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Clinical, sonographic, and molecular changes in calcific tendinitis of the shoulder following extracorporeal shockwave therapy: a prospective case–control study

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Background: Extracorporeal shockwave therapy (ESWT) is the primary treatment for calcific tendinitis of the shoulders, but what are the effects of clinical, sonographic, and molecular markers following ESWT in treating calcific tendinitis of the shoulder?
Methods: Twenty-eight patients were categorized into radiodense and radiolucent subgroups. In addition, clinical assessments included the visual analogue scale (VAS), Constant-Murley (CM) score, American Shoulder and Elbow Surgeon (ASES) score, sonographic evaluation, and serum enzyme-linked immunosorbent assay (ELISA). The participants completed a 1-year follow-up. All data were collected before and after treatment.
Results: After 1 year of follow-up, all patients showed notable improvement in VAS, CM, and ASES scores, with no significant clinical variations among the subgroups. However, the radiolucent group showed significant complete resorption and size reduction at the final follow-up. The sonographic evaluation revealed improved tissue perfusion and reduced calcification from 3 to 12 months in all patients, including those in the radiolucent group, but complete resorption of calcific deposits did not occur. The percentage of tissue perfusion was improved at 1 and 3 months after ESWT. There were no significant differences in the levels of the molecular markers interleukin-1 beta (IL-1 β) or IL-33, but the level of insulin-like growth factor 1 (IGF-1) was notably increased at 1 and 3 months post-ESWT. The BMP7 level was increased at 3 months and was then decreased significantly at 6 and 12 months.
Conclusion: ESWT improved symptoms, reduced calcification, enhanced tissue perfusion, and promoted angiogenesis and BMP7 activity. In particular, it benefited radiolucent type patients with better calcification resorption. Partial resorption led to improvements in transparency, and a second ESWT session at 3 months was recommended for optimal results.

Keywords: angiogenesis, BMP7, calcified shoulder, growth factor, shockwave

Introduction

Shoulder calcific tendinitis is a painful condition affecting ~3–7% of adults and is characterized by intractable pain, stiffness, and limitations in daily activities[1]. Although the exact etiology remains incompletely understood, it is believed to be associated with degenerative changes, repetitive stress, and metabolic dis orders. Although often considered self-limiting, treatment pri marily targets the resorption of calcifications and the alleviation of early symptoms. Traditionally, management typically com mences with a conservative approach, encompassing activity modification, oral, or injectable anti-inflammatory agents, with or without ultrasound-guided interventions such as the Barbotage procedure[2]. However, accumulating evidence sup ports the efficacy of extracorporeal shockwave therapy (ESWT) for shoulder calcific tendinitis[3]. Renowned for its noninvasive nature and high patient satisfaction rates, ESWT has emerged as a primary treatment modality for this condition.

ESWT has emerged as the primary treatment for calcific tendinitis of the shoulders[4]. Its clinical efficacy encompasses pain

HIGHLIGHTS

- ESWT effectively improves clinical symptoms.
- ESWT reduces calcification by enhancing tissue perfusion through IGF1, angiogenesis (VEGF), and BMP7.
- ESWT shows superior calcification resorption in radiolucent types.
- ESWT improves transparency of the affected area via partial, rather than complete resorption.

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reduction, calcification resorption, noninvasiveness, and functional improvement[4]. Although radial ESWT has been shown to significantly improve calcification resorption and functional outcomes[5], focused high-energy ESWT has been associated with superior functional recovery and increased patient satisfaction, with resorption rates ranging from 71 to 91%[3,6]. Given that the majority of positive results were observed with focused ESWT, the utilization of focused high-energy levels has emerged as the treatment of choice. Additionally, the type and size of calcification have been identified as prognostic factors for ESWT for shoulder calcification. In particular, Gartner and Heyer classification type I, characterized by formative and dense calcification, has been identified as the most significant negative prognostic factor for ESWT in calcific tendinitis of the shoulder[7]. However, the differential response to ESWT among different types of calcification remains unclear.

ESWT has demonstrated effectiveness in treating a range of musculoskeletal disorders, including chondroprotection, neovascularization, anti-inflammation, antiapoptosis, and tissue regeneration, by regulating functional proteins[3]. In the context of tendinopathy, pain reduction, anti-inflammation, angiogenesis, and neovascularization play crucial roles. Many studies have reported successful clinical outcomes in terms of pain reduction and radiographic calcification reduction[6,8,9]. However, calcification radiolucency does not necessarily indicate complete disappearance or resorption, and the intratendinous changes following ESWT, such as perfusion and elasticity, remain poorly understood. Additionally, the specific changes in molecular markers, including proinflammatory markers and growth factors, associated with ESWT in shoulder tendinitis patients are still unclear. To the best of our knowledge, there is limited research on the molecular changes that occur after ESWT in patients with shoulder calcified tendinitis. Furthermore, it is essential to elucidate the molecular mechanisms underlying the clinical improvement observed in these patients.

The aims of the present study were twofold. First, our primary objective was to identify the diverse clinical and molecular changes following ESWT across various types of calcification. Given that type I calcifications have been identified as poor prognostic factors, our aim was to discern these differences through a prospective study design. Our secondary objective, based on this prospective study design, was to elucidate the specific clinical, molecular, and sonographic changes following ESWT in patients with shoulder calcific tendinitis.

Furthermore, while most studies on ESWT for shoulder tendinitis have concentrated on clinical outcomes such as improvement rates and calcification resorption status, there is a notable lack of comprehensive investigations into this progression, encompassing both clinical outcomes and actual calcification resorption changes. A deeper understanding of these aspects would provide clinical practitioners with a thorough understanding of the use of ESWT in the treatment of shoulder calcific tendinitis.

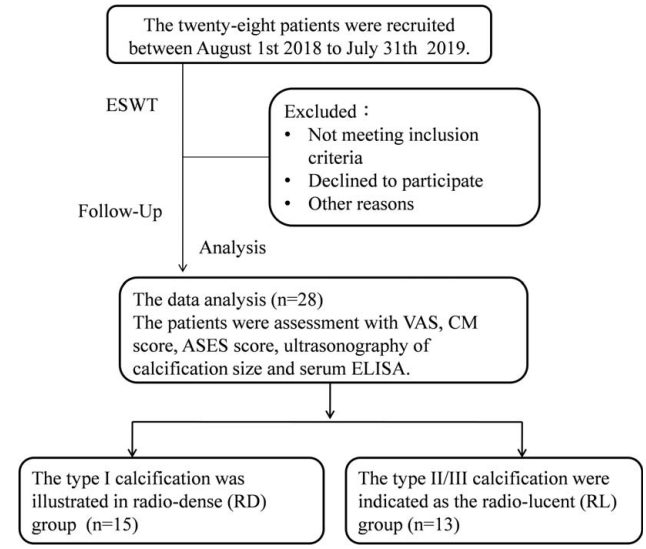

Figure 1. The CONSORT flow of patients in the study. ASES, American Shoulder and Elbow Surgeon shoulder; ESWT, extracorporeal shockwave therapy; ELISA, Enzyme-linked immunosorbent assay; RD, radiodense; RL, radiolucent; VAS, visual analogue scale; XRs, X-rays.

Methods

The participants

This prospective case–control study was approved by the Institutional Review Board of the hospital (201701870B0C601), and the work has been reported in line with the strengthening the reporting of cohort, cross-sectional, and case–control studies in surgery (STROCSS) criteria[10] (Supplemental Digital Content 1, http://links.lww.com/JS9/D404). Additionally, the Consort flow diagram illustrating the study design is presented in Figure 1. The demographic data of the participants are summarized in Table 1. Patients who did not have contraindications such as pregnancy, coagulopathy, acute infection, or malignancy and who had failed to respond to conservative treatments (including physiotherapy, NSAIDs, or analgesics) for a period of 3 months were eligible for enrollment in the ESWT intervention group.

Group sample sizes of 10 and 10 achieve 83.126% power to reject the null hypothesis of equal means when the population

Table 1

Patient demographics characteristics.

	Total	Type I (RD)	Type II and III (RL)	P^a
Number of patients/ shoulder	28/28	15/15	13/13	$P > 0.05$
Average age (years)				
Mean ± SD	59.4 ± 9.7	58.9 ± 9.6	60.2 ± 10.2	$P > 0.05$
(Range)	(40~82)	(40~72)	(46~82)	
Sex (Males/Females)	6/22	1 /14	5/8	$P > 0.05$
Side of lesion				
Right/Left	16/12	8/7	8/5	$P > 0.05$
Duration of symptoms (months)				
Mean ± SD	12.3 ± 7.5	12.3 ± 7.5	12.2 ± 7.9	$P > 0.05$
(Range)	(6~30)	(6~24)	(6~30)	
Calcification resorption				$P < 0.05$
Complete	16(57%)	6 (40%)	10 (77%)	
Incomplete	12(43%)	9 (60%)	3 (23%)	
Follow durations (months)				
Mean ± SD	12 ± 0	12 ± 0	12 ± 0	
(Range)	(12)	(12)	(12)	

[a]The *P*-value indicates that there is a significant difference between Type II and III and Type I, with a significance level of $P < 0.05$.

RD, radiodense group; RL, radiolucent group.

mean difference is $\mu1-\mu2 = 1.3-2.5 = -1.2$ with SDs of 0.7 for group 1 and 1.0 for group 2 and with a significance level (alpha) of 0.050 using a two-sided two-sample unequal variance *t*-test. To minimize patient inclusion and assessment biases, all patients were recruited by a single physician in a prospective manner, and comprehensive follow-up was planned. Patient enrollment spanned 1 year, with follow-up extending to the second year. Our goal was to enroll a minimum of 10 patients in each group[5,11].

Extracorporeal shockwave therapy

The patients underwent shockwave treatment without the administration of anesthesia or analgesics. The focused shockwave was administered using Orthospec equipment (Medispec Ltd.). With a level seven intensity setting (0.32 mJ/mm^2), 3000 impulses and 4 Hz were applied under image guidance directly to the tendon area with calcific deposition, following the protocol established in a previous study[8].

Study design

This study prospectively enrolled patients with calcific tendinitis who had failed to respond to previous conservative treatment for more than 3 months. The initial diagnosis was based on clinical symptoms and plain X-rays (including shoulder anteroposterior view and scapular Y view). The clinical evaluations included the assessment of symptom improvement (pain intensity, Constant-Murley [CM] score, and American Shoulder and Elbow Surgeon [ASES] score) as well as radiographic resorption. Sonographic assessments included evaluating local perfusion, elastography, and calcification resorption status. Several molecular markers associated with ESWT, such as proinflammatory markers (IL-1β and IL-33), angiogenesis markers (IGF-1 and vascular endothelial growth factor [VEGF]), and a calcification resorption marker (BMP7), were analyzed in the serum of patients collected before ESWT and at 1 month, 3 months, 6 months, and 12 months after ESWT. Molecular changes in the serum of patients were correlated with clinical symptoms and radiographic findings. All parameters were recorded before treatment as well as at 1 month, 3 months, 6 months, and 12 months post-ESWT. The patients were stratified into two groups according to calcification density: radiodense (RD) (Gartner & Heyer type I) and radiolucent (RL) (type II/III) groups, facilitating comparisons between different types of calcification[12]. However, for the overall analysis, all patients were collectively treated as a single group to evaluate serial parameter changes before and after ESWT.

Clinical and radiographic evaluation

The clinical assessment comprised the evaluation of pain intensity using the visual analogue scale (VAS), as well as the determination of the CM score and the ASES score. The radiographic evaluation involved assessing the size and types of calcification through the anteroposterior (AP) view and scapular Y view. Measurements of size (in millimeters) and extent were obtained from the AP view, while the types of calcification were classified according to the Gartner and Heyer classification of calcific tendinitis[12]. The classification includes type I (well-circumscribed, dense calcification, and formative), type II (clearly circumscribed, translucent, cloudy, and dense), and type III (cloudy and translucent, resorptive). Additionally, we calculated the percentage calcification size reduction, which represents the reduction rate before and 12 months after ESWT.

Sonographic evaluations (vascularity and tissue stiffness)

An experienced musculoskeletal sonographer assessed the calcific plaques of supraspinatus tendons using a Siemens Acuson S2000 ultrasound system (Siemens Healthcare) with a linear-array transducer with a bandwidth of 4–9 MHz. The vascularity of calcific tendinitis was graded on a 1- to 4-point system as described by Newman *et al*.[13]:

Grade 1: normal or minimal tissue perfusion with no or only local dark red power of the Doppler signal.

Grade 2: mild hyperemia with dark red to red power of the Doppler signal.

Grade 3: moderate hyperemia with red to orange power of the Doppler signal.

Grade 4: marked hyperemia with orange to yellow Doppler signal power, representing confluent surrounding vascular blush.

In this study, compressive ultrasound elastography was used to evaluate tissue stiffness. The pressure of the transducer on the skin should be controlled as the quality factor should remain at least 60 to achieve good color imaging[14]. The region of interest (ROI) was located at the calcific plaques. Commercial software[a] was used to acquire an RGB-coded image, and the RGB-coded image was then converted to a hue histogram composed of hue, saturation, and brightness (HSB) using the 'HSB Stack' function. After that, our investigators manually circled the calcified plaques as the ROIs for further imaging analysis. This monotonic grays cale image had its own hue value (ranging from 0 to 255) repre senting a different level of relative stiffness within the ROI, with 0 being the hardest and 255 being the softest.

Enzyme-linked immunosorbent assay for serum molecular markers

ESWT-modulated biological markers, including inflammatory markers (IL-1β and IL-33), angiogenic markers (IGF-1 and VEGF), and a calcific resorption marker (BMP7), were investigated. The serum levels of IL-1β (catalog number: HSLB00D), IL-33 (catalog number: D3300B), VEGF (catalog number: DVE00), IGF-1 (catalog number: DG100B), and BMP7 (catalog number: BDP700) were measured using ELISA kits (R&D Systems) with specific reagents according to the manufacturer's instructions.

Statistical analysis

Commercial software[b] was used for the statistical analysis. The results are presented as the mean ± SD. A normality test of each variable was performed using one-way ANOVA. For normally distributed variables, the Mann–Whitney test (P-value^2) was used for comparisons between two groups. For nonparametric variables, the Kruskal–Wallis H test (P-value^1) was used for intragroup evaluation, and the Wilcoxon signed-rank test and χ^2 test (*P-value) were used to compare the differences between the different time points. A value less than 0.05, 0.01, or 0.001 was considered to indicate statistical significance.

Results

The participants

The CONSORT flowchart of the patients is shown in Figure 1. Twenty-eight patients (mean age 59 years, range 40–82 years, 6

Table 2

Clinical and radiographic outcomes before and after ESWT.

Score	Total ($N=28$)	Type I (RD) ($N=15$)	Type II and III (RL) ($N=13$)	P^a
Before treatment				
Intensity of pain	5.35 ± 1.22 (1–8)	5.4 ± 0.9 (4–7)	5.3 ± 1.5 (1–8)	> 0.05
Constant score	48.43 ± 10.11 (31–73)	48.5 ± 11.3 (31–73)	48.3 ± 9.0 (38–66)	> 0.05
ASES score	65.71 ± 9.94 (46–93)	65.9 ± 8.6 (50–77)	65.5 ± 11.7 (46–93)	> 0.05
Calcified size (mm)	9.44 ± 4.82 (2.9–22.6)	9.3 ± 4.8 (4.5–22.6)	9.5 ± 5.0 (2.9–20.0)	> 0.05
Post-1 month treatment				
Intensity of pain	4.36 ± 0.83 (3–6)*	4.3 ± 0.9 (3–6)*	4.5 ± 0.8 (3–6)	> 0.05
Constant score	54.64 ± 10.48 (35–74)*	54.2 ± 11.1 (35–73)*	55.2 ± 10.1 (38–74)*	> 0.05
ASES score	68.32 ± 7.91 (50–84)*	67.5 ± 8.1 (50–78)*	69.2 ± 7.9 (56–84)*	> 0.05
Calcified size (mm)	7.05 ± 5.06 (0–22.6)*	8.4 ± 4.9 (3.3–22.6)	5.5 ± 5.0 (0–15.5)	> 0.05
Post-3 months treatment				
Intensity of pain	3.21 ± 1.17 (1–5)*	3.2 ± 0.9 (2–5)*	3.2 ± 1.4 (1–5)	> 0.05
Constant score	61.21 ± 10.37 (38–80)*	60.3 ± 8.4 (51–76)*	62.2 ± 12.6 (38–80)*	> 0.05
ASES score	72.29 ± 8.48 (56–92)*	71.1 ± 6.8 (62–83)*	73.6 ± 10.2 (56–92)*	> 0.05
Calcified size (mm)	4.53 ± 4.08 (0–16.1)*	8.4 ± 4.2 (0–16.1)*	3.4 ± 3.8 (0–11.4)*	> 0.05
Post-6 months treatment				
Intensity of pain	2.89 ± 1.62 (0–7)*	2.8 ± 1.2 (1–5)*	3.0 ± 2.0 (0–7)	> 0.05
Constant score	64.39 ± 11.42 (42–90)*	62.7 ± 8.5 (51–76)*	66.3 ± 14.2 (42–90)*	> 0.05
ASES score	75.64 ± 9.65 (59–93)*	74.1 ± 8.0 (62–93)*	77.5 ± 11.3 (59–92)*	> 0.05
Calcified size (mm)	4.04 ± 4.09 (0–16.1)*	5.1 ± 4.6 (0–16.1)*	2.9 ± 3.2 (0–10.3)*	> 0.05
Post-12 months treatment				
Intensity of pain	2.21 ± 1.45 (0–5)*	2.3 ± 1.5 (1–5)*	2.1 ± 1.4 (0–5)	> 0.05
Constant score	70.39 ± 12.25 (43–93)*	69.6 ± 10.8 (51–84)*	71.3 ± 14.1 (43–93)*	> 0.05
ASES score	80.36 ± 10.01 (61–95)*	80.3 ± 9.4 (62–95)*	80.5 ± 11.1 (61–94)*	> 0.05
Calcified size (mm)	2.90 ± 4.28 (0–16.1)*	4.3 ± 5.1 (0–16.1)*	1.3 ± 2.3 (0–7.5)*	> 0.05
Calcification size reduction(%)	67.52 ± 41.18 (0–100)	54.7 ± 45.3 (0–100)	82.3 ± 31.2 (12.8–100)	< 0.001

[a]The *P*-value indicates that there is a significant difference between Type II and III and Type I, with a significance level of $P < 0.05$ and 0.001.

*P-value indicates that after treatment (post-1, 3, 6, and 12 months) is compared to before treatment with a significance level of $P < 0.05$.

men and 22 women) were recruited for the present study from 1st August 2018 to 31st July 2019, and all the patients completed the comprehensive assessment at all of the follow-ups. The demographic distributions are listed in Table 1. There are no significant differences in the number of patients, average age, sex, side of lesion, or duration of symptoms between the groups. However, Table 1 shows a significant difference in calcification resorption between the radiodense (RD, type I) and radiolucent (RL, type II and III) groups. The result demonstrated that the resorption of type II and III was significantly better than type I.

Clinical and radiographic outcomes after ESWT

In the analysis of the total participants, significant improvements were observed in all parameters, including the VAS score, CM score, ASES score, and regression of calcification size, as indicated in Table 2, spanning from the first month after treatment to the 12th month. These improvements were consistently observed throughout the duration of follow-up. A significant reduction in size was noted at 3 months after treatment (9.44 ± 4.82 to 4.53 ± 4.08). According to the subgroup analysis, both groups of patients exhibited consistent improvement in all parameters, except for a less significant reduction in calcification size observed in the first month of follow-up. However, there were no significant differences between the RD and RL groups in terms of pain, CM and ASES scores, or calcification reduction. It is worth noting that the RL group showed a significant complete resorption rate (RD:RL = 40%:70%, $P = 0.045$; Table 1) and size reduction percentage at the 12-month follow-up (RD: RL = 54.7 ± 45.3%:82.3 ± 31.2%, $P < 0.001$; Table 2), suggesting that ESWT contributes to the reduction in calcification size, particularly in radiolucent types.

The sonographic outcome of shoulder analysis after ESWT

Sonography revealed that all the calcifications were exclusively observed within the tendon portion of either the supraspinatus or infraspinatus muscles, with the supraspinatus being the most common site. The ultrasound results demonstrated a correlation between the regression of calcification and the radiographic findings. The groups of calcification density were identified as the radiodense (RD) (type I) and radiolucent (RL) (type II/III) groups (Fig. 2). However, significant reductions in sonographic calcification were observed only from 3 to 12 months in all patients and in the RL subgroup (Fig. 2 and Table 3). Furthermore, ultrasound revealed more pronounced calcification than radiography. Complete resorption of calcific deposits in the tendon was not observed in any of the patients using ultrasound imaging. This suggests that ESWT resulted in a reduction in calcification size and improved the transparency of the affected area, indicating partial resorption rather than complete elimination. In terms of tendon elasticity and perfusion, there were no significant changes in elasticity. However, a notable improvement in the tissue perfusion percentage was observed at 1 and 3 months after ESWT (Fig. 2D). It is important to note that by 6 months post-treatment, the improvement in tissue perfusion became insignificant,

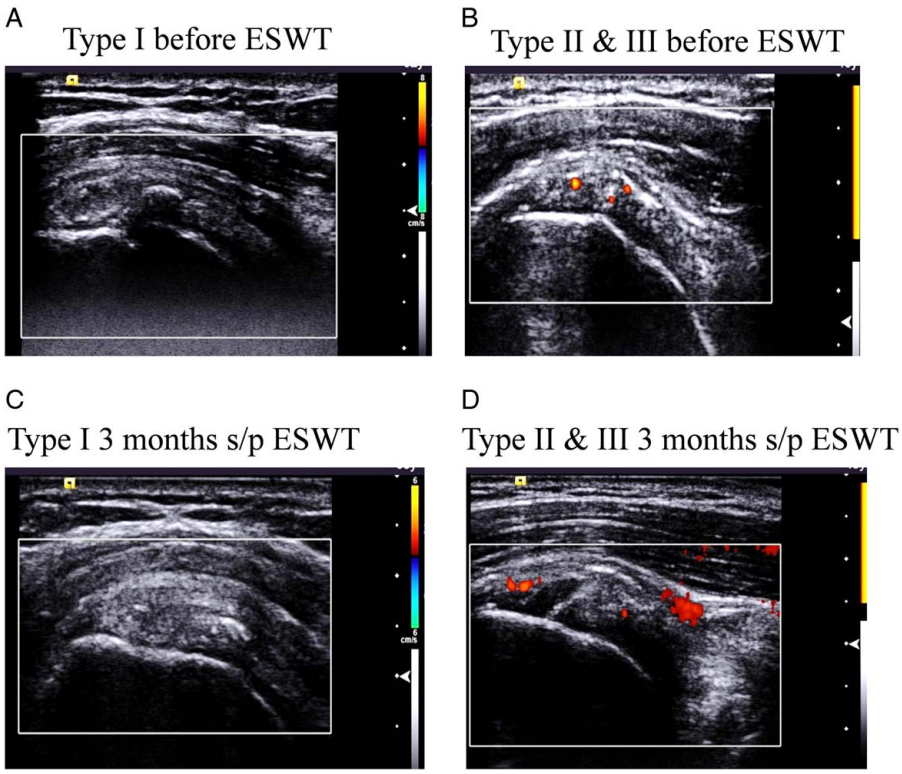

Figure 2. Sonographic analysis. (A) Type I calcification density before ESWT. (B) Type II and III calcification density before ESWT. (C) Type I calcification density after ESWT at 3 months. (D) Type II and III calcification density after ESWT at 3 months. Red color indicates the blood flow.

indicating that the local tissue perfusion effect peaked between the first and third months but subsequently subsided.

Enzyme-linked immunosorbent assay for inflammatory markers and growth factors

The serum levels of the proinflammatory markers IL-1β and IL-33 did not significantly differ throughout the entire follow-up period (Fig. 3 and Supplemental Table 1, Supplemental Digital Content 2, http://links.lww.com/JS9/D405). However, ELISA revealed a significant increase in the IGF-1 level at 1, 3, and 12 months and in the VEGF level at 6 months after ESWT (Fig. 3 and Supplemental Table 1, Supplemental Digital Content 2, http://links.lww.com/JS9/D405). Additionally, there was a notable increase in the BMP7 level at three months, followed by a significant decrease at 6 and 12 months (Fig. 3 and Supplemental Table 1, Supplemental Digital Content 2, http://links.lww.com/JS9/D405). Subgroup analysis demonstrated less pronounced differences. These findings suggested that angiogenesis and BMP7 play crucial roles in the early stage (first 3 months after ESWT), contributing to clinical improvement and calcific resorption (Fig. 3 and Supplemental Table 1, Supplemental Digital Content 2, http://links.lww.com/JS9/D405). Conversely, the late effects appear to be primarily related to angiogenesis (Fig. 3 and Supplemental Table 1, Supplemental Digital Content 2, http://links.lww.com/JS9/D405). There were no significant differences in serum markers among the subgroups of type I and type II/III at any time point. Notably, ESWT yielded similar molecular changes across all types of calcification.

Discussion

The findings of the study demonstrated that ESWT leads to significant improvement in symptoms and a reduction in calcification across all types of calcific tendinitis in the shoulder. There was a superior calcification reduction effect in the radiolucent type. However, complete resorption of the calcific deposits was not observed. This indicated that while ESWT effectively reduces the size and opacity of calcifications and improves symptoms, it does not completely eliminate calcific deposits within the tendon. The study also revealed an increase in local tissue perfusion within the first 3 months following ESWT. This enhancement in tissue perfusion may contribute to the therapeutic effects of ESWT, such as enhancing the expressions of nitric oxide, VEGF, PCNA, and IGF1 to stimulate angiogenesis to improve blood flow, which can facilitate the healing process and promote tissue repair[15–17]. However, it is worth mentioning that the improvement in tissue perfusion subsided by 6 months post-treatment, suggesting that the effects of ESWT on local perfusion may be temporary. The ELISA results further suggested that the clinical improvement observed in the early stage (first 3 months after ESWT) was associated with angiogenesis and BMP7, while the late effects were primarily related to angiogenesis. There were no significant differences in the subgroup analysis.

To investigate differences in clinical outcomes and calcification resorption, we prospectively subgrouped patients to observe the effects in difference calcification types. The subgroup comparison revealed no significant differences in local tissue perfusion, tendon elasticity, and molecular markers. This suggests that patients with calcific tendinitis of the shoulder undergo the same

Table 3

Sonographic outcomes before and after ESWT.

	Total	Type I (RD)	Type II and III (RL)	
	(*N* = 28)	(*N* = 15)	(*N* = 13)	*P*[a]
Calcified size				
Before treatment	12.37 ± 4.36 (5.6–20.4)	11.3 ± 4.5 (5.6–20.4)	13.7 ± 4.0 (6.8–20.2)	> 0.05
Post 1 month treatment	11.45 ± 3.76 (3.7–18.4)	10.9 ± 4.1 (4.5–17.1)	12.1 ± 3.4 (3.7–18.4)	> 0.05
Post 3 months treatment	10.58 ± 3.73 (4.5–18.8)*	10.0 ± 3.4 (4.5–16.2)	11.2 ± 4.1 (5.9–18.8)*	> 0.05
Post 6 months treatment	9.19 ± 3.04 (4.4–17.7)*	8.8 ± 4.1 (0–17.7)	8.9 ± 2.6 (5.2–14.9)*	> 0.05
Post 12 months treatment	8.01 ± 3.61 (3.10–16.7)*	6.8 ± 4.3 (0–16.7)	8.1 ± 3.8 (3.6–16.6)*	> 0.05
P[b]	< 0.001	> 0.05	< 0.001	
Tendon elasticity				
Before treatment	34.19 ± 17.48 (18.44–85.81)	38 ± 21 (18–86)	31 ± 12 (18–61)	> 0.05
Post 1 month treatment	34.12 ± 15.37(16.19–74.04)	35 ± 17 (16–68)	33 ± 14 (17–74)	> 0.05
Post 3 months treatment	35.56 ± 14.64 (15.07–65.82)	34 ± 15 (16–64)	37 ± 14 (15–66)	> 0.05
Post 6 months treatment	38.16 ± 19.45 (15.47–84.11)	36 ± 16 (16–70)	41 ± 23 (15–84)	> 0.05
Post 12 months treatment	37.95 ± 13.20 (13.09–65.77)	38 ± 15 (13–66)	36 ± 12 (17–53)	> 0.05
P[b]	> 0.05	> 0.05	> 0.05	
Tendon perfusion: (1) no. (2) mild. (3) moderate.				
Before treatment	(1)20(71%) (2)7(25%) (3)1(4%)	(1)11(73%) (2)4(26%)	(1)9(69%) (2)3(23%) (3)1(8%)	> 0.05
Post 1 month treatment	(1)10(36%) (2)15(54%) (3)3(10%)	(1)4(27%) (2)10(67%)* (3)1(6%)	(1)6(46%) (2)5(38%) (3)2(16%)	> 0.05
Post 3 months treatment	(1)9(32%) (2)17(61%) (3)2(7%)	(1)5(33%) (2)9(60%) (3)1(7%)	(1)3(31%) (2)10(69%)* (3)0(0%)	> 0.05
Post 6 months treatment	(1)15(54%) (2)11(39%) (3)2(7%)	(1)9(60%) (2)5(33%) (3)1(7%)	(1)6(46%) (2)6(46%) (3)1(8%)	> 0.05
Post 12 months treatment	(1)17(60%) (2)10(36%) (3)1(4%)	(1)10(67%) (2)5(33%)	(1)7(54%) (2)5(38%) (3)1(8%)	> 0.05
P[b]	> 0.05	> 0.05	> 0.05	

[a]The *P*-value indicates that there is a significant difference between Type II and III and Type I, with a significance level of $P < 0.05$ and 0.001.

[b]*P*-value indicates that all treatment times were compared together in Total, Type I, and Type II and III groups. A significance level is $P < 0.001$.

*P-value indicates that after treatment (post-1, 3, 6, and 12 months) is compared to before treatment with a significance level of $P < 0.05$.

mechanism of action after ESWT. The observed differences in calcification resorption and symptom improvement appear to be related to the physical density characteristics of the calcifications. The hypothesized degenerative nature of calcified tendinitis is supported by the efficacy of ESWT in promoting tissue healing through angiogenesis and neovascularization. Dr Wang and colleagues proposed the mechanism of action of ESWT, suggesting that it induces a biological response characterized by the upregulation of factors such as BMP-2, eNOS, VEGF, and PCNA, which improve blood supply and ultimately lead to tissue regeneration[16]. To our knowledge, this was the first prospective study to directly demonstrate the clinical, ultrasound, and mole cular changes induced by ESWT in calcific shoulder tendinitis patients. Our findings suggested that the effect of ESWT on shoulder calcific tendinitis is mediated through its angiogenic properties and its ability to promote calcification size and improvements in clinical symptoms lasting up to 12 months, which are particularly pronounced within the first 3 months. Additionally, we observed a superior reduction in calcification in the radiolucent subtype. Furthermore, our results implied that the optimal timing for a second session of ESWT is 3 months fol lowing the index treatment.

The mainstays of treatment for shoulder calcific tendinitis, including rest, physical therapy, activity modification, and anti-inflammatory medications, remain conservative. Pulsatile lavage and needling are alternative options. Additionally, there is growing evidence supporting the use of focused ESWT in treating calcifying tendinopathy of the shoulder[3]. A study comparing ultrasound-guided needling with subacromial steroid injection and high-energy-focused ESWT showed no difference in func tional outcomes but revealed greater radiographic resorption in the needling group[18]. Although the functional outcomes were similar, ultrasound-guided needling requires greater technical proficiency and adherence to sterile procedures. These findings suggested that invasive procedures may further compromise cuff integrity, highlighting the superiority of ESWT in shoulder calci fic tendinitis due to its less invasive nature and lower technical demands, leading to consistent treatment results. The present study further confirmed the clinical efficacy of ESWT, with effects lasting up to 1 year, particularly in the first 3 months, demon strating both clinical improvement and a reduction in calcification size.

Few reports have investigated the varying effects of ESWT on radiodense and radiolucent calcifications. This study provides further support for previous findings[19] by demonstrating that ESWT leads to superior radiographic complete resorption and a

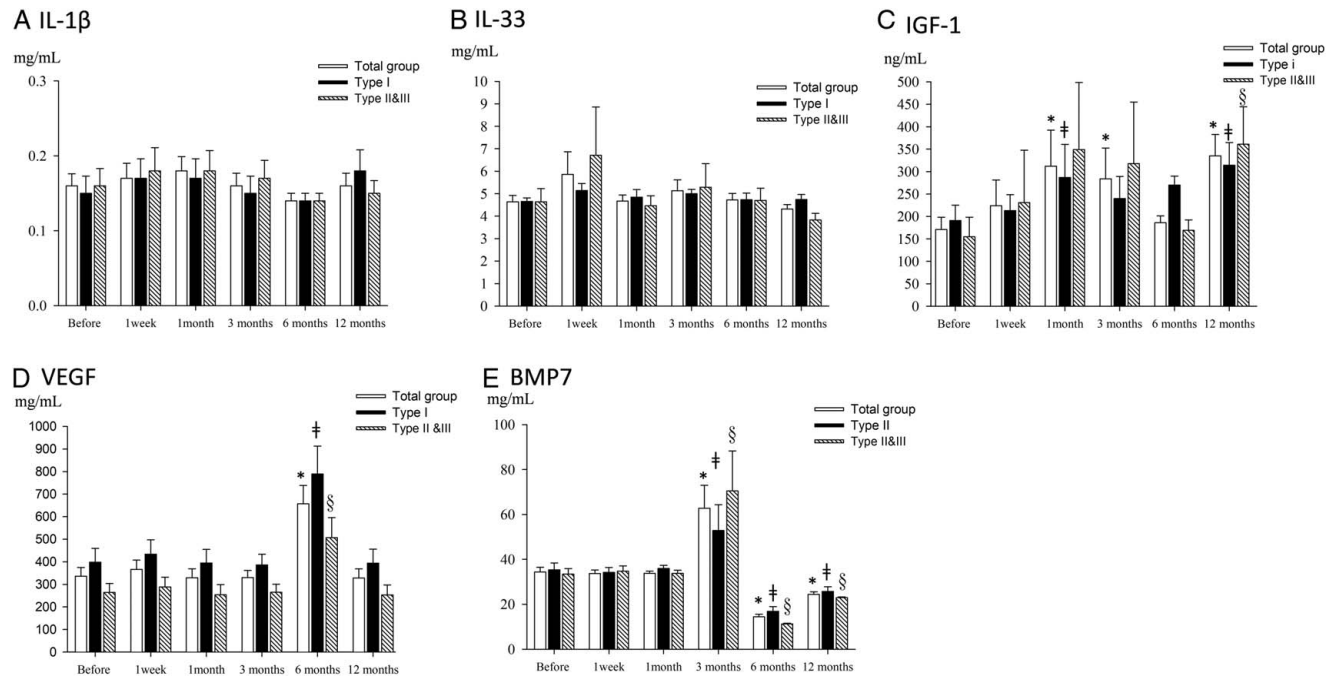

Figure 3. The serum markers of calcific tendinitis of the shoulder after ESWT. The serum markers of (A) IL-1β, (B) IL33, (C) IGF-1, (D) VEGF, and (E) BMP7 were measured before and after ESWT at 1 week, 1, 3, 6, and 12 months. The *$P < 0.05$ is the total group compared with before treatment. The *$P < 0.05$ is that type I group compared with before treatment. §$P < 0.05$ is that type II and III group compared with before treatment.

greater percentage of sonographic calcification reduction in radi olucent (type II and III) calcifications at the 1-year follow-up (Fig. 2, Table 1 and Table 2). However, no significant clinical differences were observed between the radiodense (RD) and radiolucent (RL) groups. Notably, there was an increase in perfusion in the RL group at the 3-month follow-up and in the RD group at the 1-month follow-up after treatment. These findings suggested that ESWT promotes early-stage (first 3 months) tendon perfusion, although the presence of a solid structure hampers complete resorption (Fig. 2). Notably, no patients exhibited complete sonographic resorption. Furthermore, the molecular changes were similar between the RD and RL groups. These results suggested that ESWT physically disrupts the calcification structure and promotes molecular resorption. However, only one session of ESWT cannot fully restore the quality of the tendon from a state of degenerative calcification to a normal state.

Bone morphogenetic protein 7 (BMP7) is a multifunctional protein that belongs to the transforming growth factor beta (TGF-β) superfamily[20]. It is known for its potent anti-in flammatory properties and plays a critical role in several biologi cal processes and development, including the musculoskeletal system, major end organs, exocrine gland, lymphoid organs, and spinal cord[20–22]. Several studies have suggested that BMP7 pos sesses anti-inflammatory activity and inhibits calcification by enhancing M2 macrophage differentiation and anti-in flammatory cytokine production[21,23]. ESWT promotes the expression of BMP7 to activate cell proliferation and bone regeneration in the treatment of musculoskeletal disorders[24]. In addition, a previous study showed that ESWT not only stimulates a shift in the macrophage phenotype from M1 to M2 but also suppresses the activity of M1 macrophages and the activation of M2 macrophages[25,26]. Based on the available evidence, it appears that ESWT could increase the serum expression of BMP7, leading to anti-inflammatory effects and the activation of M2 macrophages. This activation may aid in the post-treatment resorption of calcium deposits in the early stage of shoulder cal cification (Tables 1, 2, and 3). Furthermore, IGF-1 and VEGF are known to promote angiogenic processes in tissue[15]. Our study revealed a noticeable increase in the serum IGF-1 concentration at 1, 3, and 12 months, which may have a positive impact on angiogenesis and blood perfusion (as shown in Tables 1, 2, and 3). Additionally, we observed an increase in the expression of VEGF at 6 months, which could also contribute to angiogenesis and blood perfusion. Furthermore, there was an increase in the expression of serum BMP7 at 3 months, which might regulate inflammation by activating M2 macrophages, thereby aiding in the resorption of calcification in patients with calcific tendinitis of the shoulder following ESWT. Nevertheless, the specific mechanisms through which IGF-1, VEGF, and BMP7 promote the resorption of calcification in tendinitis of the shoulder require further elucidation.

The present study had certain limitations that need to be acknowledged. First, this prospective analysis did not encompass a comprehensive range of molecular markers associated with ESWT. Although several prominent markers were incorporated, it is important to note that other relevant markers were not included, potentially limiting our understanding of the complete molecular mechanism within this clinical context. Second, while 2 or 3 sessions of ESWT are commonly administered in clinical practice, the study focused solely on one session. Consequently, the findings may not fully elucidate the comprehensive working mechanism observed with multiple treatment sessions. Third, our study was conducted with limited resources and funding, which restricted our ability to recruit a larger sample size. Despite this,

we ensured rigorous methodology and data analysis to maximize the validity and reliability of our findings. Although our sample size is relatively small, we employed appropriate statistical techniques to analyze the data and draw meaningful conclusions. Our analyses accounted for the variability within our sample and provided initial evidence supporting our hypotheses. Fourth, to enhance the statistical power of our analysis, it would have been advantageous to enroll a larger cohort of patients. A larger sample size would contribute to greater generalizability and potentially strengthen the validity of the conclusions.

In summary, our findings indicated that ESWT enhances tissue perfusion through the upregulation of key factors such as IGF1, VEGF, and BMP7, thereby facilitating calcific resorption. Importantly, we also observed superior calcification resorption in the radiolucent type, albeit complete tendon recovery was not achieved, suggesting that a single dose of ESWT induces partial rather than complete resorption, leading to improved transparency of the affected area. The temporal analysis of treatment effects revealed a substantial reduction in calcification size and enhanced tissue perfusion within the first 3 months post-ESWT, indicating an optimal window for a second session of treatment at this time point. This observation has significant clinical implications for treatment scheduling and underscores the importance of early intervention to maximize therapeutic outcomes.

Moving forward, future research should focus on elucidating the molecular mechanisms underlying the observed therapeutic effects of ESWT and exploring strategies to enhance its efficacy in achieving complete tendon recovery. Furthermore, large-scale randomized controlled trials are warranted to validate our findings and establish standardized treatment protocols. Additionally, investigating the potential synergistic effects of ESWT with adjunctive therapies may further enhance treatment outcomes and broaden its therapeutic utility.

Ethical approval

The prospective case–control study is approved by the Institutional Review Board of Chang Gung Memorial Hospital (IRB number: 201701870B0C601). The information is in the participants of the methods in the manuscript.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

W.-Y.C.: conceptualization, data curation, funding acquisition, investigation, methodology, supervision, validation, writing – original draft, and writing – review and editing; K.-T.W.: formal analysis, investigation, and writing – original draft; P.-C.C.: methodology, validation, and writing –original draft; S.-W.J.: formal analysis, data curation, and writing – original draft; C.-F.W.: data curation, methodology, and validation; J.-H.C.: conceptualization, writing – original draft, and writing – review and editing.

Conflicts of interest disclosure

The authors have declared that they did not receive any honoraria or consulting fees in writing this manuscript. No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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Data availability statement

The dataset used and analyzed in this study were obtained from the corresponding authors upon reasonable request.

Provenance and peer review

Invited paper for the special issue 'Shockwave treatment' and the guest editor is Dr Kandiah Raveendran.

Patient involvement statement

Study participants were not involved in the design, conduct, interpretation, or translation of the current research.

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