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ORIGINAL ARTICLE

Efficacy of therapeutic ultrasound in the treatment of chronic calcific shoulder tendinitis: a randomized trial

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ABSTRACT

BACKGROUND: Calcific shoulder tendinitis (CST) is characterized by hydroxyapatite crystals deposition in the rotator cuff tendons. Therapeutic exercises have been the mainstay of CST treatment, and evidence for therapeutic ultrasound (T-US) utilization and efficacy is lacking.
AIM: This study aimed to determine whether 4500 J T-US combined with therapeutic exercises is superior to therapeutic exercises alone regarding calcification size reduction and symptom improvement in chronic symptomatic CST.
DESIGN: This is a double-blind, placebo-controlled study.
SETTING: This study was conducted at a University Department for Rheumatic Diseases and Rehabilitation of a University Hospital.
POPULATION: Patients with chronic CST were analyzed.
METHODS: After eligibility allocation, 46 patients with sonographically confirmed CST were divided into two groups (56 shoulders, 26 per group). Both groups performed the same therapeutic exercises for half an hour under physiotherapist supervision. In the treatment group T-US (4500 J, 10 minutes per session at a frequency of 1 MHz and an intensity of 1.5 W/cm^2), and in the placebo group, sham T-US was applied for 4 weeks. Patients were assessed for: calcification size, shoulder pain, global health (GH), shoulder mobility (ROM), handgrip strength, Health Assessment Questionnaire Disability Index (HAQ-DI), Shoulder Pain and Disability Index (SPADI), and overall rehabilitation satisfaction.
RESULTS: All assessed variables improved in both groups. A significantly greater reduction in calcification size was recorded in the treatment group compared to placebo: -10.92% (IQR 4.61% to 19.38%) versus -5.04% (2.30% to 7.22%), P=0.008. There was a significantly greater decrease in HAQ-DI, reduction of VAS GH, and an increase in hand grip strength in the treatment group, while no significant differences were observed for other parameters between the groups.
CONCLUSIONS: Our results showed that adding the 4500 J T-US to therapeutic exercises in chronic symptomatic CST therapy resulted in greater calcification size reduction immediately following the treatment, as well as hand grip strength, HAQ-DI, and VAS GH improvement.
CLINICAL REHABILITATION IMPACT: 4500 J T-US combined with therapeutic exercises is more effective in reducing calcification size than therapeutic exercises alone in the treatment of chronic symptomatic CST.

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KEY WORDS: Rotator cuff; Ultrasonic therapy; Rehabilitation; Exercise.

Calcific shoulder tendinitis (CST) is characterized by the deposition of hydroxyapatite crystals in the rotator cuff (RC) tendons with a prevalence between 2.7% and 22%.[1, 2] CST most commonly affects women aged 30-50 years, with bilateral involvement in 10% of patients.[1, 3] Deposits are usually localized in the supraspinatus (ap-

prox. 1.5 to 2 cm from the supraspinatus insertion) and infraspinatus tendons, mostly noted[1, 4-6] as an incidental finding on standard radiographs in asymptomatic patients.[1, 7] The calcification pathogenesis has not yet been fully elucidated and different theories such as reactive calcification, enchondral ossification, and chondral metaplasia are proposed.[8] Degeneration of RC tendons caused by overuse and aging plays a role in the puzzle that precedes calcification.[8] Although the exact etiology is unknown, CST has been linked to type one diabetes and some thyroid disorders.[9]

CST can be divided into three distinct stages: pre-calcific (the predilection site for calcification undergoes fibrocartilaginous transformation), calcific (formative, resting, and resorptive), and post-calcific (tendon healing with fiber realignment and resolution of the deposit).[1, 7] Approximately half of the CST patients experience pain with acute or chronic range of motion (ROM) limitation which interferes with daily activities.[10] In some patients, CST shows a tendency of spontaneous and rapid regression over a different period of time.[11]

Diagnostic ultrasound (D-US), as a non-invasive, non-ionizing, and relatively inexpensive imaging method, is safe and reliable in assessing RC pathology. D-US can reliably distinguish between the following: CST (degenerative changes with calcification that are displayed in grayscale (B-mode) as hyperechoic structures, with or without acoustic shadow and accompanying inflammatory response), tendinopathy (degenerative changes without calcification), subacromial bursitis, or complete tendon rupture.[12, 13] A positive Doppler signal (increased flow from the inflammatory response to crystals) in the tendon around the calcification correlates with pain intensity.[14] Based on D-US findings, Chiou *et al.* classified calcifications into four types: type I is arcuate, type II fragmented or punctiform, type III nodular, and type IV cystic.[15] Spontaneous resorption may occur in types III and IV.

Depending on the calcification stage there are several treatment options such as surgery, percutaneous needle aspiration, extracorporeal shock-wave therapy (ESWT), and therapeutic US (T-US).[1, 16-18] Due to its thermal and non-thermal effects, T-US is often used in the treatment of musculoskeletal pathology.[19, 20] Pulse mode T-US is commonly used in the treatment of acute conditions and continuous mode in chronic ones.[21, 22] The frequency of T-US is selected depending on the depth of the targeted structure: 3 MHz frequency is used to treat surface structures, while 1 MHz is used for deeper (up to 5 cm) structures.[23] According to the Union of European Medical Specialists, Physical and Rehabilitation Medicine Section (UEMS-PRM) guidelines, the basis of CST therapy is therapeutic exercises to improve RC function and shoulder stabilizer muscle strength in order to restore full shoulder mobility. Passive therapeutic procedures such as T-US, transcutaneous electrical nerve stimulation (TENS), and other types of electrotherapy are treatments of choice.[24]

This double-blind, placebo-controlled study aimed to determine whether T-US (with total energy per treatment of 4500 J) in combination with therapeutic exercises is superior to therapeutic exercises alone, regarding the reduction of calcification size and pain, increased shoulder mobility, functional improvement, and overall satisfaction with rehabilitation outcome in patients with chronic symptomatic CST.

Materials and methods

Patients with sonographically confirmed CST between April 2021 and December 2021 at the University Department for Rheumatic Diseases and Rehabilitation, University Hospital Center (UHC) Zagreb participated in the study. The inclusion criteria were: calcification type I and II (according to Chiou *et al.*)[15] with a size 5 mm and more on sonogram, symptom duration of more than 2 months, Visual Analog Scale (VAS) pain 4 and more with limited ROM. The exclusion criteria were: calcification type III and IV (according to Chiou *et al.*)[15] with size less than 5 mm on sonogram, symptom duration less than 2 months, VAS pain 3 and less with full ROM, sonographically proven RC tear or subacromial/subdeltoid bursitis, history of shoulder intraarticular glucocorticoid injection within the past three months, oral glucocorticoid therapy, any type of shoulder physical therapy within the past six months, shoulder shock wave therapy within the past year, history of percutaneous calcification irrigation, diagnosis of frozen shoulder, cervical syndrome, cervicobrachial syndrome or inflammatory rheumatic disease, scapular dyskinesia with positive assisted and repositioning scapular test, acute shoulder trauma, history of shoulder surgery, the use of forearm/underarm crutches, pregnancy and the history of cancer.

Randomization

A spreadsheet program (The R Project for Statistical Computing) was used to generate a list of random numbers. Since patients could have CST in one or both shoulders, randomization was conducted according to shoulders, so the same patient could receive the T-US on one and the

sham T-US on the other shoulder. The patient and the physicians who performed the D-US were blinded regarding intervention.

Interventions

All patients underwent a standardized D-US examination of the shoulder[25] before and immediately after finishing the treatment (Philips Ultrasound, Inc., Affiniti 70, USA). Two independent examiners performed a D-US examination of each patient. First, calcification size was measured three times in both planes (longitudinal and transverse) by each physician, and the average values for each evaluator were taken into account. Using obtained average values, secondary average values were calculated for calcification size in both, longitudinal and transverse scans. Their product was calculated and considered as the final parameter of calcification size. Before and after the treatment all patients were assessed for: shoulder pain intensity at rest, at night, and during movement using VAS (ranges from 0 [no pain] to 10 [severe pain]), VAS global health (GH) (ranges from 0 [best health] to 10 [worst health]), passive and active shoulder ROM (goniometer in degrees), handgrip strength (hydraulic dynamometer in kilograms, measures were taken in a seated position, with the arm supported, elbow flexed at 90 degrees and the hand in a neutral position holding the dynamometer). Health Assessment Questionnaire Disability Index (HAQ-DI) was administered to assess everyday functionality and the Shoulder Pain and Disability Index (SPADI) to assess shoulder functional status.[26, 27] Immediately after the treatment, a five-point Likert Scale (1-extremely dissatisfied, 2-mostly dissatisfied, 3-neither satisfied nor dissatisfied, 4-mostly satisfied to 5-extremely satisfied) was used to assess overall therapy satisfaction.

Basic demographic data were obtained: gender, age, Body Mass Index (BMI), cigarette smoking, symptom duration, affected shoulder, type, and location of the calcification. According to the treated shoulder, patients were divided into two groups. The first group (the treatment group) performed therapeutic exercises for half an hour, and the T-US was applied for 10 minutes. The second group (the placebo group) performed the same therapeutic exercises for half an hour and the sham T-US was applied for 10 minutes. The T-US in a continuous mode was administered for 10 minutes per session at a frequency of 1 MHz and an intensity of 1.5 W/cm^2 over the area of calcification. The transducer (Sonopuls 490u, Enraf-Nonius, Rotterdam, The Netherlands) size is 5 cm^2 with a surface area of 10 cm^2 (two US head sizes). The total energy per treatment was 4500 J, calculated as a product of spatial average-temporal average (W/cm^2), transducer head size or effective radiating area (cm^2), and time per treatment (seconds). The device was initially standardized, while output was monitored regularly. An indifferent aqueous gel was used as the coupling. The position of the arm was adduction and internal rotation in CST supraspinatus, adduction and external rotation of the arm in CST subscapularis, and adduction with the palm over the opposite shoulder in CST infraspinatus. The sham T-US was administered in the same way but with the ultrasonic generator turned off. Therapeutic exercises consisted of shoulder girdle stretching exercises (trapezius, pectoralis, subscapularis, infraspinatus, triceps, serratus, rhomboids), shoulder girdle strengthening exercises, RC and scapular stabilizer strengthening (same muscles plus supraspinatus, deltoid, levator of the scapula). Patients exercised in the Clinic under the supervision of a physiotherapist for half an hour (10 minutes for stretching and 20 minutes for strengthening exercises). Treatment lasted for 4 weeks (5 times a week, a total of 20 times). The procedure was safe and well tolerated. Patients recorded how many times per day they used analgesics. Acetaminophen and tramadol were allowed for occasional pain relief except for two days prior to the final evaluation due to possible interference with the results. Nonsteroidal anti-inflammatory drugs and cryotherapy were prohibited.

All participants provided written informed consent and the study has been performed under the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study was approved by the Ethical Committees of the University Hospital Centre Zagreb and the University of Zagreb, School of Medicine. The study is registered to ClinicalTrials.gov with an ID NCT04822779.

Outcome measures

The primary outcome was the reduction in calcification size after the treatment. Secondary outcomes included subjective and objective measures: pain reduction, increased shoulder mobility, improved functional status (HAQ-DI, SPADI), and overall rehabilitation satisfaction (a five-point Likert Scale).

Statistical analysis

The sample size was determined using statistical software G*Power for Windows, version 3.1.9.7. By analyzing the power of the Mann-Whitney U Test in the analysis of the difference in calcification size reduction between the treatment and the placebo group with an assumed effect size of 0.9, a significance level α of 0.05, and a test power of

80%, the required sample size was at least 22 participants per group.

Smirnov-Kolmogorov Test was used in the analysis of continuous data distribution and according to the obtained results, appropriate non-parametric tests were used in the further analyses. Differences in categorical data between the groups were analyzed using the Fisher-Freeman-Halton exact test, or Fisher's Exact Test in the case of 2x2 format tables. Wilcoxon signed-rank test was used to test paired data for each group. Mutual differences in continuous variables between the groups were analyzed by the Mann-Whitney U test. The percentage change in value was calculated according to the formula (change (%) = ((Measured value after therapy / Measured value before therapy)-1) * 100. All P values below 0.05 have been considered significant. Statistical analyses have been performed by licensed program support The R Project for Statistical Computing.

Results

A total of 52 patients (58 shoulders) were enrolled in the study, out of which 46 patients (52 shoulders, 26 per group) completed the study. Drop out was due to irregular therapy attendance (four patients – four shoulders; one in the treatment and three in the placebo group), severe pain (one patient – one shoulder; treatment group), and development of cervicobrachial syndrome (one patient – one shoulder; treatment group). Six patients received bilateral treatment: one patient received T-US treatment for both shoulders, two patients received sham T-US for both shoulders, and three patients received T-US for one shoulder and sham T-US for the other (Figure 1). There were no significant differences regarding age, gender, smoking, employment, BMI, dominant hand, affected shoulder, calcification type and location, use of analgesics, symptom duration, and overall rehabilitation satisfaction between the treatment and the placebo group (Table I, II). The median overall rehabilitation satisfaction was 4.0 (IQR 4.0 to 5.0) in both groups.

The change in SPADI, VAS pain at rest, at night, and during movement, VAS GH, active and passive ROM, hand grip strength, calcification size, and HAQ-DI values before and after the treatment within each group are shown in Table III.[26, 27] No significant differences in total

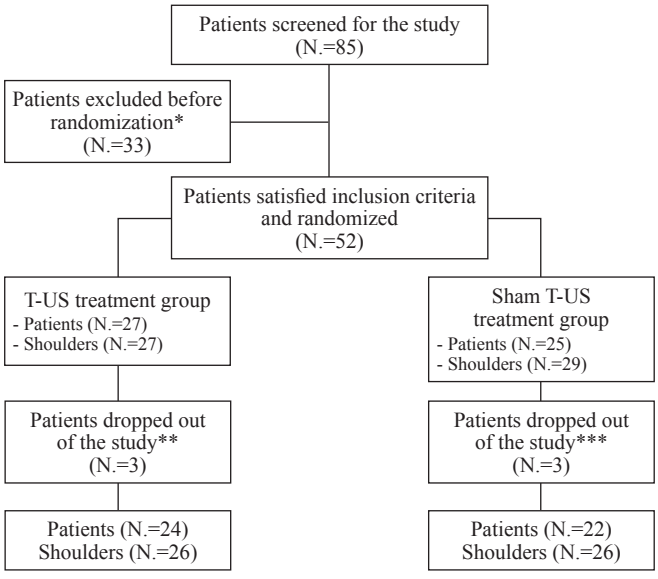

Figure 1.—Patients who were screened and randomized in the study. *Due to exclusion criteria 33 patients were not included in the study: 5 had an effusion in the tendon of the long head of the biceps, 8 had a complete supraspinatus rupture and 10 had a partial rupture with or without calcification, 5 had bursitis, 3 had tendinosis, and 2 patients had normal US finding; **one patient dropped out due to irregular therapy attendance, one developed cervicobrachial syndrome, and one withdrew due to severe pain; ***three patients dropped out due to irregular therapy attendance.

TABLE I.—*Differences in participants' characteristics between the groups at baseline: gender, cigarette smoking, dominant hand, affected shoulder, employment, calcification location and type, and the use of analgesics.*

		Placebo group N.=26		Treatment group N.=26		P
		N.	%	N.	%	
Gender	Male	4	15.40%	7	26.90%	0.499
	Female	22	84.60%	19	73.10%	
Smoking cigarettes *	0	18	69.20%	11	42.30%	0.052
	1	8	30.80%	11	42.30%	
	2	0	0.00%	4	15.40%	
Dominant hand	R	22	84.60%	26	100.00%	0.110
	L	4	15.40%	0	0.00%	
Affected shoulder	R	16	61.50%	14	53.80%	0.779
	L	10	38.50%	12	46.20%	
Employment **	0	15	57.70%	17	65.40%	0.780
	1	7	26.90%	7	26.90%	
	2	4	15.40%	2	7.70%	
Calcification location	Infra	2	7.70%	1	3.80%	0.224
	Sub	3	11.50%	0	0.00%	
	Supra	21	80.80%	25	96.20%	
Calcification type α	1	23	88.50%	21	80.80%	0.703
	2	3	11.50%	5	19.20%	
Use of analgesics β	1	17	65.40%	14	53.80%	0.474
	2	8	30.80%	11	42.30%	
	3	1	3.80%	0	0.00%	
	4	0	0.00%	1	3.80%	

*0: nonsmoker; 1: smoker; 2: former smoker (>5 years); **0: non-physical worker; 2: physical worker; 3: ex-physical worker; Infra: infraspinatus tendon; Sub: subscapularis tendon; Supra: upraspinatus tendon; α1: arcuate; 2: fragmented or punctiform; β1: no use of analgesics; 2: occasional pain relief (max three times a week); 3: daily pain relief (once a day); 4: daily pain relief (several times a day); R: right; L: left.

TABLE II.—*Differences in participants' characteristics between the groups at baseline: age, BMI, symptom duration, and overall rehabilitation satisfaction.*

	Groups	Min	Max	Percentiles			Mann-Whitney U	Z	P
				25.	Median	75.			
Age (years)	Placebo	33.00	76.00	52.50	57.00	65.00	253.0	-1.6	0.119
	Treatment	31.00	71.00	46.50	53.00	59.00			
BMI (kg/m^2)	Placebo	18.37	34.29	22.18	25.73	29.38	298.0	-0.7	0.464
	Treatment	18.37	32.05	23.00	27.99	29.75			
Symptom duration (months)	Placebo	3.00	24.00	5.75	8.00	11.25	316.0	-0.4	0.692
	Treatment	3.00	36.00	5.00	6.50	12.00			
Overall rehabilitation outcome satisfaction *	Placebo	2.00	5.00	4.00	4.00	5.00	270.0	-1.4	0.163
	Treatment	3.00	5.00	4.00	4.00	5.00			

BMI: Body Mass Index.
*Likert Scale (ranges from 1:– extremely dissatisfied, 2 – mostly dissatisfied, 3 – neither satisfied nor dissatisfied, 4 – mostly satisfied to 5 – extremely satisfied).

TABLE III.—*The change in measured variables before and after the treatment within each group: SPADI, VAS pain at rest/at night/during movement/general health, hand grip strength, active and passive ROM, calcification size, and HAQ-DI.*[26, 27]

	Groups					
	Placebo			Treatment		
	Mean±SD	Z	P	Mean±SD	Z	P
Δ total SPADI	-28.5±17.7	-4.458[a]	0.000*	-35.9±27.0	-4.286[a]	0.000*
Δ total SPADI (%)	-0.2±0.1	-4.458[a]	0.000*	-0.3±0.2	-4.286[a]	0.000*
Δ SPADI pain	-11.6±6.7	-4.459[a]	0.000*	-14.6±9.8	-4.289[a]	0.000*
Δ SPADI pain (%)	-0.2±0.1	-4.459[a]	0.000*	-0.3±0.2	-4.289[a]	0.000*
Δ SPADI disability	-16.9±12.1	-4.374[a]	0.000*	-21.3±18.0	-4.158[a]	0.000*
Δ SPADI disability (%)	-0.2±0.2	-4.374[a]	0.000*	-0.3±0.2	-4.158[a]	0.000*
Δ VAS pain at rest	-3.2±1.6	-4.460[a]	0.000*	-3.4±1.5	-4.458[a]	0.000*
Δ VAS pain at night	-3.7±2.0	-4.459[a]	0.000*	-4.2±1.9	-4.459[a]	0.000*
Δ VAS pain during movement	-3.6±1.5	-4.460[a]	0.000*	-4.2±1.8	-4.459[a]	0.000*
Δ VAS global health	-0.3±0.4	-3.645[a]	0.000*	-0.6±0.3	-4.400[a]	0.000*
Δ hand grip strength (kg)	1.6±2.0	-3.315[b]	0.001*	3.4±3.5	-4.220[b]	0.000*
Δ active flexion (°)	22.0±19.5	-4.383[b]	0.000*	24.2±16.9	-4.471[b]	0.000*
Δ active extension (°)	0.8±1.8	-2.000[b]	0.046*	1.5±3.1	-2.271[b]	0.023*
Δ active abduction (°)	32.3±26.9	-4.466[b]	0.000*	41.7±27.3	-4.462[b]	0.000*
Δ active adduction (°)	1.0±3.2	-1.518[b]	0.129	1.0±2.0	-2.236[b]	0.025*
Δ active internal rotation (°)	19.0±14.8	-4.295[b]	0.000*	13.5±14.0	-4.241[b]	0.000*
Δ active external rotation (°)	7.5±8.5	-3.695[b]	0.000*	7.7±12.4	-2.839[b]	0.005*
Δ passive flexion (°)	13.1±17.4	-3.749[b]	0.000*	13.5±16.0	-3.537[b]	0.000*
Δ passive extension (°)	0.4±2.0	-1.000[b]	0.317	0.6±3.3	-0.828[b]	0.408
Δ passive abduction (°)	25.6±26.9	-3.925[b]	0.000*	36.8±24.4	-4.294[b]	0.000*
Δ passive adduction (°)	0.2±3.9	-0.322[b]	0.748	0.6±2.6	-1.134[b]	0.257
Δ passive internal rotation (°)	16.3±15.3	-3.930[b]	0.000*	12.9±17.1	-3.638[b]	0.000*
Δ passive external rotation (°)	3.8±6.4	-2.844[b]	0.004*	7.3±12.6	-2.952[b]	0.003*
Δ calcification size (cm)	-0.084±0.226	-4.026[a]	0.000*	-0.154±0.185	-4.305[a]	0.000*
Δ HAQ-DI[4]	-0.4±0.3	-4.164[a]	0.000*	-0.6±0.4	-4.295[a]	0.000*

SPADI: Shoulder Pain and Disability Index;[27] VAS: Visual Analogue Scale; HAQ-DI: Health Assessment Questionnaire Disability Index;[26] [a]based on positive ranks; [b]based on negative ranks
*Statistically significant; °range of movement expressed in degrees

SPADI, VAS pain at rest, at night, and during movement, VAS GH, hand grip strength, and calcification size were observed between the groups before and after the treatment, except for HAQ-DI (Table IV).[26, 27] The HAQ-DI value was significantly lower in the treatment group after the therapy (P=0.021). In order to quantify the change of calcification size values, active and passive ROM, SPADI, VAS pain at rest, at night, and during movement, VAS GH, hand grip strength, and HAQ-DI between the groups before and after the treatment, relative (percentage) changes were calculated (Table V, VI).[26, 27] The primary outcome, a significantly greater reduction in the calcification size after the therapy in the treatment group compared to the placebo group, was achieved (Table VI).[26, 27] As for the second-

TABLE IV.—*Differences in HAQ-DI, VAS pain at rest/at night/during movement/general health, hand grip strength, total SPADI, and calcification size before and after the treatment between the groups.*[26, 27]

	Groups	Min	Max	Percentiles			Mann-Whitney U	Z	P
				25.	Median	75.			
HAQ-DI before therapy	Placebo	0.63	1.88	0.75	1.00	1.28	337.0	0.0	0.985
	Treatment	0.25	2.50	0.72	1.00	1.38			
HAQ-DI after therapy	Placebo	0.00	1.25	0.47	0.69	0.88	212.5	-2.3	0.021*
	Treatment	0.00	2.38	0.09	0.38	0.63			
VAS pain at rest before therapy	Placebo	4.00	8.90	4.18	4.80	7.55	313.0	-0.5	0.647
	Treatment	4.00	9.20	4.60	5.25	5.98			
VAS pain at rest after therapy	Placebo	0.30	7.20	0.93	1.80	3.50	304.5	-0.6	0.539
	Treatment	0.00	5.30	0.68	1.30	3.13			
VAS pain at night before therapy	Placebo	0.50	8.50	4.68	5.65	7.68	329.0	-0.2	0.869
	Treatment	0.50	9.00	4.98	5.75	6.73			
VAS pain at night after therapy	Placebo	0.10	6.90	0.38	1.30	3.63	271.5	-1.2	0.222
	Treatment	0.00	6.20	0.20	0.60	2.53			
VAS pain during movement before therapy	Placebo	4.20	8.80	5.08	5.85	8.00	323.0	-0.3	0.784
	Treatment	4.70	8.90	5.38	6.15	6.93			
VAS pain during movement after therapy	Placebo	0.20	7.00	1.43	2.20	3.73	262.5	-1.4	0.167
	Treatment	0.00	6.00	0.68	1.60	3.05			
VAS global health before therapy	Placebo	0.50	6.00	2.00	3.00	3.85	276.5	-1.1	0.256
	Treatment	0.90	5.00	2.00	2.95	3.00			
VAS global health after therapy	Placebo	0.50	6.00	1.73	2.80	3.50	240.5	-1.8	0.072
	Treatment	0.50	4.30	1.73	2.00	2.50			
Hand grip strength *** before therapy	Placebo	14.00	64.00	17.75	26.00	32.00	313.5	-0.4	0.653
	Treatment	12.00	44.00	18.75	27.00	32.25			
Hand grip strength *** after therapy	Placebo	14.00	66.00	21.50	26.00	32.00	268.0	-1.3	0.200
	Treatment	14.00	46.00	24.00	30.50	37.25			
Total SPADI before therapy	Placebo	19.00	124.00	66.00	83.00	101.00	336.5	0.0	0.978
	Treatment	24.00	114.00	67.00	85.00	94.25			
Total SPADI$^{\alpha}$ after therapy	Placebo	2.00	91.00	27.00	56.50	73.00	289.0	-0.9	0.370
	Treatment	0.00	111.00	23.75	45.50	60.50			
Calcification size$^{\alpha}$ before therapy	Placebo	0.22	4.87	0.43	0.52	0.84	233.0	-1.9	0.055
	Treatment	0.24	3.75	0.51	0.92	1.46			
Calcification size$^{\alpha}$ after therapy	Placebo	0.21	3.72	0.41	0.51	0.81	256.0	-1.5	0.133
	Treatment	0.24	3.15	0.44	0.80	1.16			

*Statistically significant difference in efficacy between the groups; ***expressed in kg; $^{\alpha}$absolute change in calcification size.
HAQ-DI: Health Assessment Questionnaire Disability Index;[26] VAS: Visual Analogue Scale; SPADI: Shoulder Pain and Disability Index.[27]

ary outcomes, there was a significantly greater decrease in HAQ-DI, a reduction of VAS GH, and an increase in hand grip strength in the treatment group (considering relative changes) compared to the placebo group, while no significant differences were observed for other measured parameters between groups (Table V, VI).[26, 27]

Discussion

Therapeutic exercises and non-steroidal anti-inflammatory drugs represent the first-line treatment of CST.[28, 29] However, if CST becomes chronic ESWT (including radial, low-energy/high-energy focused ESWT), ultrasound-guided needling, TENS, and T-US are considered in the treatment.[30] In a systematic literature review and meta-analysis on the efficacy of conservative treatment of chronic CST, Wu *et al.* concluded that among the above-mentioned procedures radial and high-energy-focused ESWT, as well as ultrasound-guided needling, alleviate pain and achieve complete calcification resolution and ought to be considered first when initial conservative treatment fails.[30] Moreover, for promoting functional recovery, high-energy-focused ESWT has proven to be the best therapy when compared to low-energy-focused ESWT, TENS, and T-US.[30] Even though T-US is not considered the most effective procedure in the treatment of chronic CST,[30] it is a relatively inexpensive, safe, and widely accessible therapeutic procedure. Furthermore, it is necessary to have other potentially effective options as a treatment of choice in chronic CST, given that not all rehabilitation facilities have high-energy-focused ESWT at their disposal. Next, there are several contraindications

TABLE V.—*Differences in active and passive ROM before and after the treatment between the groups expressed in percentage change.*

	Groups	Min	Max	Percentiles			Mann-Whitney U	Z	P
				25.	Median	75.			
Change in active flexion (%)	Placebo	0.00	83.33	5.88	10.85	22.11	310.5	-0.5	0.614
	Treatment	2.86	60.00	5.88	12.50	30.77			
Change in active extension (%)	Placebo	0.00	16.67	0.00	0.00	0.00	312.0	-0.7	0.489
	Treatment	0.00	50.00	0.00	0.00	2.78			
Change in active abduction (%)	Placebo	2.86	121.43	6.06	14.04	43.97	251.0	-1.6	0.111
	Treatment	5.88	157.14	12.50	30.95	57.87			
Change in active adduction (%)	Placebo	-11.11	50.00	0.00	0.00	0.00	319.5	-0.5	0.622
	Treatment	0.00	25.00	0.00	0.00	0.00			
Change in active internal rotation (%)	Placebo	0.00	250.00	14.29	27.92	66.67	249.5	-1.6	0.105
	Treatment	0.00	166.67	6.67	16.67	35.00			
Change in active external rotation (%)	Placebo	0.00	70.00	0.00	7.18	14.29	296.5	-0.8	0.429
	Treatment	-14.29	225.00	0.00	0.00	22.89			
Change in passive flexion (%)	Placebo	0.00	56.52	0.00	3.37	12.95	337.0	0.0	0.985
	Treatment	-2.78	50.00	0.00	5.88	14.55			
Change in passive extension (%)	Placebo	-12.50	14.29	0.00	0.00	0.00	323.5	-0.4	0.687
	Treatment	-20.00	33.33	0.00	0.00	0.00			
Change in passive abduction (%)	Placebo	0.00	125.00	2.14	10.80	30.43	234.0	-1.9	0.056
	Treatment	0.00	100.00	10.85	26.79	50.54			
Change in passive adduction (%)	Placebo	-25.00	50.00	0.00	0.00	0.00	317.0	-0.6	0.576
	Treatment	-14.29	50.00	0.00	0.00	0.00			
Change in passive internal rotation (%)	Placebo	0.00	200.00	4.41	21.54	63.54	273.5	-1.2	0.232
	Treatment	0.00	183.33	0.00	9.38	32.69			
Change in passive external rotation (%)	Placebo	0.00	41.67	0.00	0.00	6.25	309.0	-0.6	0.550
	Treatment	0.00	150.00	0.00	0.00	12.95			

TABLE VI.—*Differences in HAQ-DI, VAS pain at rest/at night/during movement/global health, hand grip strength, SPADI, and calcification size after the treatment between the groups expressed in percentage change.*[26, 27]

	Groups	Min	Max	Percentiles			Mann-Whitney U	Z	P
				25.	Median	75.			
Change HAQ-DI (%)	Placebo	-100.00	20.00	-60.00	-36.93	-23.75	192.0	-2.7	0.007*
	Treatment	-100.00	0.00	-89.29	-69.05	-47.50			
Change VAS pain at rest (%)	Placebo	-93.02	-7.58	-83.26	-62.54	-40.97	312.0	-0.5	0.634
	Treatment	-100.00	-5.36	-85.18	-69.37	-42.94			
Change VAS pain at night (%)	Placebo	-97.87	-4.92	-90.83	-78.24	-47.34	270.5	-1.2	0.217
	Treatment	-100.00	-3.23	-95.94	-81.77	-55.03			
Change VAS pain during movement (%)	Placebo	-95.74	-7.89	-80.09	-59.31	-46.78	261.0	-1.4	0.159
	Treatment	-100.00	-7.69	-88.64	-74.79	-48.72			
Change VAS global health (%)	Placebo	-50.00	0.00	-21.25	-7.70	0.00	163.0	-3.2	0.001*
	Treatment	-50.00	0.00	-34.17	-20.00	-16.00			
Change in hand grip strength (%)	Placebo	0.00	42.86	0.00	2.71	10.61	199.5	-2.6	0.010*
	Treatment	0.00	100.00	3.72	7.42	20.00			
Change in SPADI total (%)	Placebo	-91.30	-7.59	-61.87	-37.22	-17.55	297.0	-0.8	0.453
	Treatment	-100.00	0.00	-61.84	-47.05	-24.96			
Change in SPADI pain (%)	Placebo	-91.30	-5.56	-58.52	-33.74	-19.32	270.0	-1.2	0.217
	Treatment	-100.00	0.00	-66.33	-46.09	-28.56			
Change in SPADI disability (%)	Placebo	-85.42	-9.30	-64.14	-33.96	-17.27	291.0	-0.6	0.522
	Treatment	-100.00	14.06	-62.88	-49.32	-26.21			
Change in calcification size (%)	Placebo	-23.45	5.03	-7.22	-5.04	-2.30	193.0	-2.7	0.008*
	Treatment	-41.85	4.25	-19.38	-10.92	-4.61			

*Statistically significant.
HAQ-DI: Health Assessment Questionnaire Disability Index;[26] VAS: Visual Analogue Scale; SPADI: Shoulder Pain and Disability Index.[27]

for ESWT, such as severe coagulopathy, and side effects of high-energy-focused ESWT like hematoma, or as in patients with a reduced pain threshold.[16, 31] There is a low body of evidence regarding its efficacy in the treatment of CST with only a few studies (that used different T-US performances) published on a total of 131 patients/146

shoulders analyzing calcification size reduction after the treatment.[32-34] Proper analysis of other available studies in the treatment of chronic joint pain (including shoulder pain) using the T-US is difficult due to their heterogeneity (lack of blindness, bias, insufficient follow-up, selection of T-US performances).[35-37] Consequently, a systematic literature review by Alexander *et al.* revealed that there are not enough studies to confirm or rule out the benefits of T-US in the treatment of shoulder soft tissue pathology (including CST), but a positive effect can be expected only if the total energy applied per treatment is higher than 2250 J.[38]

To the best of our knowledge, our study is the first to use 4500 J T-US in the treatment of chronic symptomatic CST. Since the effect of continuous mode T-US (thermal effects) is dose-dependent,[23] the results of our study will significantly contribute to the overall knowledge of T-US utilization in clinical practice. Our results showed that adding T-US to therapeutic exercises leads to a more significant calcification size reduction, as well as improvement in hand grip strength, HAQ-DI, and VAS GH than therapeutic exercises alone in the treatment of chronic CST. As for the primary endpoint, calcification size decreased in both groups after the therapy, but the size reduction was significantly greater in the treatment group -10.92% (IQR 4.61% to 19.38%) as opposed to -5.04% (2.30% to 7.22%) in the placebo group (P=0.008, (Table VI).[26, 27] Similar results were obtained by Ebenbichler *et al.* who treated 54 patients (a total of 61 shoulders) with either pulsed (ratio 1:4, frequency 0.89 MHz, intensity 2.5 W/cm^2) or sham T-US.[32] Interestingly, they noted improvement in both groups at the nine-month follow-up, probably because CST symptoms are self-limiting.[32] Since the results of our study support the efficacy of continuous mode T-US, it seems that calcification size reduction is primarily attributed to the thermal effects of T-US. It is assumed that at higher intensities T-US could trigger or accelerate the disruption of apatite-like microcrystals which then may stimulate macrophages to remove calcifications by phagocytosis.[32, 39-41] Another study conducted by Shomoto *et al.* on 40 patients concluded that T-US (frequency 3 MHz, intensity 1.0-2.0 W/cm^2 applied for 5 minutes 3 times a week) in combination with therapeutic exercises leads to calcification size reduction with a shorter duration of the disease in comparison with therapeutic exercises alone.[33] However, this clinical study had intermittent and variable rehabilitation duration with undefined total T-US energy per treatment.[33] We observed a greater reduction in pain at rest, during movement, and at night in the treatment group (comparing absolute values), although it did not reach statistical significance (Table IV).[26, 27] A significant difference in VAS GH after the therapy between the groups was observed, implying the patients considered their global health improved significantly better than those in the placebo group (Table VI).[26, 27] There was no difference between the groups when analyzing relative improvement in the total SPADI, as well as its domains of pain and disability. On the contrary, a significant difference between the groups was observed in the relative improvement of the HAQ-DI after the therapy between groups, as shown in Table VI.[26, 27] HAQ-DI score was reduced in both groups after the therapy which implies their function had improved, moreover a significantly greater HAQ-DI score reduction was observed in the treatment group.

The results of a 10-year follow-up study of patients with CST treated with T-US (both the structure and function-related long-term course) confirmed that there is a high likelihood that calcium deposits will resolve and that symptoms and function will fully recover in the long term. Thus, adding the T-US to the treatment would provide a good short- and intermediate-term improvement regarding calcification resorption and gain of function.[34] Therefore, T-US could speed up the process of rehabilitation. The authors also pointed out that no association between shoulder function and the presence of a calcium deposit in RC structures was identified, suggesting that calcium deposits as incidental findings on standard radiographs (X-rays) are probably unrelated to painful symptoms and impaired shoulder function.[34] RC tendinopathies with or without partial/complete RC tears, bursitis, impingement syndrome, inflammatory rheumatic diseases, and visceral referred pain can co-exist with CST in patients with chronic shoulder pain and contribute to nociceptive pain. Furthermore, the size and anatomical location of calcification can play a role in impingement syndrome (indirectly due to concomitant bursa inflammation or directly due to the subacromial space narrowing with greater calcification causing more pronounced symptoms). Thus, and small deposits are sometimes associated with more pronounced symptoms than large ones, especially if intra-bursal migration occurs.[34, 42, 43] Our study included only patients with chronic symptomatic CST (symptom duration of more than 2 months, VAS pain 4 and more with limited ROM), which with broad and other specific exclusion criteria reduced the possibility of bias and left CST as the sole cause of chronic shoulder pain.

The influence of eccentric exercises in the treatment of

tendinopathy is well known.[44] While positive results were obtained in the treatment of Achilles tendinopathy,[45] the results in the treatment of CST are lacking and therefore in our study eccentric exercises were not performed. A study by Carlisi *et al.* on the impact of focused ESWT in combination with eccentric exercises on pain, function, and strength in patients with calcific supraspinatus tendinopathy concluded that adding supervised eccentric training of the abductor's muscles did not improve pain and function, although a mild, but statistically not significant increase in the maximum isometric abduction strength was observed.[46] In our study, active and passive shoulder ROM was increased in both groups after the therapy, without any significant differences between the groups (Table V), although passive abduction in the treatment group after the therapy approached the borderline of significance (P=0.056). It is interesting that a significantly greater range of active adduction after the therapy was observed in the treatment group (P=0,025), while in the placebo group the change was not statistically significant (P=0,129, Table III).[26, 27] Nevertheless, both therapeutic exercises combined with T-US, as well as therapeutic exercises alone increase shoulder ROM and therefore are rightly considered the basis of chronic CST therapy.[24, 29]

As far as we know, our study is the first in which hand grip strength was analyzed in patients with chronic CST after US therapy. Our findings showed a significant difference in hand grip strength improvement in the treatment group after the therapy, as shown in Table VI.[26, 27] The exact cause of this is not yet known, but increased capillary blood flow and tissue metabolism contribute to inflammatory mediators' outflow and consequently could lead to pain reduction,[23, 47, 48] which in combination with therapeutic exercises possibly increases hand grip strength.

Limitations of the study

The are two main limitations of the study. First, since the randomization was done according to shoulder rather than the patient, 6 participants received bilateral treatment and their HAQ-DI results can be confounding, given that HAQ-DI, as a functional index, is not solely limited to the function of the treated shoulder. Second, the inability to analyze the calcification size in three dimensions since D-US is a two-dimensional imaging method. Therefore, studies with both magnetic resonance imaging and D-US are warranted to compare the post-therapy calcification size reduction in three (volume) and two dimensions, with adequate follow-up.

Conclusions

This study showed that T-US combined with therapeutic exercises is superior to therapeutic exercises alone in the treatment of chronic symptomatic CST providing a good immediate improvement regarding several outcomes (calcification size reduction, hand grip strength, HAQ-DI, and VAS GH improvement). Our findings favor its wider implementation in chronic CST therapy protocol after a basic conservative treatment fails and other modalities, such as ESWT are not available, given it is an effective, inexpensive, and safe procedure.

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