

# The effect of extracorporeal shock wave therapy on the treatment of moderate to severe knee osteoarthritis and cartilage lesion

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## Abstract

**Background:** Knee osteoarthritis (KOA) is a major cause leading to chronic bone and muscle pain. Extracorporeal shock wave therapy (ESWT) has been applied in treating KOA in recent years.

**Methods:** From April 2016 to April 2017, 82 patients were diagnosed with KOA that received ESWT were selected as the ESWT group. The treatment parameters were as follows, 2.0 bar, 0.25 mJ/mm<sup>2</sup>, and 8 Hz/s for twice a week for 4 weeks continuously. In addition, 104 patients receiving oral administration of nonsteroidal anti-inflammatory drugs (NSAIDs) from April 2015 to April 2016 were also selected as the NSAIDs group. At 4, 8, 12, and 16 weeks upon the completion of treatment, the Visual Analogue Scale (VAS) and Western Ontario and McMaster Universities Arthritis Index (WOMAC) were adopted to evaluate the changes in pain and function of patients in both groups. For the ESWT group, the 50-m quick walk time and gait analysis were applied to observe the functional recovery at 4, 8, 12, and 16 weeks upon the completion of treatment; meanwhile, patients were followed up by magnetic resonance imaging (MRI) at 24 weeks upon the completion of treatment, so as to observe the cartilage changes.

**Results:** Differences in VAS, 4, 8, and 12 weeks after treatment were statistically significant compared with that before treatment ( $4.59 \pm 0.5$ ,  $P < .05$ ;  $2.55 \pm 0.5$ ,  $P < .05$ ;  $4.39 \pm 0.49$ ,  $P < .05$ ). Differences in 4, 8, and 12 weeks after treatment were statistically significant compared with that before treatment ( $90.41 \pm 6.64$ ,  $P < .05$ ;  $59.94 \pm 3.19$ ,  $P < .05$ ;  $90.49 \pm 6.87$ ,  $P < .05$ ). Gait analysis suggested differences in 50m walk time, walking speed, swing phase, and stance phase 8 weeks after treatment were statistically significant compared with that before treatment ( $36.23 \pm 4.08$ ,  $P < .05$ ;  $1.25 \pm 0.09$ ,  $P < .05$ ;  $58.56 \pm 0.87$ ,  $P < .05$ ;  $41.44 \pm 0.87$ ,  $P < .05$ ). Differences in the VAS and WOMAC at 4 and 8 weeks after treatment between ESWT group and NSAIDs group were not statistically significant.

**Conclusions:** The ESWT has potential in reducing pain and improving knee function, and the therapeutic effects may peak at 8 weeks after the completion of treatment. Further research is needed to arrive at a definitive conclusion.

**Abbreviations:** ACR = American College of Rheumatology, CaLS = cartilage lesion score, ESWT = extracorporeal shock wave therapy, KOA = knee osteoarthritis, LROM = limitation of motion, MRI = magnetic resonance imaging, OP = osteoporosis, VAS = visual analog scale, WOMAC = Western Ontario and McMaster Universities Arthritis Index.

**Keywords:** cartilages, extracorporeal shock wave therapy, knee osteoarthritis

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## 1. Introduction

Knee osteoarthritis (KOA) is the most common joint lesion, which is also the major cause resulting in chronic bone and muscle pain, as well as disability.<sup>[1-3]</sup> It is characterized by the clinical features of progressive knee joint pain, swelling, and rigidity. In some severe cases, it can result in joint deformity, finally leading to the loss of normal living and working ability.<sup>[4]</sup> With the acceleration of social population aging in the world, the morbidity of KOA is increasing. At present, knee replacement remains the most effective method targeting advanced KOA, but it will inevitably add to the surgical risk and economic loss in patients. Therefore, treating early-medium KOA and delaying its development remain the important problems to be urgently solved in clinic. Extracorporeal shock wave therapy (ESWT) is a non-invasive non-surgical method, which has been applied in treating KOA in recent years.<sup>[5]</sup> Scholar Zhao had first carried out a clinical study on KOA treated with shock wave therapy in the world, and the results suggested favorable therapeutic effect with no severe adverse reaction.<sup>[6]</sup> In that study, shockwaves of 4000 pulses in total were applied at 0.25 mJ/mm<sup>2</sup> and a frequency of 6

Hz/s. And they did not find adverse events during and after ESWT. Thereafter, numerous scholars worldwide have carried out similar studies. In these studies, scholars compared with different treatments, such as kinesiotherapy, eccentric training, and intra-articular hyaluronic acid injections, to observe the effect of ESWT on the treatment of KOA. The energy of their application is also different from 0.25 to 0.4 mJ/mm<sup>2</sup>. But all of them suggested that shock wave can serve as one of the treatments on KOA.<sup>[7-10]</sup> Notarnicola et al<sup>[11]</sup> had verified through in vitro cell experiment that, ESWT could upregulate the expression of IL-10, while down-regulating that of N-cadherin and  $\beta$ -catenin. Yilmaz et al<sup>[12]</sup> had treated the KOA rats through ESWT and confirmed that, ESWT could promote the proliferation and regeneration of cartilage tissues in rats. Its mechanisms of action may be attributed to the following aspects. ESWT acts on the subchondral bone, delay the structural changes in subchondral bone, and thus suppress the degenerative changes in cartilage. ESWT is a mechanical stimulation, which affects some mechanical sensitive signaling pathways in the cartilage cells, thus accelerating cartilage cell proliferation and delaying its degeneration. Another hypothesis<sup>[13]</sup> suggests that osteoporosis (OP) is closely associated with OA, and the interaction between them may promote the genesis and development of these two. ESWT may improve the bone density in OP patients, thus improving the OA symptom. We have discovered 2 problems deserving our attention when applying ESW in treating KOA. Firstly, ESW is a mechanical stimulation, whose therapeutic effect is associated with timeliness. Most patients will develop the phenomenon of recurrence within a certain period after the completion of a course of treatment. Additionally, indexes in existing literature that evaluates the efficacy of ESW in treating KOA are mostly subjective evaluation indexes, while objective evaluation standard is lacking. Therefore, extending the follow-up period, carrying out follow-up observation using the objective evaluation indexes, analyzing the functional recovery of knee joint at different time points, and providing more valuable data for clinical treatment are the focuses of current study. This experiment proposed to explore the variation trend of ESWT therapeutic effect on treating KOA through evaluating the therapeutic effect of ESWT on KOA based on the subjective score, objective indexes, and imaging technique, so as to provide reference foundation for formulating the therapeutic strategy in the next step.

## 2. Materials and methods

### 2.1. Objects of study

A total of 267 patients consulted with the chief complaints of knee pain and limitation of motion (LROM) during the study period. One hundred seventy six of them were excluded, including 154 not conforming to the inclusion criteria, 15 not signing the informed consent, and 7 with other reasons.

### 2.2. Inclusion and exclusion criteria

Inclusion criteria: Patients diagnosed with KOA according to the diagnostic criteria of American College of Rheumatology (ACR) who wanted to receive shock wave therapy. ACR criteria included that of knee pain, osteophytes, and 1 of the following: age >50 years, morning stiffness <30 minutes duration, or crepitus on active motion of the knee.<sup>[14]</sup> The enrolled patients were over 45 years old, with unilateral knee joint symptoms, knee

pain in the past 3 months, K-L classification of grade 2 or 3, and cartilage MRI diagnosis of Recht grade II or III. Exclusion criteria: patients with bilateral knee joint symptoms; patients with a history of spinal stenosis; patients with a history of nervous system disease or secondary arthritis (inflammatory or metabolic); patients receiving surgery in the involved knee joint or intra-articular injection within the past 6 months; and patients with any contraindication of magnetic resonance imaging (MRI) or radiology. This study was approved by the Ethics Committee of China Armed Police General Hospital. All patients had signed the written informed consent to participate in this study.

### 2.3. Experimental methods

The enrolled patients were treated using the radial extracorporeal shock wave therapeutic machine (EMS, Swiss Dolor Clast). Generally, different flexion angles were selected based on the different site of cartilage injury; meanwhile, the tenderness points in knee joint were used as the therapeutic points after positioning based on the body surface anatomical markers with the pain points. The treatment parameters were selected based on literature<sup>[6]</sup> and our treatment experience, as shown below, 2.0 bar, 0.25 mJ/mm<sup>2</sup>, and 8 Hz/s for twice a week for 4 weeks continuously.

At 4, 8, 12, and 16 weeks upon the completion of treatment, the Visual Analogue Scale (VAS) and Western Ontario and McMaster Universities Arthritis Index (WOMAC) were adopted to evaluate the changes in pain and function of patients in both groups. Moreover, the cartilage morphology and component of KOA patients in ESWT group before and after treatment were investigated by the cartilage lesion score (CaLS) and the T2 value of articular cartilage; whereas the 50-m fast walk time and gait analysis (step speed, stride, as well as the percentages of stance phase and swing phase) were utilized to objectively assess the knee functional recovery in KOA patients before and after treatment. The baseline data were recorded before treatment; afterwards, patients were followed up for 5 times, namely, at 4, 8, 12, 16, and 24 weeks after treatment. Of them, the VAS, WOMAC, 50m fast walk time and gait analysis were recorded in the follows-up at 4, 8, 12, and 16 weeks after treatment. The cartilage changes (CaLS and T2 value) were evaluated through MRI at 24 weeks after the completion of ESWT treatment.

### 2.4. CaLS and T2 value

CaLS is a novel full normal scoring system targeting cartilage injury.<sup>[15]</sup> It is a new cartilage injury scoring system designed according to data provided by scholars Alizai et al<sup>[15]</sup> from University of San Francisco based on the Osteoarthritis Initiative (OAI). In early articular cartilage, the collagen structure and tissue anisotropy have resulted in increased water fluidity; in other words, the free water content in cartilage is increased. The free water content is positively correlated with the T2 value of articular cartilage; consequently, changes in T2 value measured through T2 mapping can reflect the cartilage degeneration.<sup>[16]</sup>

### 2.5. Statistical analysis of data

Data were proposed to be analyzed using repeated measures one-way analysis of variance in this study. All data, except for the cartilage injury evaluation indexes, were analyzed using general linear model with repeated measures, with follow-up period as the within-subject factor. If the data could not satisfy Mauchly

test of sphericity, the Bonferroni post-hoc test was employed for analysis. The VAS, WOMAC, and cartilage changes were analyzed through independent sample *t* test (Gaussian population), paired *t* test (Gaussian population), or Wilcoxon test (non-Gaussian population). Level of significance for all tests was set at  $\alpha < 0.05$ . SPSS 24.0 (IBM Corp., SPSS Statistics for Windows, Version 24.0. Armonk, NY) was used for all analyses.

### 3. Results

#### 3.1. General conditions

A total of 267 patients consulted with the chief complaints of knee pain and LROM during the study period. One hundred seventy-six of them were excluded, including 154 not conforming to the inclusion criteria, 15 not signing the informed consent, and 7 with other reasons. Nine patients could not complete the experiment during treatment, 7 were lost to follow up due to unknown reason, and 2 people accepted other treatments during the treatment period. The precise statistical information is presented in Table 1. Finally, a

total of 82 patients had completed the experiments were selected as the ESWT group. At the same time, 104 patients receiving oral administration of nonsteroidal anti-inflammatory drugs (NSAIDs) from April 2015 to April 2016 were also selected into the NSAIDs group to compare with the ESWT group (Table 2).

#### 3.2. Pain, function, and symptom evaluation

Four, 8, and 12 weeks after treatment, differences in VAS and WOMAC were statistically significant compared with those before and 16 weeks after treatment. Eight weeks after treatment, the therapeutic effects reached a peak, and the differences were statistically significant compared with those 4 and 12 weeks after treatment. Took WOMAC-total as an example, the WOMAC-total 4 weeks after treatment was remarkably reduced by 18.5 compared with that before treatment (95% confidence interval [CI]: 16.635–20.365) ( $P < .05$ ). Eight weeks after treatment was markedly lowered by 48.98 (95% CI: 47.419–50.532) ( $P < .05$ ). Twelve weeks after treatment was markedly decreased by 18.43 (95% CI: 16.518–20.335) ( $P < .05$ ). Sixteen weeks after

**Table 1**  
Demographic information and the causes of mid-term lost patient.

No	Lost to follow up reason	Gender	Age, y	Weight, kg	Height, cm	BMI, kg/m <sup>2</sup>	Pain duration, y
1	Unknown	Female	53	72	156	29.59	3
2	Unknown	Male	49	86	155	35.8	5
3	Unknown	Female	65	69	165	25.34	1
4	Unknown	Male	63	79	162	30.1	2
5	Unknown	Female	52	80	160	31.25	2
6	Unknown	Female	58	86	153	36.74	2
7	Unknown	Male	70	90	152	38.95	1
8	Accepted other treatments	Female	69	69	164	25.65	3
9	Accepted other treatments	Male	69	80	159	31.64	1

BMI=body mass index.

**Table 2**  
Demographic and clinical characteristics.

	ESWT group	NSAIDs group	$\chi^2/t$	<i>P</i>
Demographic characteristics				
Female n (%)	47 (57.3)	61 (58.7)	0.03	.85
Age, y	59.3±5.57	58.48±7.43	0.86	.39
Weight, kg	77.68±9.7	79.18±8.78	-1.1	.27
Height, cm	163.71±7.55	165.1±8.82	-1.15	.25
BMI, kg/m <sup>2</sup>	29.08±3.97	29.25±4.13	-0.26	.8
Pain duration, y	2.7±1.41	2.13±1.07	-2.15	.03
Kellgren and Lawrence grade II and III, n (%)	49 (59.8)/33 (40.2)	67 (64.4)/37 (35.6)	0.43	.51
Recht grade II and III, n (%)	45 (54.9)/37 (45.1)	63 (60.6)/41 (39.4)	0.61	.43
Clinical characteristics				
VAS score	5.52±1.14	5.41±1.11	0.67	.51
WOMAC score				
Total	108.91±6.87	107.16±8.8	1.48	.14
Pain	21.02±2.55	20.57±2.62	1.19	.23
Stiffness	11.67±1.76	11.35±1.31	1.39	.17
Function	76.22±6.61	75.47±7.69	0.70	.49
50 meter's time	40.12±4.65			
Walking speed, m/s	1.1±0.12			
Stride length, cm	58.12±3.38			
Stance, %gait cycle	60.57±0.91			
Swing, %gait cycle	39.43±0.91			

Data are expressed as mean standard deviation unless otherwise indicated.

BMI=body mass index; ESWT=extracorporeal shock wave therapy; NSAIDs=nonsteroidal anti-inflammatory drugs.

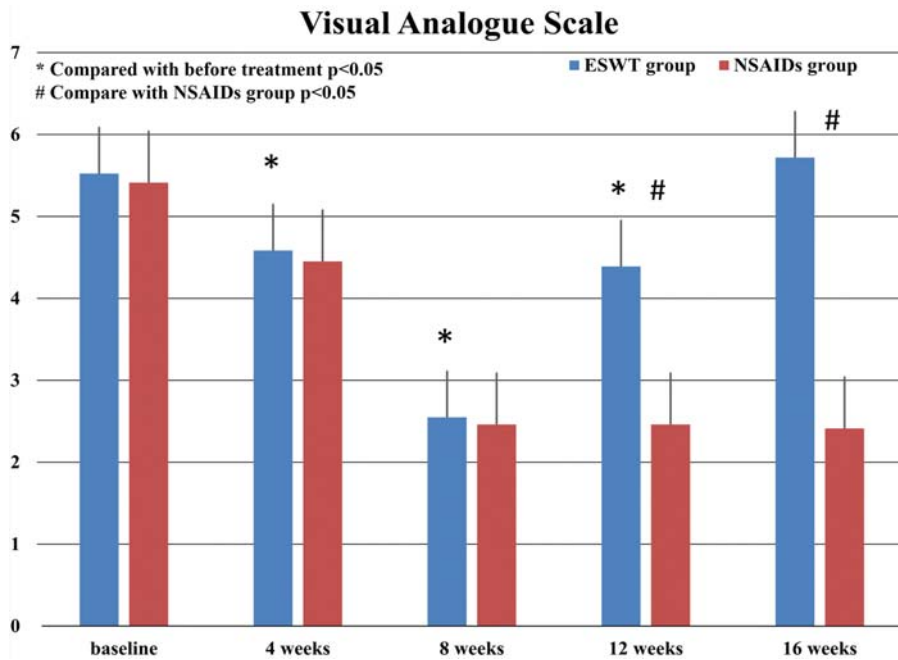


Figure 1. The development of the VAS during therapeutical intervention. VAS=visual analog scale.

treatment was lowered by 1.27 (95% CI: -2.099–2.148) ( $P < .05$ ). In the meantime, the WOMAC-total 8 weeks after treatment was markedly reduced by 30.47 compared with that 4 weeks after treatment (95% CI: 29.534–31.418) ( $P < .05$ ) and distinctly lowered by 30.55 compared with that 12 weeks after treatment (95% CI: 29.01–32.087) ( $P < .05$ ). Compared with NSAIDs group, differences in VAS and WOMAC at 4 weeks and 8 weeks after treatment showed no statistical significance; after 8 weeks of treatment, the VAS and WOMAC in ESWT group was reduced by 26.3 points compared with that in NSAIDs group, and the difference was statistically significant (Figs. 1 and 2).

### 3.3. 50m fast walk time and gait analysis

Differences in the 50 m fast walk time, stride speed, stance phase, and swing phase between 8 weeks after treatment and before treatment were statistically significant ( $P < .05$ ), while those in the other time points showed no statistical significance compared with those before treatment ( $P > .05$ ). Took 50m fast walk time as an example, 8 weeks after treatment, the time was dramatically reduced by 3.89 compared with that before treatment (95% CI: 2.052–5.728) ( $P < .05$ ), and the difference was statistically significant. Difference in stride length (cm) within 6 months

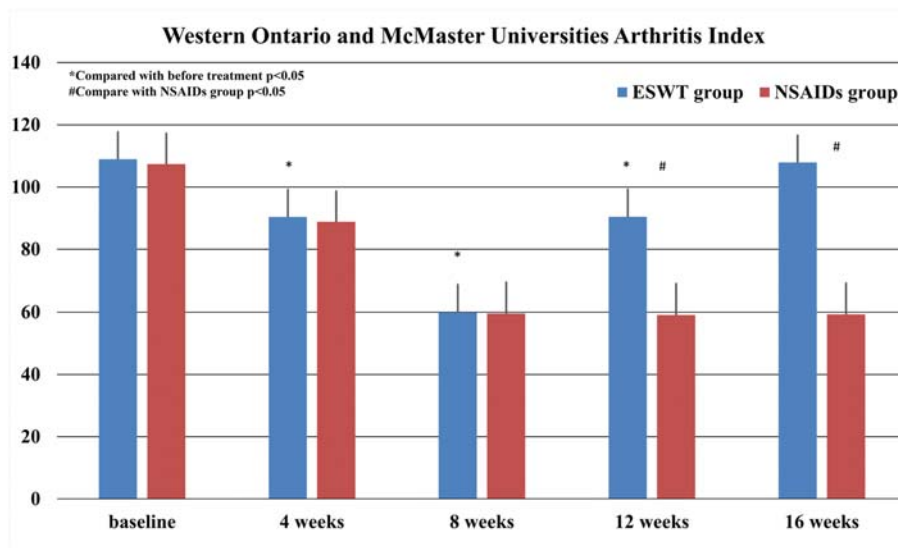
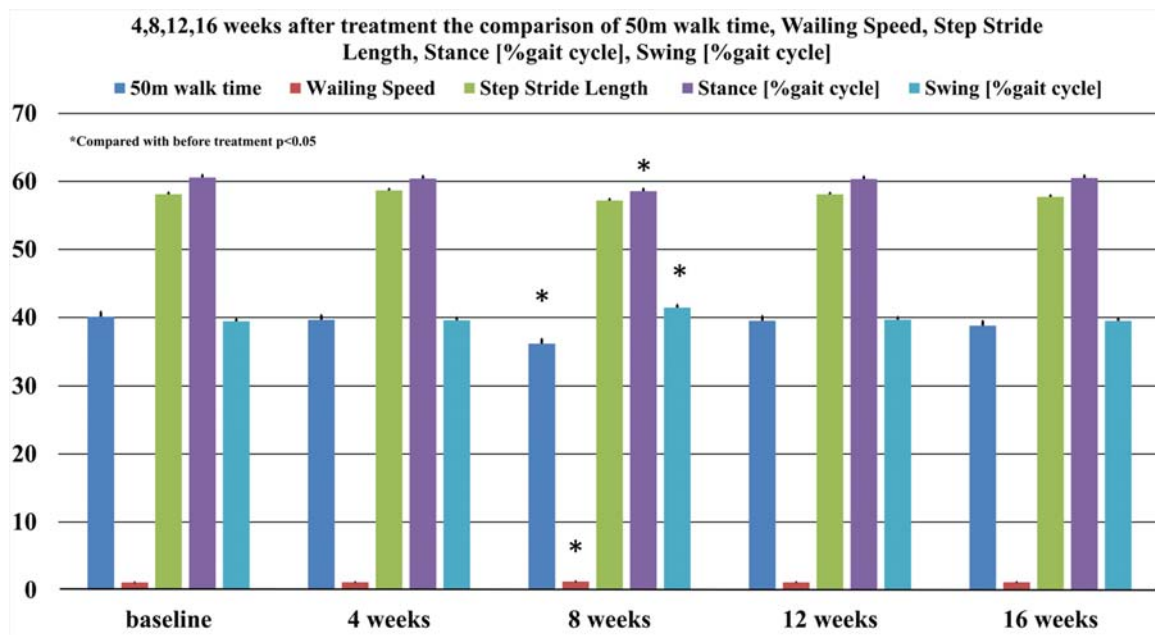


Figure 2. The development of the WOMAC during therapeutical intervention. WOMAC=Western Ontario and McMaster Universities Arthritis Index.



**Figure 3.** The development of the 50m walk time, wailing speed, step stride length, stance (%gait cycle) and swing (%gait cycle) during therapeutical intervention.

after treatment was not statistically significant compared with that before treatment ( $P > .05$ ) (Fig. 3).

### 3.4. Changes in CaLS and T2 value

A total of 76 cartilage injuries were found in the 82 patients. Twenty four weeks after treatment, differences in CaLS and T2 values in patella region, trochlear region, medial femur region, lateral femur region, medial tibia region, and lateral tibia region showed no statistical significance compared with those before treatment ( $t = -1.859, P = .076$ ) (Table 3, Figs. 4 and 5).

It was discovered through clinical practice and statistical analysis that, the subjective feeling changes were positively correlated with the BMI in patients, and a greater BMI indicated more obvious therapeutic effect of shock wave therapy (Fig. 6).

## 4. Discussion

We had proposed a hypothesis in this study, namely, the therapeutic effect of ESWT on KOA would fluctuate with the extension of time, which would finally disappear completely. At the same time, ESWT was suggested in plenty of animal and in

vitro experiments to promote cartilage regeneration, and we also expected to observe the cartilage changes when applying ESWT to treat KOA in human beings. Therefore, we had extended the follow-up period and used the objective indexes to evaluate the variation trend of ESWT therapeutic effect and cartilage changes. We discovered after a 6-month follow-up that, ESWT could alleviate knee joint pain and recover the knee joint function; typically, the therapeutic effect peaked at 8 weeks after treatment.

KOA is a disease causing great harm to the middle-aged and senile people. It can be treated with a variety of methods. Numerous non-surgical treatments basically aim to achieve symptom alleviation and functional restriction relief.<sup>[17,18]</sup> In 2012, the ACR guideline<sup>[19]</sup> recommends that drug therapy combined with non-drug therapy is the ideal therapeutic scheme for KOA. ESWT is a mechanical stimulation, which also has great potential in treating KOA. Wang et al<sup>[20-22]</sup> had reported that ESWT could protect the damaged cartilage and promote its recovery when it was used to treat rat KOA. In clinical trial, ESWT shows extremely marked effect on relieving pain.<sup>[23]</sup> Some studies indicate that ESWT may relieve pain through suppressing P substance release.<sup>[24]</sup> Besides, ESW can also down-regulate the

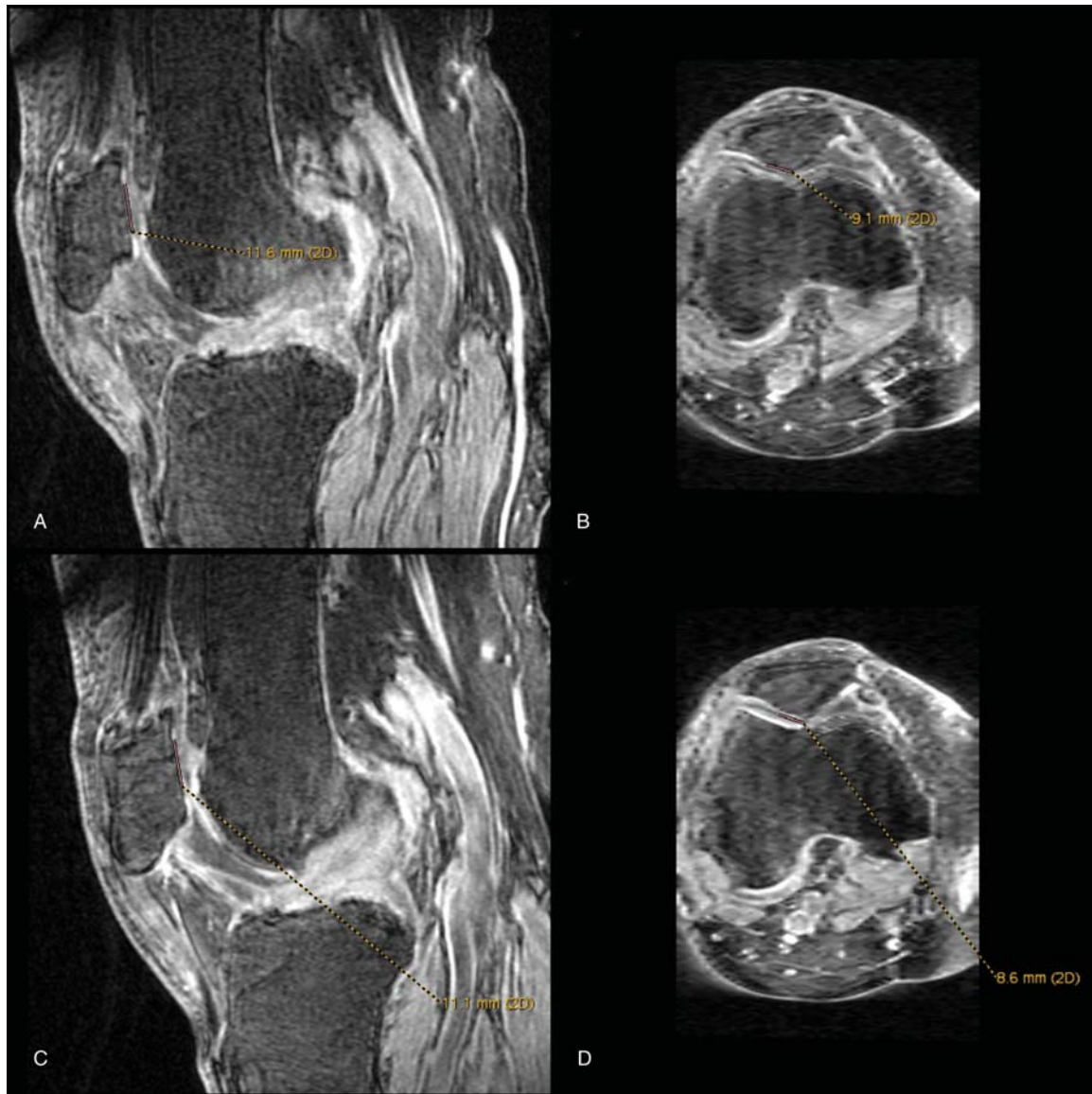
**Table 3**

Mean change before and after the treatment for cartilage in term of volumes by the T2 value and the CaLS.

	Number	T2 value				CaLS score			
		Baseline	24 weeks	t	P	Baseline	24 weeks	z	P
Patella	28	54.6 ± 4.5	53.4 ± 4.4	1.631	.114	193.5 ± 69.6	201.3 ± 75.8	-0.41	.68
Trochlea	16	51.3 ± 4.9	52.7 ± 4.8	-1.543	.134	152.3 ± 48.6	153.4 ± 43.4	-0.26	.80
Medial femur	12	49.9 ± 4.3	50.4 ± 4.8	-0.932	.359	128.9 ± 53.1	126.5 ± 51.6	-1.618	.11
Lateral femur	11	50.0 ± 6.4	50.6 ± 5.7	-0.486	.63	45.1 ± 19.0	47.4 ± 20.8	-0.18	.86
Medial tibia	0	47.7 ± 4.2	46.9 ± 5.5	0.57	.573	0	0		
Lateral tibia	9	49.1 ± 5.2	50.3 ± 4.9	-0.999	.326	19.7 ± 3.6	19.6 ± 2.7	-0.17	.89

Data are expressed as mean (95% confidence intervals). CaLS=cartilage lesion score.





**Figure 4.** The CaLS of a 52-year-old female patient before and after treatment. The picture A and B are before treatment. The picture C and D are after treatment. CaLS=Cartilage Lesion Score.

expression of pain-related calcitonin gene related peptide in dorsal root ganglion.<sup>[2,5]</sup> Additionally, it can directly act on the peripheral sensory nerve ending, improve the pain threshold,<sup>[26]</sup> and prevent the production and propagation of pain signal.

The therapeutic effect of ESWT peaked at 8 weeks and then began to disappear. The reasons may be time dependence and accumulative effect. The time dependence of ESWT suggests that, the ESWT efficacy can only display after a certain period of time after intervention, which has been studied by numerous scholars at home and abroad.<sup>[20,21,27-29]</sup> The accumulative effect is formed as a result of the feature of ESW itself. As a mechanical stimulation, the efficacy of ESW can be easily dissipated. Therefore, the treatment cycle should be a long process, while when to initiate the second course of treatment is a key problem deserving our attention.

The efficacy of ESW has long been a source of controversy, which can be attributed to the lack of objective indexes in

previous studies. On this account, this study has applied the 50 m fast walk time and gait analysis meter in analyzing the efficacy. Gait analysis technology is not susceptible to other factors due to its objective results, which has thus been extensively applied at present in evaluating the efficacy.<sup>[30-32]</sup> The 50 m fast walk time, stride speed, stance phase and swing phase in patients 8 weeks after treatment show significant differences compared with those at other time points, which is partially correlated with the subjective scores in patients.

Additionally, we have also observed an interesting phenomenon, which is that obese patients (patients with high BMI) are more sensitive to ESWT, and more prominent efficacy can be achieved. Therefore, it can be indirectly speculated that KOA pain is not only closely associated with cartilage, but is also closely correlated with the surrounding soft tissue. Therefore, the effect of KOA surrounding soft tissue on the knee joint should be the focus of future research.

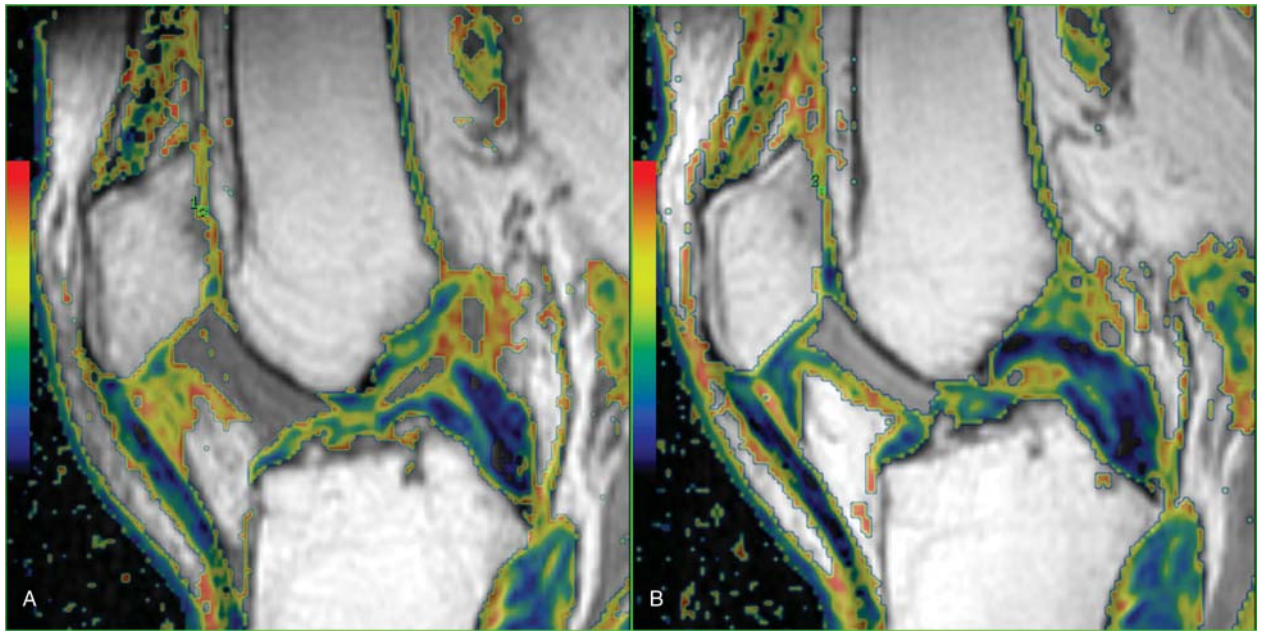


Figure 5. The T2 value of a 52-year-old female patient before and after treatment. The picture A is before treatment. The picture B is after treatment.

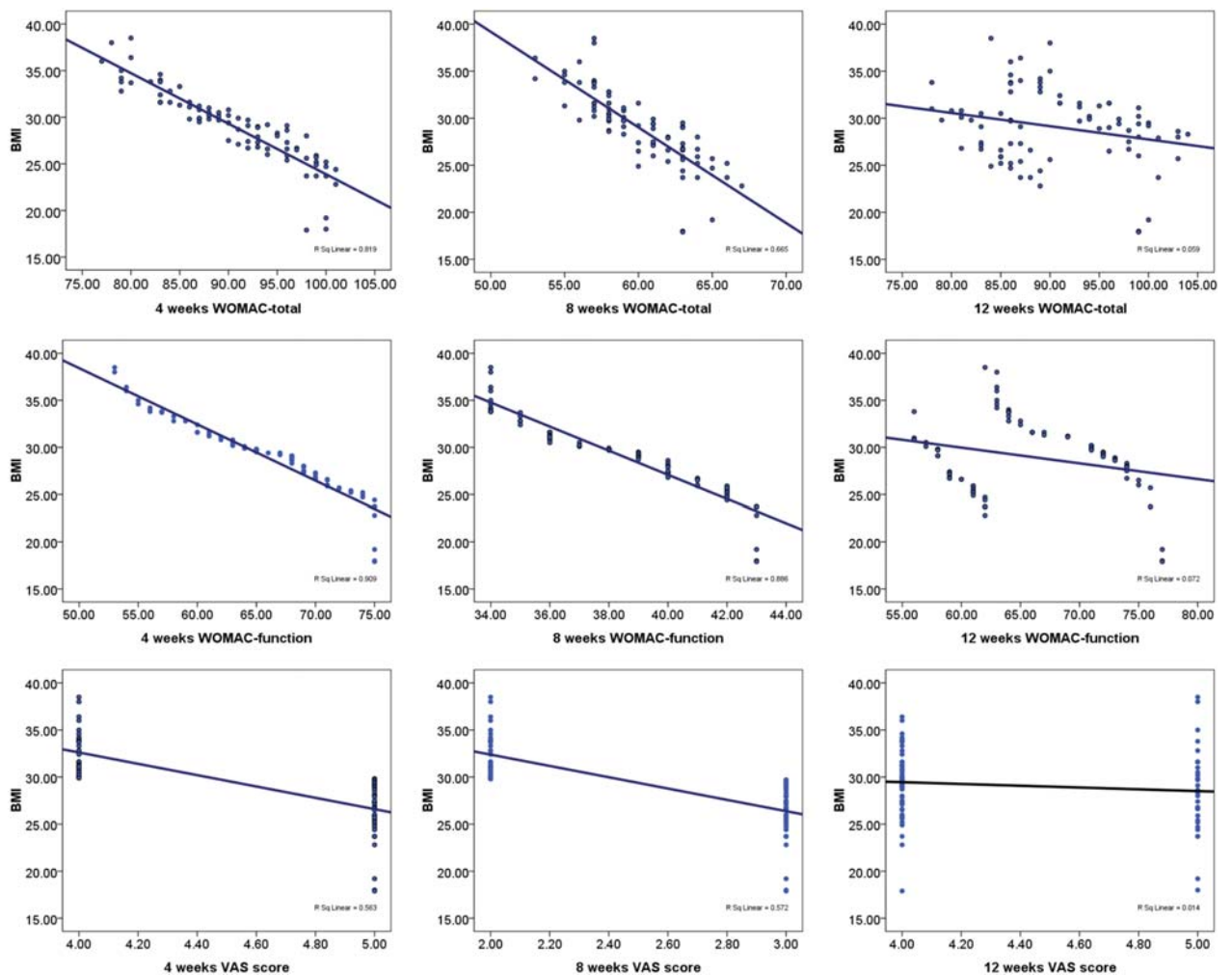


Figure 6. The X axis represents the VAS or WOMAC, the Y axis represents the BMI. The scores showed a decreasing trend with increasing BMI. This trend becomes smaller with time. BMI=body mass index; VAS=visual analog scale; WOMAC=Western Ontario and McMaster Universities Arthritis Index.

We evaluate the effect of ESWT on cartilage changes in KOA patients by CaLS morphological scoring and T2 value component measurement. No obvious changes can be observed; but it can not necessarily demonstrate that ESWT cannot repair the cartilage. The possible reasons are found to be responsible. Human body is more complicated than the animal model, but the existing shock wave parameters are deduced based on the animal model. Thus it is possible that the energy is not sufficient. Scholar Kim et al<sup>[7]</sup> had also carried out related study and indicated that ESW with moderate energy had lower efficacy in treating KOA than the low energy group. Additionally, some scholars once reported<sup>[33]</sup> that, the sites in which ESW promoted cartilage regeneration was specific, which might account for the fact that no changes were observed in this study.

As a result, we have proposed a new ESWT scheme for treating KOA, which is twice a week for 4 consecutive weeks in each course of treatment, followed by 8 weeks of rest before initiating the second course of treatment, and a total of 4 courses of treatment are required. The following parameters are selected in the first course of treatment, 4000 pulses are applied at 2.0 bar, 0.25 mJ/mm<sup>2</sup>, and the frequency of 8 Hz/s. It is recommended that the second to fourth courses of treatment should be carried out at the maximal patient capacity with the energy of no greater than 2.6 bar, and the remaining conditions are the same as those in the first course of treatment.

## 5. Conclusion

ESWT could potentially alleviate pain and improve knee joint function, and the therapeutic effect peaked at 8 weeks upon the completion of treatment. However, to obtain more accurate results, multicenter, randomized, and double-blind trials are required in the future.

## 6. Study limitations

Nevertheless, the current study is associated with certain limitations. Firstly, this is a follow-up observation, which has low evidence grade. Therefore, randomized, double-blind and multicenter clinical trials with large sample size are required for further intensive investigation. Secondly, effective records on the patients' daily life are lacking, and there may be some factors affecting the conclusions, making it impossible for well control. Therefore, more detailed questionnaire can be adopted to follow up the enrolled patients. Thirdly, biochemical indexes of synovial fluid are not observed in this study, but according to literature reports, ESWT can change the biochemical indexes of synovial fluid in KOA animal model. Consequently, these indexes can be added in future clinical study.

## Author contributions

**Formal analysis:** Yongming Xu, Kun Wu, Yu Liu, Haochong Zhang, Shuitao Liu, Hongying Qu.

**Funding acquisition:** Huan Geng.

**Writing – original draft:** Yongming Xu.

**Writing – review & editing:** Gengyan Xing.

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