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Impact of soft tissue around the knee on the efficacy of extracorporeal shockwave therapy in knee osteoarthritis

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Abstract

Knee osteoarthritis (KOA) is the leading cause of knee pain in middle-aged and older individuals. Extracorporeal shockwave therapy (ESWT) has been applied to treat patients with KOA to reduce pain and improve function. Patients (n = 123) diagnosed with KOA who received ESWT were selected to participate in this study, and were grouped according to their body mass index (BMI). The treatment parameters were as follows: 8000 pulses, 2.0 bar, 0.25 mJ/mm^2, and 6 Hz/s once per week for 8 weeks. The visual analog scale (VAS), Lequesne index, and Western Ontario and McMaster University Osteoarthritis Index (WOMAC) were measured to assess knee pain and functional recovery according to BMI groups. Radiographs were used to measure the richness of the soft tissue around the knee joint. The correlation between the distribution of tissue, pain, and functional improvement was analyzed using the receiver operator characteristic curve. All the patients showed a reduction in pain after treatment compared to that before treatment ($P < .01$). As measured by the VAS, the Lequesne and WOMAC indexes, after the intervention, the pain and functional index of the overweight and above BMI group improved to a greater extent than that of the normal or below normal BMI group ($P < .01$). The area under the curve showed, with VAS as the demarcation criterion, when the tibial plateau soft tissue ratio, femoral intercondylar apex soft tissue ratio, and medial tibial soft tissue ratio exceeded 1.538, 1.534, and 1.296, respectively, the patient's pain relief was more pronounced the ESWT treatment was better. With pain in WOMAC as the demarcation criterion, the tibial plateau soft tissue ratio, femoral intercondylar apex soft tissue ratio, and medial tibial soft tissue ratio also are positively correlated with pain relief in patients. When the Lequesne and WOMAC scores were the demarcation criteria, the patients' function improved significantly when the patella apical soft tissue ratio exceeded 2.401 and 2.635, respectively. ESWT can effectively alleviate pain and improve knee function in patients with KOA, and the soft tissue around the knee joint should also be an important reference factor in KOA treatment.

Abbreviations: BMI = body mass index, CT = computed tomography, ESWT = extracorporeal shockwave therapy, FAATL = fibula apical apex tibia line, FIASTR = femoral intercondylar apex soft tissue ratio, K–L = Kellgren and Lawrence, KOA = knee osteoarthritis, MRI = magnetic resonance imaging, MTSTR = medial tibial soft tissue ratio, NBB = normal or below normal BMI, OA = osteoarthritis, OAB = overweight and above BMI, PASTR = patella apical soft tissue ratio, ROC = receiver operator characteristic, TPJSL = tibial plateau joint surface line, TPSTR = tibial plateau soft tissue ratio, VAS = visual analog scale, WOMAC = Western Ontario and McMaster University Osteoarthritis.

Keywords: extracorporeal shockwave therapy, knee, osteoarthritis, soft tissue

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

The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

The experimental protocol was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of Zhejiang Armed Police Force Hospital (Clinical study of extracorporeal shock waves in the treatment of patients with knee osteoarthritis, NO.2021-01). Written informed consent was obtained from individual or guardian participants.

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1. Introduction

Osteoarthritis (OA) has long been considered a "wear and tear" disease. However, recent evidence suggests that it is an inflammatory disease of the entire synovial joint, including not only the mechanical degeneration of the articular cartilage, but also the structural and functional changes of the entire joint, including the synovium, meniscus (knee joint), peri-joint ligaments, and subchondral bone.[1] Knee osteoarthritis (KOA) is one of the most common degenerative diseases that causes disability in older adults, with an estimated 240 million people worldwide suffering from symptomatic, limited mobility OA. The knee joint is the most commonly affected joint. Nearly 30% of individuals over the age of 45 show radiographic findings indicative of knee OA, and about half show symptoms in the knee.[2] This is similar to the prevalence in Chinese populations, with an epidemiological study in China reporting an overall incidence of symptomatic KOA of 8.1%, a higher prevalence of symptomatic KOA in women than in men, and an increase in the prevalence of symptomatic KOA with age.[3]

Current nonsurgical treatments for KOA include health education, self-management, exercise, bariatric surgery, or biomechanical interventions such as support devices and orthoses. Medical treatment includes paracetamol, topical or oral nonsteroidal anti-inflammatory drugs, or intra-articular corticosteroids.[4] Pain is the primary reason patients with KOA seek clinical intervention. Many therapies, including nonpharmacological and pharmacological interventions, have been applied to patients with OA, but none of these methods completely eliminate pain or improve patient dysfunction, and knee replacement with postoperative rehabilitation has become the ultimate treatment for patients with advanced KOA.[5]

Over the past 20 years, extracorporeal shockwave therapy (ESWT) has advanced as an effective treatment for musculoskeletal disorders such as terminal tendon disease, lateral epicondylitis, calcified tendonitis, and long bone fracture nonunion, as well as bone ischemic necrosis.[6] In recent years, ESWT has been introduced for the treatment of OA as a noninvasive and low-risk treatment modality. Studies have demonstrated that ESWT can improve the pathological changes of OA, including changes in the cartilage and subchondral bone.[7] There were also studies revealing that ESWT can accelerate the healing of meniscal degeneration and exert a cartilage protective effect in OA.[8] ESWT treatment can enhance the activity of chondrocytes, reduce cartilage cleavage, and regulate apoptosis of chondrocytes.[9] ESWT has been shown to have a protective effect on cartilage in the early or late stages of OA.[10] In addition, in clinical trials, ESWT treatment can reduce OA pain and improve motor function.[11] These studies suggest that ESWT as a novel OA treatment is a promising candidate for clinical study.

In our ESWT clinical research work, we observed that a very strong relationship exists between body mass index (BMI) and the distribution of tissue around the knee joint and the effectiveness of KOA treatment. The soft tissue around the knee joint also crucially impacts the progression and treatment of knee joint disease.[12] The main method of diagnosing OA is still radiography. Kellgren and Lawrence (K–L) described the first formal attempt to establish an OA radiological classification in 1957[12]; the K–L classification is currently the most widely used clinical tool in diagnostic imaging of OA.[13] The K–L classification ignores the soft tissue correlation, therefore most of the focus has been on the interrelationship between bones. For patients with KOA, assessment primarily involves evaluation of the degeneration of the knee joint and the degree of joint space stenosis, and radiography is rarely used to evaluate the distribution of soft tissue around the knee joint. Therefore, in the process of studying ESWT, we actively attempt to find a convenient and feasible method to evaluate the distribution of soft tissue around the knee joint. After considering various factors, we decided to use radiography to evaluate the richness of the soft tissue around the knee joint. In this study, we explored the relationship between the distribution of tissue around the knee joint and the clinical efficacy of ESWT in the treatment of KOA and aimed to determine the possible pathogenesis of KOA from the perspective of imaging evaluation and clinical efficacy of ESWT.

2. Materials and Methods

We conducted a retrospective clinical study of patients with KOA who were written informed consent to participate in this study. Patients were treated with ESWT at the Zhejiang Provincial General Hospital of the Chinese Armed Police Force from January 2021 to January 2022. ESWT treatment was approved by the Hospital Ethics Committee. This study was approved by the Ethics Committee of Zhejiang Armed Police Corps Hospital (NO.2021-001). The related indicators of all patients were compared before and after treatment different BMI groupings were compared, and the relevant indicators of the soft tissue around the knee joint and changes in the pain and function improvement scores after treatment were analyzed using the receiver operator characteristic (ROC) curve of the participants.

2.1. Participants

The inclusion criteria were as follows: patients diagnosed with KOA according to the diagnostic criteria of the American College of Rheumatology who desired to receive shock wave therapy. The American College of Rheumatology criteria included knee pain, osteophytes, and one of the following: age >45 years, morning stiffness <30 minutes duration, or crepitus on active motion of the knee.[14] We enrolled patients with unilateral knee joint symptoms, knee pain in the past 3 months, K-L classification grade 2 or 3. Exclusion criteria: bilateral knee joint symptoms; a history of spinal stenosis; a history of nervous system disease or secondary arthritis (inflammatory or metabolic); underwent surgery in the involved knee joint or intra-articular injection within the previous 6 months; and any contraindication for radioscopy; known causes of arthritis (infection, post-infectious or metabolic); a medical condition involving hip or knee trauma, or intra-articular hip, or knee injection within 1 month; other reasons for pain in the knee; accepted other non-pharmacological or pharmacological treatment 1 month preceding baseline evaluation and during the study period; ESWT during the preceding 12 months; serious varus or valgus deformity; bilateral knee arthroplasties; serious acute or chronic organic disease or mental disorder.

All patients provided written informed consent to participate in the study.

2.2. Shockwave intervention

The participants were instructed to maintain their previous lifestyle and not to participate in any other regular rehabilitation programs. During the 2-month intervention, the participants would be taught no other treatment. Shockwave treatment involved the use of a DJO FRANCE SAS instrument (Intelect Radial Pressure Wave; 2074 Model; Mouguerre, France). Patients received 8000 pulses of shockwave at 2.0 bar, 0.25 mJ/mm^2, at a frequency of 6 Hz, once per week for 8 weeks. The interventions were conducted by physical therapists trained and experienced in ESWT. At each treatment session, patients were placed in a supine position with the affected knee unbent or flexed at 90°. The treatment area with coupling agent and the shock wave probe was held stationary on a trigger point around the knee or at the patello-femoral and tibio-femoral borders of the target knee. Meanwhile, the tenderness points in the knee joint were used as the therapeutic points after positioning based on the body surface anatomical markers with the pain points, avoiding direct placement on the peroneal nerve or vessel. To

reduce the loss of shockwave energy at the interface, aqueous gel was used as a coupling medium between the probe of the device and the skin.

2.3. Definition and measurement of the proportion of soft tissues around the knee joint

In the clinical treatment process, it was found that the distribution of tissue around the knee joint has a profound impact on the treatment effect. We included the soft tissue evaluation index below the X line in the study, in order to objectively show the soft tissue around the knee joint such as the upper end of the patella, the distal femur, the proximal tibia, the upper end of the fibula soft tissue richness. We selected the target site of the soft tissue cross-sectional length/corresponding to the ratio of the bone cross-section length to evaluate the surrounding soft tissue richness of different areas of the knee joint of each patient. The parameters were tibial plateau soft tissue ratio (TPSTR), patella apical soft tissue ratio (PASTR), femoral intercondylar apex soft tissue ratio (FIASTR), and medial tibial soft tissue ratio (MTSTR). The specific definition and measurement are illustrated in Figure 1.

All proportions of soft tissue around the knee were measured on an X-ray orthopedic piece at the standard standing position of the knee joint, as shown in the illustration (Fig. 1): ① Line: The tibial plateau joint surface line (TPJSL) is the baseline by connecting the apex of the lateral edge of the tibia through the base of the intercondylar crest base; the 2 ends of the line are extended to intersect the inner and outer skin, and the 2 intersections are connected as the TPJSL (shown in the figure as the length of the solid line + dotted line); TPJSL is defined as the TPSTR; ② Line: The patellar line was drawn parallel to the baseline through the apex of the upper patella. The connection between the patella superior and the medial and lateral cortex intersection of the femur is the patella apical femur line (as shown in Fig. 1); the intersection line that extended the intersection of the line with the inner and outer skin was the patella apical femoral soft tissue transection line (shown in the figure as the length of the solid line + dotted line), the patella apical femoral soft tissue transection line/patella apical femur line is defined as the PASTR; ③ Line: The same principle determined the formal intercondylar apex line (as shown as the solid line length) and femoral intercondylar apex soft tissue transection line (shown as the solid line + dotted line length), and defined femoral intercondylar apex soft tissue transection line/formal intercondylar apex line as the FIASTR; ④ Line: The same method determined the fibula apical apex tibia line (FAATL) (length of the solid line) and the MTST transection line (length of the solid line + dotted line), and defined the MTST transection line/FAATL as the MTSTR.

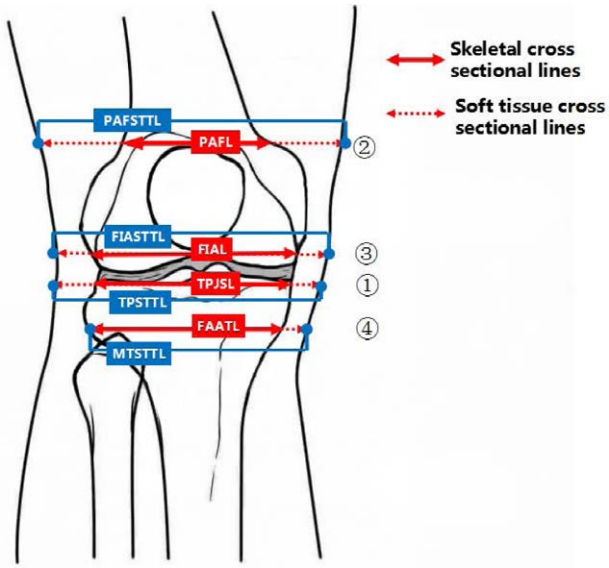

Figure 1. The specific definition and measurement were illustrated in Figure 1.

2.4. Outcome measures

Clinical assessment of pain on movement, physical function, and patient global assessment were measured. The primary outcome measure was painful movement measured by a 10-cm visual analog scale (VAS),[15] with 0 indicating no pain and 10 denoting extreme and unbearable pain.

The secondary outcome was disability on the Lequesne index, the Western Ontario and McMaster University Osteoarthritis Index (WOMAC).

The disease-specific, aggregated multidimensional Lequesne index includes questions about knee discomfort, endurance of ambulation, and difficulties in daily life.[16] A maximum score of 24 indicates the greatest degree of dysfunction; a score >13 indicates extremely severe disease. The WOMAC assesses symptoms of OA and is a validated disease-specific self-reporting questionnaire referring to the 48 hours preceding assessment.[17] The WOMAC score ranges from 0 (best) to 96 (worst), with higher scores representing worse symptom severity.

2.5. Statistical analysis

SPSS21.0 (SPSS Inc., Chicago, IL) was used to analyze the general data and scoring information of patients. The measurement data were tested using independent samples t test, and the counting data were tested using the χ^2 test; the truncation point of treatment effect evaluation was analyzed by the ROC of the participant's work curve; the comparative results of the various scoring tables of patients before and after the evaluation of treatment were paired t test, and the test level was set at $\alpha = 0.05$; $P < .05$ was considered statistically significant.

3. Results

3.1. Clinical characteristics of patients

We included 123 patients (male: 85; 38 in the normal or below normal BMI [NBB] group (<25 kg/m^2) and 47 in the overweight and above BMI (OAB) group (≥25 kg/m^2).[18] The mean ages of patients were (58.85 ± 5.61) and (59.84 ± 5.77) years in the NBB and OAB groups, respectively. Most patients in both groups were female (NBB: 64%, OAB: 73%). There were no difference in sex, age, affected limb site, and Kellgren–Lawrence grade ($P > .05$). The proportion of soft tissue around the knee joint in different BMI groups was statistically different, presented by the following indices: TPSTR, FIASTR, PASTR and MTSTR ($P < .01$) (Table 1).

3.2. Measurement of pain severity (VAS score)

After the entire course of treatment, all participants confirmed reduced pain during movement ($P < .01$) (Table 2). In all cases, the median of the VAS difference was 2, the outcome variable was reassigned using the VAS difference indicator. As measured by VAS, after the intervention, pain in the OAB group was reduced markedly compared to that in the NBB group at the end of treatment ($P < .01$). The mean VAS scores of the OAB and NBB groups were (1.63 ± 0.85) and (2.27 ± 1.44), respectively ($P < .01$) (Table 3).

Table 1

Demographic and baseline clinical characteristics of patients in the intent-to-treat population.

Characteristics	NBB group (n = 59)	OAB group (n = 64)	χ^2/t	*P* value
Male	21	17	1.173	.279
Female, n (%)	38 (64)	47 (73)		
Left knee	44	41	1.589	.207
Right knee	15	23		
Kellgren–Lawrence grade II	36	49	3.475	.062
Kellgren–Lawrence grade III	23	15		
Age (yr)	58.85 ± 5.61	59.84 ± 5.77	–0.970	.334
TPSTR	1.48 ± 0.12	1.57 ± 0.14	–3.634	<.001
FIASTR	1.54 ± 0.13	1.65 ± 0.19	–3.449	.001
PASTR	2.41 ± 0.26	2.55 ± 0.30	–2.739	.007
MTSTR	1.25 ± 0.07	1.32 ± 0.09	–4.461	<.001

FIASTR = femoral intercondylar apex soft tissue ratio, MTSTR = medial tibial soft tissue ratio, NBB = normal or below normal body mass index, OAB = overweight and above body mass index, PASTR = patella apical soft tissue ratio, TPSTR = tibial plateau soft tissue ratio.

Table 2

VAS, Lequesne, and WOMAC scores of patients before and after treatment in the intent-to-treat population.

Evaluation indicators	Patients (n = 123)	*T*	*P*
Pretreatment VAS	4.36 ± 1.13	29.384	<.001
Posttreatment VAS	1.93 ± 1.21		<.001
Pretreatment Lequesne	7.43 ± 2.37	22.378	<.001
Posttreatment Lequesne	3.75 ± 2.36		<.001
Pretreatment WOMAC	41.61 ± 11.41	30.510	<.001
Posttreatment WOMAC	26.72 ± 9.94		<.001
Pretreatment pain	8.72 ± 2.26	27.184	<.001
Posttreatment pain	4.10 ± 2.44		<.001
Pretreatment stiffness	3.55 ± 1.06	16.698	<.001
Posttreatment stiffness	2.35 ± 0.98		<.001
Pretreatment function	28.34 ± 8.16	26.894	<.001
Posttreatment function	20.28 ± 7.28		<.001

VAS = visual analog scale, WOMAC = Western Ontario and McMaster University Osteoarthritis.

3.3. Disability by the Lequesne index and WOMAC

In this study, the patients' functional index such as Lequesne index and WOMAC improved significantly ($P < .01$) after treatment (Table 2). In all cases, the median of the WOMAC score difference was 13, the median of the stiffness score-difference was 1, the median of the pain, functional difference, and Lequesne scores was 4, 8, and 3.5, respectively. The outcome variables were reassigned using the above 5 scoring measures. As measured by Lequesne and WOMAC, after the intervention, the functional index of the OAB group improved to a greater extent than that of the NBB group ($P < .01$). Following treatment, the mean Lequesne scores of the OAB and NBB groups were (4.47 ± 2.76) and (3.09 ± 1.68), respectively ($P < .01$). Between the OAB and NBB groups after treatment, the WOMAC score also exhibited similar results as the Lequesne score ($P < .01$). In the WOMAC score, the stiffness index of OAB and NBB patients was (4.47 ± 2.76) and (3.09 ± 1.68), respectively. Comparison of the 2 groups revealed a statistically significant between-group difference in stiffness improvement in patients receiving ESWT treatment based on BMI ($P < .05$). In the WOMAC function score, it was found that the functional score of the OAB group (18.45 ± 5.84) was significantly improved compared with that of the NBB group (22.25 ± 8.17); ($P < .01$) (Table 3).

3.4. Correlation analysis of knee soft tissue ratios with VAS, Lequesne, and WOMAC scores

The truncation point of treatment effect evaluation was analyzed using the ROC curve.

3.4.1. Pain relief. When VAS was used as the demarcation criterion, TPSTR, FIASTR, MTSTR were positively correlated with the patient's pain relief (Fig. 2), and we found through the ROC working curve that when the TPSTR, FIASTR, and MTSTR exceeded 1.538, 1.534, and 1.296, respectively, the more obvious the pain relief, and the better the treatment effect (Table 4). When using pain in WOMAC as the demarcation criterion, we arrived at a similar conclusion, TPSTR, FIASTR, and MTSTR were positively correlated with the patient's pain

Table 3

VAS, Lequesne, and WOMAC scores of patients before and after treatment in the NBB and OAB groups.

Evaluation indicators	NBB group (n = 59)	OAB group (n = 64)	*T*	*P* value
Pretreatment VAS	4.32 ± 1.18	4.39 ± 1.09	–0.335	.739
Posttreatment VAS	2.27 ± 1.44	1.63 ± 0.85	3.069	.003
Pretreatment Lequesne	7.35 ± 2.47	7.50 ± 2.28	–0.356	.723
Posttreatment Lequesne	4.47 ± 2.76	3.09 ± 1.68	3.382	.001
Pretreatment WOMAC	40.58 ± 11.82	40.46 ± 11.11	–0.031	.957
Posttreatment WOMAC	29.80 ± 11.28	23.89 ± 7.57	3.433	.001
Pretreatment pain	8.64 ± 2.36	8.78 ± 2.19	–0.335	.739
Posttreatment pain	5.00 ± 2.74	3.27 ± 1.78	4.197	<.001
Pretreatment stiffness	3.53 ± 1.09	3.58 ± 1.04	–0.275	.784
Posttreatment stiffness	2.54 ± 1.15	2.17 ± 0.75	2.136	.035
Pretreatment function	28.41 ± 8.44	28.28 ± 7.96	0.085	.933
Posttreatment function	22.25 ± 8.17	18.45 ± 5.84	2.986	.003

NBB = normal or below normal body mass index, OAB = overweight and above body mass index, VAS = visual analog scale, WOMAC = Western Ontario and McMaster University Osteoarthritis.

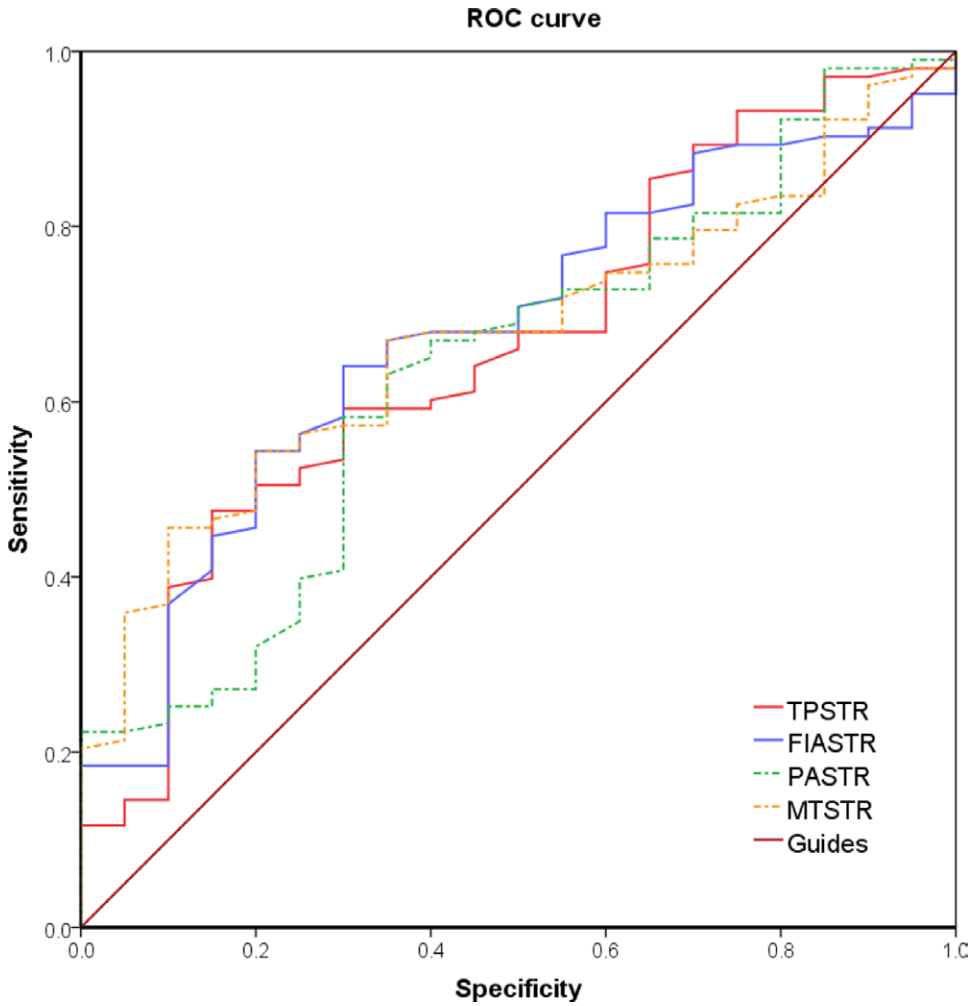

Figure 2. When VAS was used as the demarcation criterion, TPSTR, FIASTR, MTSTR were positively correlated with the patient's pain relief. FIASTR = femoral intercondylar apex soft tissue ratio, MTSTR = medial tibial soft tissue ratio, TPSTR = tibial plateau soft tissue ratio, VAS = visual analog scale.

Table 4

VAS as the demarcation criterion.

Outcome	AUC	Youden index	Threshold value	Sensitivity	Specificity	95% CI	*P* value
TPSTR	0.663	0.326	1.538	0.476	0.850	(0.539–0.787)	.021
FIASTR	0.678	0.344	1.534	0.544	0.800	(0.562–0.794)	.012
PASTR	0.638	–	–	–	–	(0.511–0.764)	.052
MTSTR	0.673	0.344	1.296	0.544	0.800	(0.565–0.781)	.015

AUC = area under the curve, CI = confidence interval, FIASTR = femoral intercondylar apex soft tissue ratio, MTSTR = medial tibial soft tissue ratio, PASTR = patella apical soft tissue ratio, TPSTR = tibial plateau soft tissue ratio, VAS = visual analog scale.

relief (Fig. 3), and the pain relief was more pronounced when the TPSTR, FIASTR, and MTSTR exceeded 1.539, 1.657, and 1.322, respectively (Table 5). Due to the different scales of pain measurement, there would be different ratios for pain relief, but it could also be shown that the distribution of tissue around the knee joint played a very important role in knee pain relief.

3.4.2. Improvement in function. When Lequesne was used as the demarcation criterion, it was found that only the PASTR was positively correlated with functional improvement (Fig. 4), and the patient's function improved significantly when the PASTR was 2.401 (Table 6); when functioning in the WOMAC score was the demarcation criterion, the PASTR was positively correlated with functional improvement (Fig. 5), and the functional improvement was more obvious when the PASTR exceeded 2.635 (Table 7). Throughout the study, there was no correlation between TPSTR, FIASTR, PASTR, MTSTR and the improvement of knee stiffness, the values of area under the curve 0.454, 0.474, 0.537, and 0.446, respectively; 95% CI: 0.338 to 0.571, 0.365 to 0.583, 0.412 to 0.661, 0.556 to 0.336, respectively. The *P* values were 0.458, 0.672, 0.551, and 0.379, respectively of soft tissue around the knee joint was not associated with improving knee stiffness ($P > .05$).

At the end of study, there was no correlation between TPSTR, FIASTR, PASTR, MTSTR and the total WOMAC score, the values of area under the curve were 0.564, 0.560,

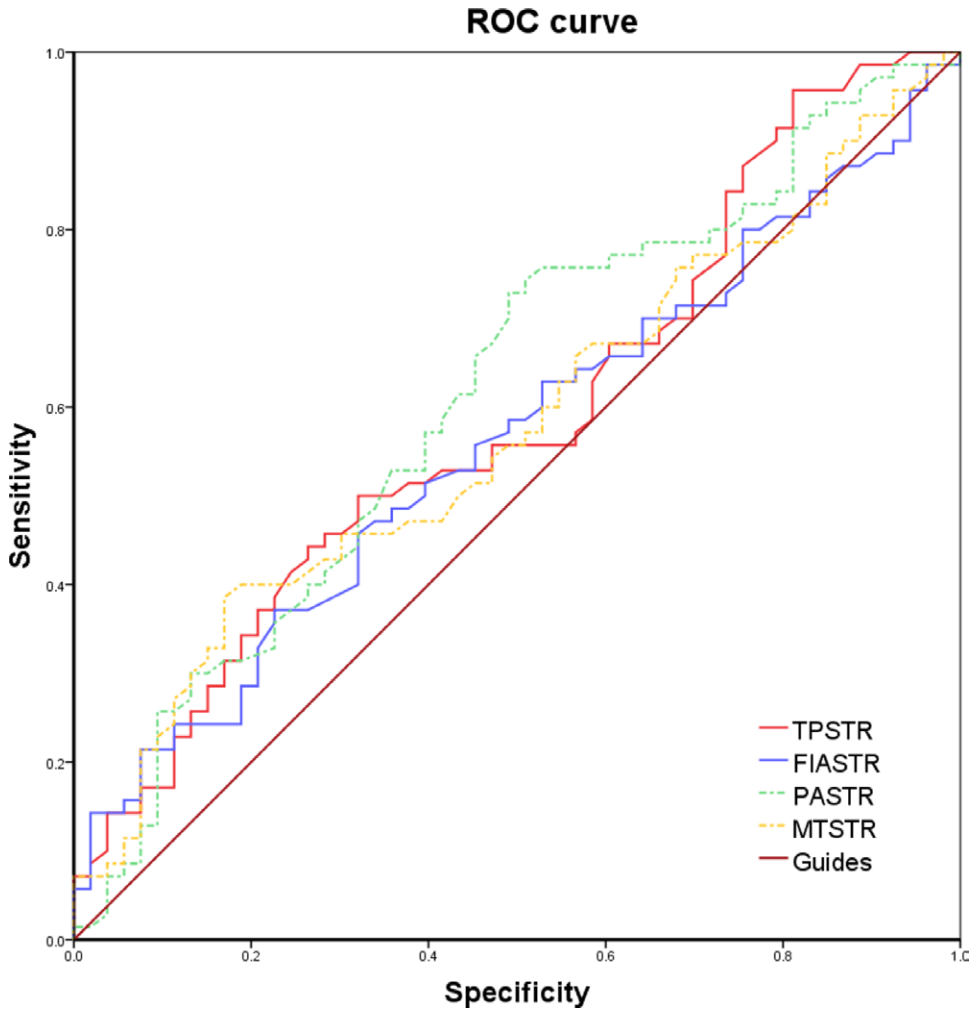

Figure 3. When using pain in WOMAC as the demarcation criterion, TPSTR, FIASTR, and MTSTR were positively correlated with the patient's pain relief. FIASTR = femoral intercondylar apex soft tissue ratio, MTSTR = medial tibial soft tissue ratio, TPSTR = tibial plateau soft tissue ratio, WOMAC = Western Ontario and McMaster University Osteoarthritis.

Table 5

Pain component of the WOMAC score as the demarcation criterion.

Outcome	AUC	Youden index	Threshold value	Sensitivity	Specificity	95% CI	*P* value
TPSTR	0.660	0.323	1.539	0.517	0.806	(0.555–0.766)	.005
FIASTR	0.643	0.280	1.657	0.391	0.889	(0.541–0.744)	.013
PASTR	0.589	–	–	–	–	(0.478–0.700)	.122
MTSTR	0.653	0.321	1.322	0.460	0.861	(0.553–0.753)	.008

AUC = area under the curve, CI = confidence interval, FIASTR = femoral intercondylar apex soft tissue ratio, MTSTR = medial tibial soft tissue ratio, PASTR = patella apical soft tissue ratio, TPSTR = tibial plateau soft tissue ratio, WOMAC = Western Ontario and McMaster University Osteoarthritis.

0.589, and 0.569 respectively; 95% CI: 0.462 to 0.667, 0.458 to 0.662, 0.496 to 0.700, 0.467 to 0.671, respectively. The P values were 0.221, 0.253, 0.063, and 0.187, respectively, and evaluation of the proportion of soft tissue around the knee joint was not associated with total WOMAC score ($P > .05$) (Fig. 6). There was no correlation in the WOMAC total score. The WOMAC score was a comprehensive score, which may be affected by the degree of knee stiffness and cannot comprehensively assess the relationship between the improvement in knee function and the distribution of tissue around the knee joint; another reason may be due to the impact of the WOMAC score range such as (0–96 or 0–2400); a decline in WOMAC score led to no significant association.[19]

4. Discussion

ESWT had shown an effect on OA in both some animal experiments and clinical studies, ESWT could be recommended in the treatment of OA as a noninvasive therapy with safety and effectiveness.[20] Our study also confirmed KOA patients with ESWT significantly relieved pain and improved function in clinical trials.[20,21] We observed that ESWT achieved a significant reduction in VAS scores for patients with KOA during clinical treatment compared to before treatment, providing significant pain reduction. We evaluated knee pain and function by the Lequesne index and WOMAC scores; the patients' knee function was significantly improved after treatment, and the results

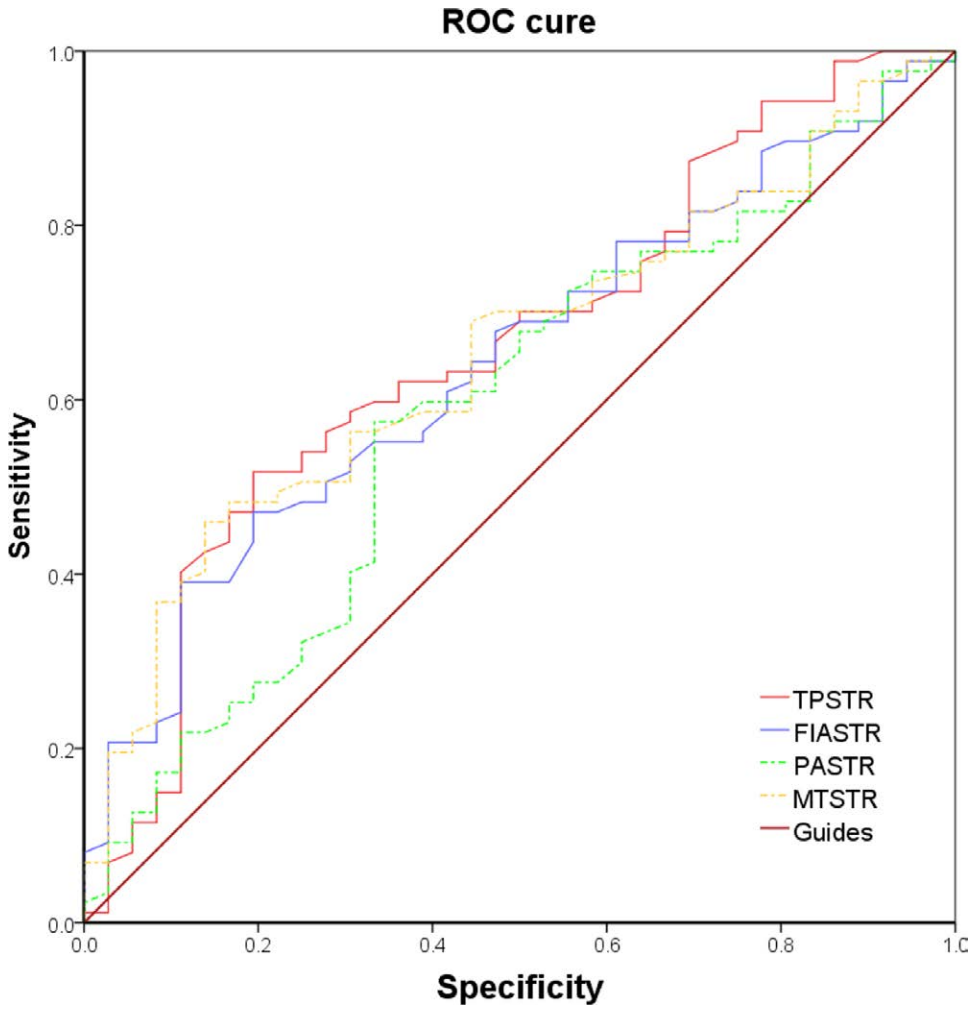

Figure 4. When Lequesne was used as the demarcation criterion, it was found that only the PASTR was positively correlated with functional improvement. PASTR = patella apical soft tissue ratio.

Table 6

Lequesne as the demarcation criterion.

Outcome	AUC	Youden index	Threshold value	Sensitivity	Specificity	95% CI	*P* value
TPSTR	0.588	–	–	–	–	(0.487–0.689)	.095
FIASTR	0.562	–	–	–	–	(0.461–0.663)	.242
PASTR	0.613	0.238	2.401	0.729	0.509	(0.512–0.714)	.032
MTSTR	0.575	–	–	–	–	(0.474–0.676)	.156

AUC = area under the curve, CI = confidence interval, FIASTR = femoral intercondylar apex soft tissue ratio, MTSTR = medial tibial soft tissue ratio, PASTR = patella apical soft tissue ratio, TPSTR = tibial plateau soft tissue ratio.

were consistent with some randomized and nonrandomized clinical trials.[22–24] During our clinical treatment, we realized that soft tissues also play a vital role in the treatment of KOA.

Clinically, it was found that there was a clear correlation between the distribution of soft tissue around the knee joint and the effect of ESWT in KOA treatment. We tried to evaluate the effect of ESWT in the treatment of KOA by summarizing a large amount of imaging data and finding clinically instructive indicators related to the distribution of tissue around the knee joint.

In clinical practice, it was found that in addition to patients with abdominal obesity, patients with larger BMI have a higher ratio of indexes such as the knee joint TPSTR and MTSTR, and improved effect of ESWT treatment for KOA, which can more effectively alleviate knee pain and improve knee function. Therefore, the soft tissue around the knee joint plays a vital role in the treatment, disease progression, and rehabilitation of patients with KOA, which indicates that more attention to soft tissues rather than to knee bones is required in future clinical diagnosis and research. To some extent, a thick lower limb knee joint for KOA patients is not necessarily unfavorable. For those who only consider BMI level as the weight loss target, weight loss may be accompanied by a considerable loss of soft tissue around the knee joint of the lower limb. This form of weight loss may not benefit the patient and may increase the risk of patients with knee disease, and even lead to the inability to use ESWT therapy after KOA.

Studies have revealed that the subchondral bone is a key target for ESWT in the treatment of KOA.[7,25] It is assumed that the thinner the local soft tissue, the more conducive it is to concentrating energy on the cartilage and subchondral bone. However,

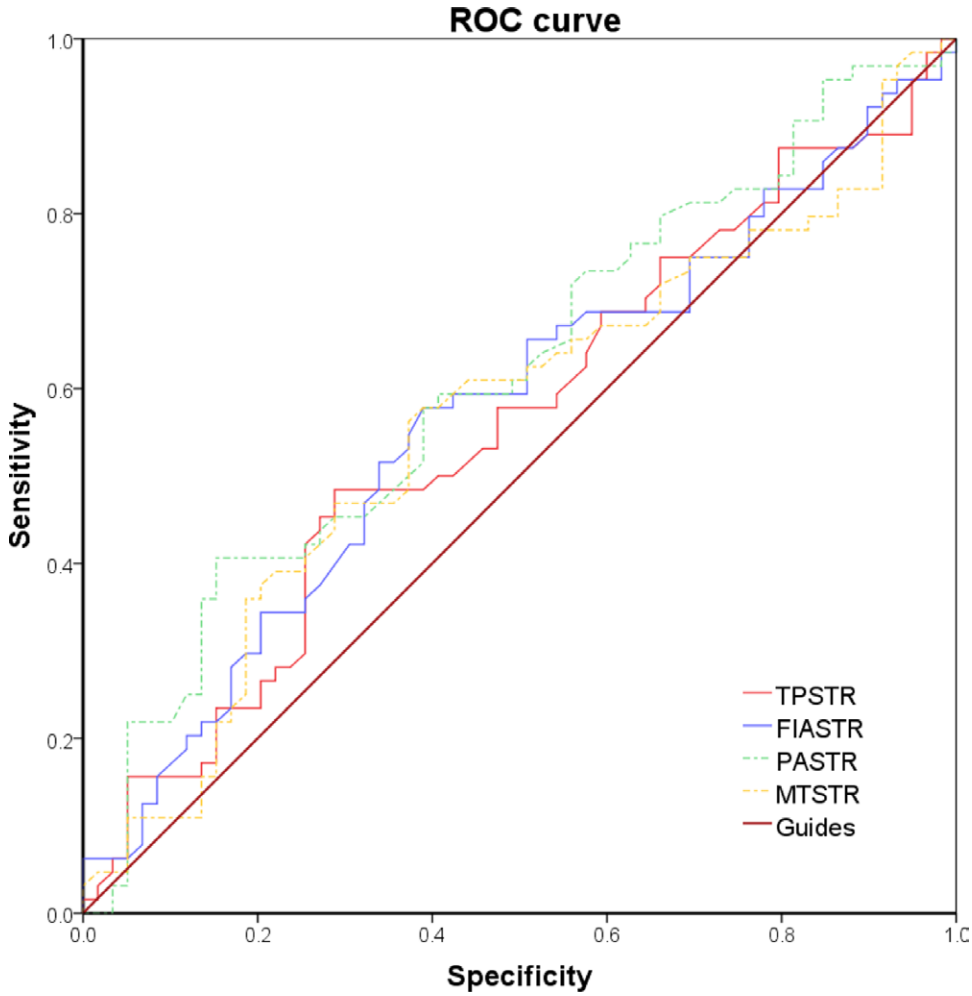

Figure 5. When functioning in the WOMAC score was the demarcation criterion, the PASTR was positively correlated with functional improvement. PASTR = patella apical soft tissue ratio, WOMAC = Western Ontario and McMaster University Osteoarthritis.

Table 7

WOMAC score as the demarcation criterion.

Outcome	AUC	Youden index	Threshold value	Sensitivity	Specificity	95% CI	*P* value
TPSTR	0.559	–	–	–	–	(0.457–0.661)	.257
FIASTR	0.571	–	–	–	–	(0.457–0.661)	.174
PASTR	0.612	0.254	2.635	0.406	0.847	(0.457–0.661)	.032
MTSTR	0.564	–	–	–	–	(0.461–0.666)	.223

AUC = area under the curve, CI = confidence interval, FIASTR = femoral intercondylar apex soft tissue ratio, MTSTR = medial tibial soft tissue ratio, PASTR = patella apical soft tissue ratio, TPSTR = tibial plateau soft tissue ratio, WOMAC = Western Ontario and McMaster University Osteoarthritis.

in clinical practice, the richer the soft tissue of the knee joint, the better the effect of ESWT in treating KOA, which leads us to question: where does ESWT concentrate energy to play a therapeutic role? To the subchondral bone and cartilage or soft tissue? Even if it is the subchondral bone, the role of soft tissue is also very important.

Basic studies on the effect of ESWT on soft tissues have found that in muscle stem cell and rat experiments, low intensity-ESWT promotes myocardial regeneration through the PERK/ATF4 signaling pathway, and low intensity-ESWT can promote vascular endothelial growth factor expression in prostate tissue through the PI3K/AKT/FOXO1 pathway to reduce inflammation, oxidative stress, and pain in rat models of prostatitis.[26–28] ESWT triggers the release of biomolecules such as adenosine triphosphate to activate cell signaling pathways, inducing C3H10T1/2 murine mesenchymal progenitor cells, primary human adipose tissue-derived stem cells, and a human Jurkat T cell line. Proliferation of these 3 stem cells promotes tissue repair.[20] Therefore, ESWT mediates the production of related biological factors, leading to increased neovascularization, proliferation of tendon cells and fibroblasts, and collagen synthesis, further enhancing tissue catabolism, healing, and remodeling to achieve tissue repair.[21] There has been no basic study of soft tissues around the knee joint, but some pain-related pathways in soft tissues have been affected or altered, thereby improving pain symptoms.

Clinical studies and practice have confirmed that ESWT can be effective in treating Achilles tendinopathy, greater trochanteric pain syndrome, medial tibial stress syndrome, patellar tendinopathy, and the proximal hamstring. For diseases such

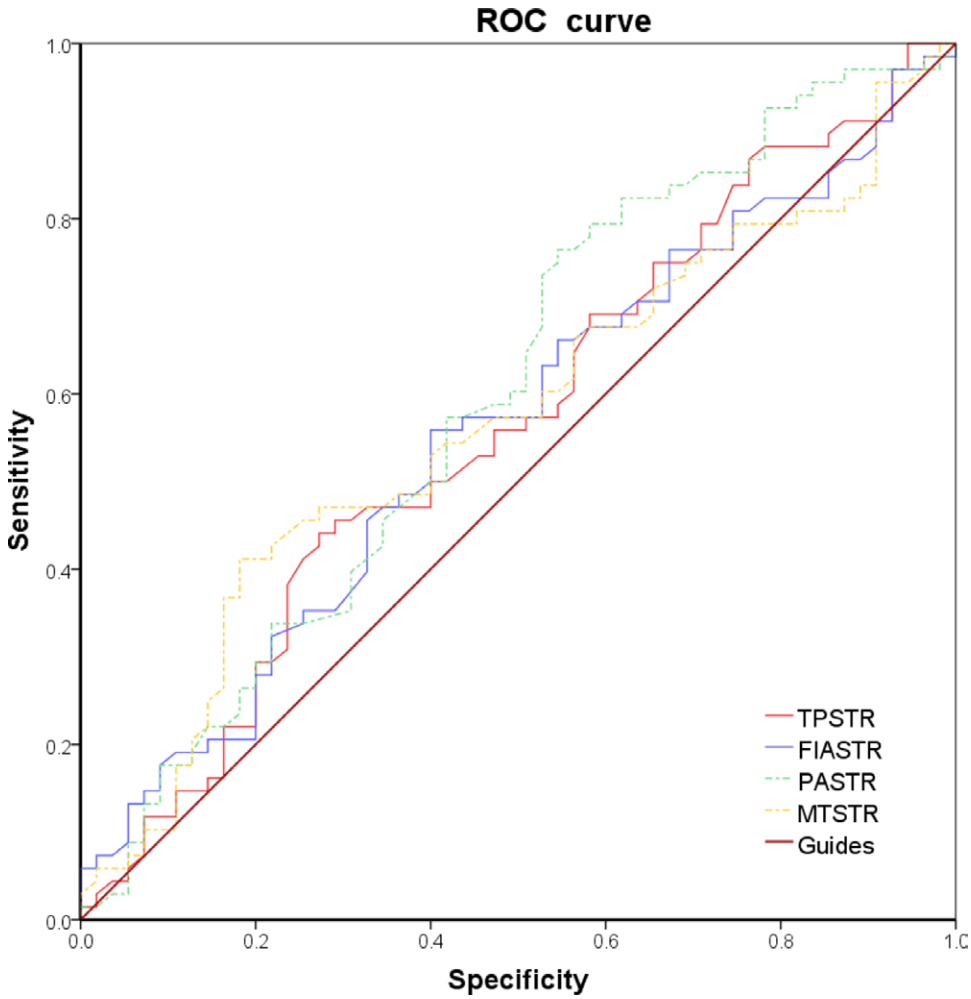

Figure 6. Evaluation of the proportion of soft tissue around the knee joint was not associated with total WOMAC score ($P > .05$). WOMAC = Western Ontario and McMaster University Osteoarthritis.

as tendinopathy, ESWT can significantly reduce pain by acting on soft tissues to improve function.[29–31] In addition to ESWT treatment, in some studies of maneuver, acupuncture and physiotherapy, they have reported that the therapeutic target within the soft tissue can still relieve pain and improve patient function in KOA patients by releasing and stimulating therapeutic targets inside soft tissues.[32–35] Therefore, the soft tissue is an important target for the treatment of disease using ESWT.

We observed that ESWT significantly relieved symptoms and improved function in patients with KOA; that the abundance of soft tissue around the knee joint was positively correlated with the treatment effect in patients with KOA. This important link was not previously reported in studies related to the treatment of KOA using ESWT. In our previous studies we observed that BMI is positively correlated with treatment outcomes,[23] but for patients with KOA who are abdominal obese,[36] ESWT may not achieve the desired effect, because the distribution of soft tissue around the knee joint in patients with abdominal obesity KOA may be weak, and the degree of soft tissue richness is not directly proportional to BMI.[37] As such, we have been thinking about exploring a more effective and practical index than BMI, an index that better serves as a clinical guide to assess the distribution of tissue around the knee joint. We have tried a series of relevant indicators, such as knee circumference, proportion of soft tissue distribution around the knee under magnetic resonance imaging (MRI), computed tomography (CT) imaging, and evaluation of the soft tissue ratio around the knee joint under X-ray alignment (TPSTR, PASTR, FIASTR, and MTSTR). In practice, the individual differences in bone morphology. For some individuals, because the bones are relatively thick, the knee joint circumference must be relatively large, but the soft tissue around the knee joint is not necessarily rich, and the knee joint circumference can only assess the patient's knee joint stoutness, and cannot reasonably evaluate the volume relationship between the soft tissue around the knee joint and the corresponding bone. Therefore, we did not choose this indicator as a research parameter. For exploration of the distribution ratio of soft tissue around the knee joint under MRI and CT imaging, due to the presence of layer thickness and layer spacing, the maximum soft tissue diameter line cannot be displayed, and during the measurement process, the display field of view of the 2 tomographies of sagittal and coronary positions is required to determine the maximum transverse longitude, which makes data collection difficult and biased. Finally, we chose X-ray images as the source of evaluation parameters because the data is easy to obtain, and for patients, in a fixed, unified, undisputed position, the index is constant and unique. For MRI and CT images, inaccuracy of data taken due to the selection bias of data collectors is inevitable. We used X-ray as a way to evaluate the richness of the soft tissue around the knee joint, which is to take the soft tissue as a whole concept in our research object, rather than any specific tissue. The soft tissue around the knee joint includes skin, fascia, fat, muscle, tendon, blood vessels, and nerves, and to some extent, these soft tissues can play a role in protection, support, and nutritional support.

We analyzed the correlation between the distribution of tissue around the knee joint and the treatment effect, and the results showed that the more abundant the soft tissue around the knee joint, such as TPSTR and MTSTR, the greater the degree to which ESWT relieved knee pain and improved function. We also found that the PASTR was positively correlated with functional improvement. The main core muscle group in this position is the quadriceps tendon, which may be the reason why exercising the lower limb core muscle group to increase knee stability can improve pain and function of knee patients,[38,39] improving the muscle strength of the lower extremities through exercise and increasing the richness of the soft tissue around the knee joint was more beneficial to ESWT treatment of KOA. To some extent, the soft tissue around the knee joint may be an effective new target for KOA diagnosis, evaluation, treatment and rehabilitation, and we expect our research to contribute to the formulation of primary prevention strategies for the prevention of KOA in older adults.

Our study possessed some limitations. We confirmed that ESWT can effectively relieve pain and improve function in patients with KOA, but in the ESWT, the settings of dose, energy, and frequency are all summaries of previous studies and clinical experience, and due to the different energies received by different populations, different energies were not selected for group comparison. We treated patients for 8 weeks, only to assess the short-term efficacy, and therefore the study lacked long-term follow-up. Further, this was a single-center study with a small sample size. At present, we only assessed the distribution of tissue around the knee joint by X-ray, and in the future, we will further follow up patients to perform MRI reconstruction of soft tissue around the knee joint, make 3-dimensional measurements of the area or volume of important structures around the knee joint through MRI to further determine the treatment target more accurately.

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References

[1] Mobasheri A, Batt M. An update on the pathophysiology of osteoarthritis. Ann Phys Rehabil Med. 2016;59:333–9.
[2] Felson DT, Naimark A, Anderson J, et al. The prevalence of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. Arthritis Rheum. 1987;30:914–8.
[3] Tang X, Wang S, Zhan S, et al. The prevalence of symptomatic knee osteoarthritis in China: results from the China health and retirement longitudinal study. Arthritis Rheumatol. 2016;68:648–53.
[4] Kan HS, Chan PK, Chiu KY, et al. Non-surgical treatment of knee osteoarthritis. Hong Kong Med J. 2019;25:127–33.
[5] Canovas F, Dagneaux L. Quality of life after total knee arthroplasty. Orthop Traumatol Surg Res. 2018;104:S41–6.
[6] Wang CJ. Extracorporeal shockwave therapy in musculoskeletal disorders. J Orthop Surg Res. 2012;7:11.
[7] Chou WY, Cheng J-H, Wang C-J, et al. Shockwave targeting on subchondral bone is more suitable than articular cartilage for knee osteoarthritis. Int J Med Sci. 2019;16:156–66.
[8] Cheng JH, Wang C-J, Chou W-Y, et al. Comparison efficacy of ESWT and Wharton's jelly mesenchymal stem cell in early osteoarthritis of rat knee. Am J Transl Res. 2019;11:586–98.
[9] Wang CJ, Weng L-H, Ko J-Y, et al. Extracorporeal shockwave therapy shows chondroprotective effects in osteoarthritic rat knee. Arch Orthop Trauma Surg. 2011;131:1153–8.
[10] Wang CJ, Weng L-H, Ko J-Y, et al. Extracorporeal shockwave shows regression of osteoarthritis of the knee in rats. J Surg Res. 2011;171:601–8.
[11] Zhao Z, Jing R, Shi Z, et al. Efficacy of extracorporeal shockwave therapy for knee osteoarthritis: a randomized controlled trial. J Surg Res. 2013;185:661–6.
[12] Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis. 1957;16:494–502.
[13] Braun HJ, Gold GE. Diagnosis of osteoarthritis: imaging. Bone. 2012;51:278–88.
[14] Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and therapeutic criteria committee of the american rheumatism association. Arthritis Rheum. 1986;29:1039–49.
[15] Carlsson AM. Assessment of chronic pain. I. Aspects of the reliability and validity of the visual analogue scale. Pain. 1983;16:87–101.
[16] Lequesne MG, Mery C, Samson M, et al. Indexes of severity for osteoarthritis of the hip and knee. Validation – value in comparison with other assessment tests. Scand J Rheumatol Suppl. 1987;65:85–9.
[17] Bellamy N, Campbell J, Stevens J, et al. Validation study of a computerized version of the Western Ontario and McMaster Universities VA3.0 Osteoarthritis Index. J Rheumatol. 1997;24:2413–5.
[18] Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. J Am Coll Cardiol. 2014;63:2985–3023.
[19] Copsey B, Thompson JY, Vadher K, et al. Problems persist in reporting of methods and results for the WOMAC measure in hip and knee osteoarthritis trials. Qual Life Res. 2019;28:335–43.
[20] Chen L, Ye L, Liu H, et al. Extracorporeal shock wave therapy for the treatment of osteoarthritis: a systematic review and meta-analysis. Biomed Res Int. 2020;2020:1907821.
[21] Simplicio CL, Purita J, Murrell W, et al. Extracorporeal shock wave therapy mechanisms in musculoskeletal regenerative medicine. J Clin Orthop Trauma. 2020;11(Suppl 3):S309–18.
[22] Chen TW, Lin C-W, Lee C-L, et al. The efficacy of shock wave therapy in patients with knee osteoarthritis and popliteal cyamella. Kaohsiung J Med Sci. 2014;30:362–70.
[23] Xu Y, Wu K, Liu Y, et al. The effect of extracorporeal shock wave therapy on the treatment of moderate to severe knee osteoarthritis and cartilage lesion. Medicine (Baltim). 2019;98:e15523.
[24] Zhong Z, Liu B, Liu G, et al. A randomized controlled trial on the effects of low-dose extracorporeal shockwave therapy in patients with knee osteoarthritis. Arch Phys Med Rehabil. 2019;100:1695–702.
[25] Wang CJ, Cheng J-H, Huang C-Y, et al. Medial tibial subchondral bone is the key target for extracorporeal shockwave therapy in early osteoarthritis of the knee. Am J Transl Res. 2017;9:1720–31.
[26] Ioppolo F, Rompe JD, Furia JP, et al. Clinical application of shock wave therapy (SWT) in musculoskeletal disorders. Eur J Phys Rehabil Med. 2014;50:217–30.
[27] Wang B, Zhou J, Banie L, et al. Low-intensity extracorporeal shock wave therapy promotes myogenesis through PERK/ATF4 pathway. Neurourol Urodyn. 2018;37:699–707.
[28] Feng B, Dong Z, Wang Y, et al. Li-ESWT treatment reduces inflammation, oxidative stress, and pain via the PI3K/AKT/FOXO1 pathway in autoimmune prostatitis rat models. Andrology. 2021;9:1593–602.
[29] van der Worp H, van den Akker-Scheek I, van Schie H, et al. ESWT for tendinopathy: technology and clinical implications. Knee Surg Sports Traumatol Arthrosc. 2013;21:1451–8.
[30] Korakakis V, Whiteley R, Tzavara A, et al. The effectiveness of extracorporeal shockwave therapy in common lower limb conditions: a systematic review including quantification of patient-rated pain reduction. Br J Sports Med. 2018;52:387–407.

[31] Zhang Q, Fu C, Huang L, et al. Efficacy of extracorporeal shockwave therapy on pain and function in myofascial pain syndrome of the trapezius: a systematic review and meta-analysis. Arch Phys Med Rehabil. 2020;101:1437–46.
[32] Au KY, Chen H, Lam WC, et al. Sinew acupuncture for knee osteoarthritis: study protocol for a randomized sham-controlled trial. BMC Complement Altern Med. 2018;18:133.
[33] Lv ZT, Shen L-L, Zhu B, et al. Effects of intensity of electroacupuncture on chronic pain in patients with knee osteoarthritis: a randomized controlled trial. Arthritis Res Ther. 2019;21:120.
[34] Nazari A, Moezy A, Nejati P, et al. Efficacy of high-intensity laser therapy in comparison with conventional physiotherapy and exercise therapy on pain and function of patients with knee osteoarthritis: a randomized controlled trial with 12-week follow up. Lasers Med Sci. 2019;34:505–16.
[35] Atalay SG, Durmus A, Gezginaslan O. The effect of acupuncture and physiotherapy on patients with knee osteoarthritis: a randomized controlled study. Pain Physician. 2021;24:E269–78.
[36] Kalinkovich A, Livshits G. Sarcopenic obesity or obese sarcopenia: a cross talk between age-associated adipose tissue and skeletal muscle inflammation as a main mechanism of the pathogenesis. Ageing Res Rev. 2017;35:200–21.
[37] Wannamethee SG, Atkins JL. Muscle loss and obesity: the health implications of sarcopenia and sarcopenic obesity. Proc Nutr Soc. 2015;74:405–12.
[38] Xie Y, Zhang C, Jiang W, et al. Quadriceps combined with hip abductor strengthening versus quadriceps strengthening in treating knee osteoarthritis: a study protocol for a randomized controlled trial. BMC Musculoskelet Disord. 2018;19:147.
[39] Zeng CY, Zhang Z-R, Tang Z-M, et al. Benefits and mechanisms of exercise training for knee osteoarthritis. Front Physiol. 2021;12:794062.