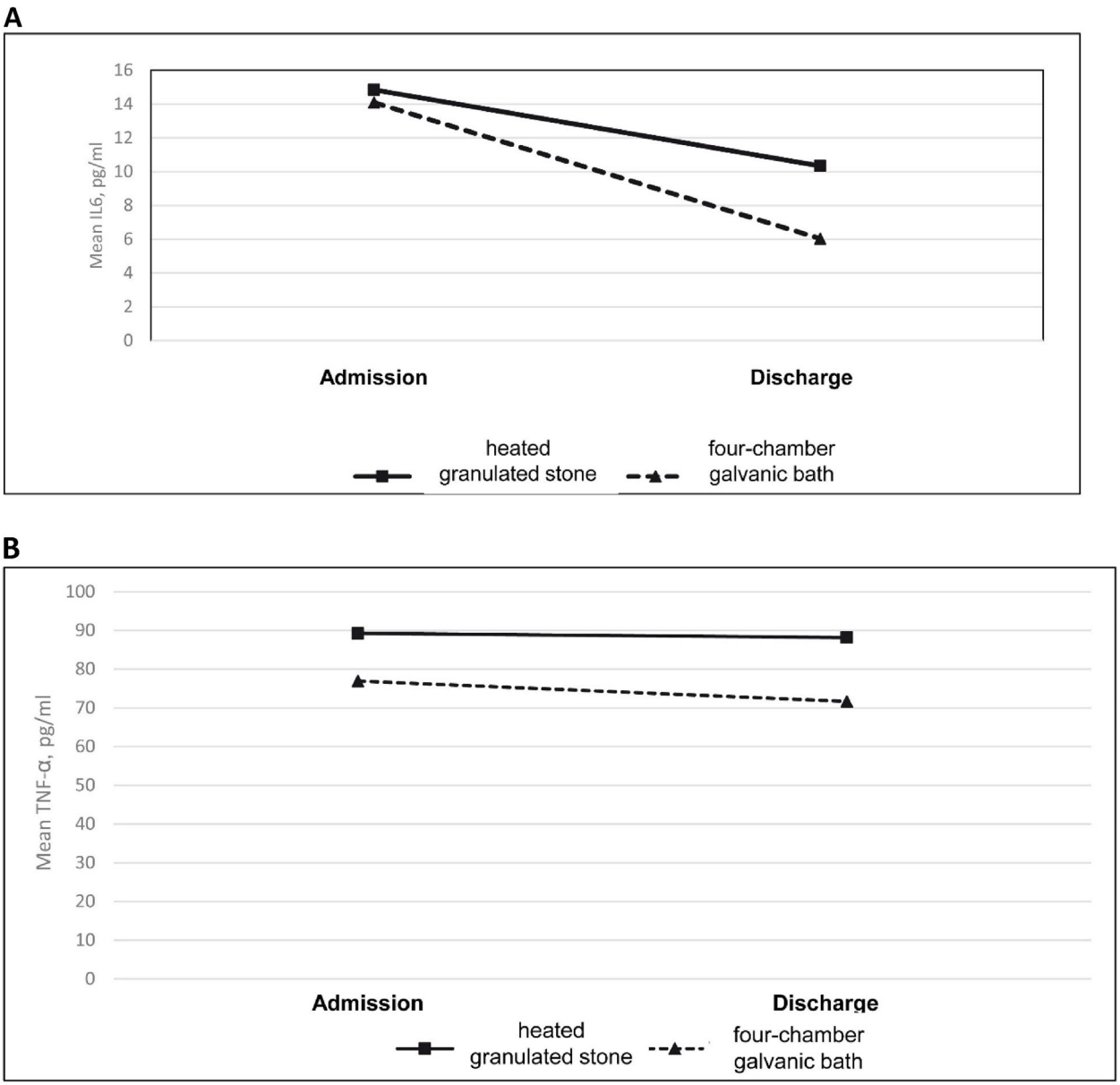

Fig. 4 Comparison of the two treatment groups at admission and discharge regarding IL-6 (**A**) and TNF-α (**B**). IL-6 reduced from 14.8 ± 18.2 to 10.3 ± 7.6pg/ml ($p = 0.20$) in the study group and from 14.1 ± 20.5 to 6.1 ± 3.7pg/ml ($p = 0.03$) in the control group. TNF-α reduced from 89.3 ± 27.7 to 88.2 ± 25.4pg/ml ($p = 0.84$) in the study group and from 76.9 ± 21.5 to 71.7 ± 12.3pg/ml ($p = 0.11$) in the control group. $N = 68$

Lifestyle changes including physical training and other nonpharmacological treatments are also recommended in diabetic sensorimotoric polyneuropathy [17–20, 22]. However, only little evidence for the success of these treatments is available. In their review, Liampas et al. found that some evidence exists for treating painful diabetic polyneuropathy with spinal cord stimulation as an adjuvant to conventional medical treatment [23]. Moreover, promising results, especially for treatment of painful diabetic peripheral neuropathy, came from trials investigating the efficacy of EMS and TENS [7–9].

In the current study, both treatment groups benefited from the treatments they received, whereas the effect of therapy with heated granulated stones was more pronounced than therapy with a four-chamber galvanic bath.

The underlying mechanism of action for direct current therapy by using a four-chamber galvanic bath is based on differences in the polarization of the membrane

potentials in cells. Hyperpolarization occurs at the anode and depolarization occurs at the cathode. Every cell has a resting potential. In the event of depolarization, this potential is reduced by the influx of sodium ions into the interior of the cell. In contrast, hyperpolarization is characterized by an increase in the resting potential. While depolarization increases the excitability of nerve and muscle cells, hyperpolarization dampens excitability. Dampening the excitability at the anode causes the analgesic effect of direct current therapy. In addition, hyperemia (increased blood flow) develops, which is caused by irritation of vasomotor nerves, the release of vasoactive substances, and the change in pH [24].

Unfortunately, the effect of therapy with heated granulated stones is not well understood. A previous study showed that a warm water footbath (with salt) improved diabetic sensorimotor polyneuropathy [25].

Current guidelines recommending that noninvasive, nonpharmacological therapy options can be used in the sense of a multimodal pain therapy and should also be considered. Here, especially transcutaneous electric nerve stimulation (TENS) and other forms of electric therapy are listed [19]. Pittler et al. reviewed so-called complementary therapies and found that the evidence is not fully convincing for most complementary and alternative medicine modalities in relieving neuropathic or neuralgic pain [25]. To the best knowledge of the authors, however, no recommendations exist for the physical treatments used in the current study as prospective studies are lacking.

Limitations

First, the medical therapy with insulin was not balanced in the study groups, which represents a study limitation. Of particular importance here is the higher proportion of patients under insulin treatment in the four-cell bath group. However, this risk factors for diabetic sensorimotor polyneuropathy symptoms was included in the multivariable model, which showed a significant effect of treatment with heated stones in comparison to the four-chamber galvanic bath (Table 2). Second, the participants and investigators were unblinded which might introduce biased assessments of outcomes. Additionally, the vibration test is a subjective method which may have been exacerbated the bias. Third, regression results have explorative nature and a final conclusion about superiority of one treatment cannot be made. Lastly, the single-center design also constitutes a limitation.

Conclusion

Although the biological mechanisms are not well understood, both footbath treatment with heated granulated stones and therapy with a galvanic four-cell bath reduced symptoms of diabetic sensorimotor polyneuropathy in patients with diabetes mellitus in this randomized study. Our study results indicate that a treatment with heated granulated stones might be a potential alternative. However, further research is needed to better understand the underlying processes.

Abbreviations

BMI	Body mass index
DN	Diabetic sensorimotoric polyneuropathy
HADS-D	Hospital Anxiety and Depression Scale-Deutschland
HbA1c	Hemoglobin A1c
IL-6	Interleukin-6
LDL-C	Low density lipoprotein-cholesterol
PAD	Peripheral arterial disease
SF-12	Short form (12)
TNF-α	Tumor necrosis factor-alpha

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Authors' contributions

AW, MR, VL and VH analyzed and interpreted the data. ASch and SuSch were major contributor in providing data. AStr and ASch were major contributor in writing the manuscript. All authors read and approved the final manuscript.

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None.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

We received approval from the ethics committee of the Saxony-Anhalt Medical Association and written consent from participants. Informed consent was obtained from all subjects and/or their legal guardian(s). This study was carried out according to the requirements of the declarations of Helsinki.

Consent to publication

Not applicable.

Competing interests

The authors declare no competing interests.

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