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Extracorporeal Shockwave Versus Chitosan-Nanoparticles Phonophoresis On Functional Improvement And Anatomical Changes Detected With Artificial Intelligence-Based Texture Analysis In Knee Osteoarthritis: A Single Blind Randomized Controlled Trial

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Abstract

Introduction: Osteoarthritis (OA) is a leading cause of disability worldwide, with knee osteoarthritis (KOA) being the most prevalent form and a major contributor to pain and functional decline. Once considered primarily a cartilage disorder, KOA is now recognized as a disease involving the entire joint, particularly the subchondral bone, which plays a crucial role in disease progression and pain generation. Recent therapeutic strategies have thus shifted focus toward modulating subchondral bone remodeling using non-invasive modalities such as extracorporeal shockwave therapy (ECSWT) and low-intensity pulsed ultrasound (LIPUS). The integration of LIPUS with bioactive agents like Chitosan nanoparticles offers a promising approach for enhancing tissue repair and reducing inflammation. Moreover, artificial intelligence (AI)-based texture analysis provides sensitive and objective quantification of subchondral bone changes, enabling early detection and precise monitoring of therapeutic effects in KOA. This study aimed to compare the effects of ChNPS-phonophoresis and ECSWT on clinical outcomes and subchondral bone microarchitecture in KOA, using AI-based texture analysis. and to assess the sensitivity and objectivity of AI-based texture analysis for detecting early bone changes and monitoring treatment responses. Materials and **Methods:** A single blind randomized trial was conducted on 120 patients aged between 40-60 years old, with mild to moderate KOA. Patients with previous knee surgery or lower limb fractures, inflammatory or neurological disorders, significant synovitis or acute inflammation were excluded. Patients were divided equally into three groups (n = 40). Group A received ChNPs gel-phonophoresis with exercise, Group B received ECSWT with exercise, and Group C (control) received exercise only. Interventions lasted 8 weeks. Pain and function were assessed using VAS and Arabic WOMAC. Subchondral bone changes were evaluated using IB Lab TX Analyzer™ via Bone Structure Value (BSV) and Fractal Dimension (FD) and recorded at baseline and post-treatment. **Results:** All groups showed significant post-treatment clinical improvements ($P < 0.001$), with Group A achieving the most pronounced reductions in VAS and WOMAC scores ($P < 0.05$). Group A also showed significant anatomical improvement: BSV increased from 0.43 ± 0.23 to 0.62 ± 0.24, and FD increased from 0.67 ± 0.11 to 0.77 ± 0.13 (both $P < 0.001$), with effect sizes of $\eta^2 = 0.081$ and $\eta^2 = 0.114$, respectively. **Conclusion:** ChNPs gel-phonophoresis yielded superior outcomes in pain, functional, and bone microarchitecture. AI-based TX enhances precision in monitoring KOA treatment response, supporting structure-targeted, non-invasive approaches.

Keywords: Subchondral Bone, Deep Learning, Bone structure value, Fractal Dimension, Medical Imaging Analysis, Chitosan, Nanotechnology, Shockwave, Texture analysis.

INTRODUCTION

Osteoarthritis (OA) ranks among the top global causes of disability, with knee osteoarthritis (KOA) being the most common and its incidence rising sharply with increased life expectancy (1,2). Once regarded as a cartilage disease, KOA is now understood to involve the subchondral bone, where early changes such as sclerosis and osteophyte formation play a pivotal role in disease progression (3–5). These alterations not only accelerate cartilage degeneration but also appear more strongly linked to pain than cartilage loss itself, explaining the weak correlation between radiographic findings and symptoms (6,7).

Despite extensive research, no curative treatment exists for KOA. Current management emphasizes non-invasive options such as exercise and physical modalities (8,9). Among them, extracorporeal shockwave therapy (ECSWT) and low-intensity pulsed ultrasound (LIPUS) have demonstrated potential in promoting subchondral bone remodeling and reducing inflammation, in particular, has demonstrated efficacy in early KOA by enhancing osteocyte activity, increasing trabecular bone number density (10–13). Combining LIPUS with bioactive delivery agents such as Chitosan-Nanoparticles (ChNPs) may further enhance therapeutic effects, as it improves encapsulation and skin permeability, offering a promising route for non-invasive targeted therapy and given Chitosan's biocompatible, anti-inflammatory, and chondroprotective properties (14,15), with studies supporting its role in modulating subchondral bone remodeling (16).

Radiographically, the Kellgren–Lawrence (K-L) scale remains the most widely used classification, but it is limited by poor sensitivity and weak correlation with symptoms (17). To overcome these limitations, artificial intelligence (AI)-based methods, particularly texture analysis (TX), have emerged as powerful tools for detecting early subchondral bone microarchitectural changes and monitoring treatment. Key metrics such as Bone Structure Value (BSV) and Fractal Dimension (FD) provide objective markers of tibial bone quality and disease progression (18–21).

Objectives

In light of this evolving understanding, the current study aimed to compare the clinical and structural effects of these interventions, ECSWT and ChNPs gel-phonophoresis, on pain relief, functional improvement, and microarchitectural changes in the tibial subchondral bone in patients with KOA. In addition, this study aimed to evaluate the utility of AI-based texture analysis as a sensitive and objective tool for detecting early subchondral bone changes and for monitoring treatment outcomes in KOA patients.

MATERIALS, PARTICIPANTS AND METHODS

Study Design:

This was a parallel-group, single-blinded, randomized controlled trial (RCT) with a 1:1:1 allocation ratio, conducted in orthopedic outpatient clinics in Egypt. The intervention lasted eight consecutive weeks: the phonophoresis and exercise groups received 24 sessions (three per week), while the ECSWT group received eight weekly sessions. Assessments were performed at baseline and immediately post-intervention. Ethical approval was obtained from the Health Research Ethics Committee, Faculty of Physical Therapy, Cairo University (P.T.REC/012/005026).

Randomization, Blinding, and Allocation Concealment:

Participants were randomly assigned to one of three groups using simple randomization in Excel, with allocation concealed through sequentially numbered, sealed, opaque envelopes by an independent researcher. Given the nature of the interventions and the necessity of supervising the study's implementation, the principal investigator was not blinded, both participants and independent outcome assessors (software engineer for TX and radiologist for radiographs) were blinded. All procedures adhered to the Declaration of Helsinki, and informed consent was obtained from all participants.

Participants

Based on sample size calculation, a total of 120 participants were randomized into three equal groups (n=40). Group A received ChNPs gel- phonophoresis and group B received ECSWT both with a structured exercise

program and both as a study group, while group C received the same exercise program only as a control group. Eligibility was determined through predefined inclusion and exclusion criteria, with referrals made by orthopedic surgeons responsible for clinical and radiological diagnosis.

Eligibility criteria

Eligible participants were men and women aged 40–60 years with radiologically confirmed KOA (K-L grade 2–3) (22). In bilateral cases, the more symptomatic knee was treated. Additional criteria included ≥3 months of persistent knee pain with functional limitations (23,24), baseline pain ≥40 mm on VAS at rest, and adequate cognitive ability to follow the protocol (26,27).

Exclusion criteria comprised prior knee surgery or lower limb fractures, chronic inflammatory or neurological disorders, moderate to severe knee synovitis, acute inflammation, pregnancy (28). Patients were also excluded if they had recent KOA treatments, including physiotherapy during the study period, Chronic inflammatory diseases (e.g., rheumatoid arthritis), intra-articular hyaluronic acid or arthroscopy within six months, or prolonged use of psychotropic/narcotic analgesics within the past eight weeks (3,26,27).

Outcome measures:

Baseline characteristics including age, height, weight, and BMI were recorded prior to intervention. The K-LG scale, based on plain radiographs, was used to classify KOA severity into five grades (0–4), considering features such as joint space narrowing (JSN), osteophyte formation, sclerosis, and deformity (17).

Pain intensity was measured using the Visual Analogue Scale (VAS), a 100 mm line anchored from "no pain" to "maximum pain." Scores were categorized as: 0–4 mm (no pain), 5–44 mm (mild), 45–74 mm (moderate), and 75–100 mm (severe) (28). Functional outcomes were assessed with the Arabic version of the WOMAC Index (Ar-WOMAC), which evaluates pain, stiffness, and physical function. The Likert version includes 24 items scored on a 0–4 scale, with total scores ranging from 0 to 96, standardized to 0–100. The Ar-WOMAC is validated and widely used in Arabic-speaking populations (29).

Interventions included ECSWT delivered via the Gymna ShockMaster (3–5 bars, 8 Hz). The ChNPs gel was supplied by Chitosan Egypt LLC and prepared in sufficient quantity. The transparent gel exhibited suitable viscosity for ultrasound application and was stored at 4°C in light-protected containers to maintain stability and prevent microbial growth (30) with a physiological pH range (5.5–6.5), which aligns with skin pH and reduces the likelihood of irritation or barrier disruption. The formulation contained 0.2% w/v low molecular weight chitosan (≥90% deacetylation) and 0.1% w/v sodium tripolyphosphate (5:1 ratio) to generate nanoparticles, with propylene glycol (8%), glycerin (5%), and Carbopol 940 (1%) added for penetration enhancement and viscosity control. Ex vivo diffusion studies confirmed enhanced transdermal penetration and drug release, supporting its use in ultrasound-mediated therapy (32,33). Therapeutic ultrasound was applied with the GymnaPulson device, ensuring consistent and reproducible treatment delivery.

For structural assessment, texture analysis was performed using the IB LAB TX Analyzer™ (ImageBiopsy Lab, Vienna, Austria), an FDA-cleared and CE-certified AI-based platform for trabecular bone evaluation. The software applies fractal-based methods to derive 3D information from 2D radiographs, focusing on Bone Structure Value (BSV) and Fractal Dimension (FD). Both markers reflect bone microarchitecture, where higher1values indicate denser, more complex structure, while lower values denote OA-related deterioration (34,35).

Procedures:

All participants were informed about the study objectives and procedures and provided written consent. They were required to discontinue any pharmacological treatments (e.g., acetaminophen, NSAIDs) at least one week before baseline assessment and throughout the study, except for restricted paracetamol use (500 mg/day). They were also instructed to avoid additional physical activity outside the treatment program. Standard knee X-rays were taken at baseline and after the 8-week intervention to evaluate subchondral bone texture. The study followed four phases: medical screening, pre-intervention assessment, treatment implementation, and post-intervention evaluation. The study was structured into four main phases: initial medical examination, pre-intervention assessment, implementation of the treatment program, and post-intervention evaluation.

Phase 1: Medical Examination (Investigations):
Participants underwent medical and musculoskeletal examination and standardized weight–bearing AP radiographs. A blinded radiologist classified KOA severity using the K–L system, while an orthopedic specialist confirmed the diagnosis clinically and radiographically.

Phase 2: Pre -Intervention Assessment:
Pain intensity level assessed using the VAS. Participants were instructed to mark a point along a 100 mm horizontal line that best reflected their average knee pain over the preceding week (28). b) Self–reported functional status was measured using the Egyptian (Ar–WOMAC) Index. Participants completed the questionnaire independently. Higher scores indicated greater impairment. Subscale scores were computed by summing item responses in the domains of pain, stiffness, and physical function. Participants were instructed to respond to all items (29).

Phase 3: Experimental Intervention (Treatment Program):
Group A (ChNPs Gel–Phonophoresis + Exercise): Participants received ChNPs gel-phonophoresis combined with a structured exercise program. The gel was applied to medial and lateral aspects of the knee as both a therapeutic medium and US coupling agent. Ultrasound was delivered at 1 MHz, 2.5 W/cm², 20% duty cycle, for 5 minutes per session (36).
Group B (ECSWT + Exercise): Participants received ECSWT with the same exercise regimen. Treatment targeted medial and lateral subchondral bone, with patient's supine and knee flexed at 90°. The treatment application parameters during each session were as follows: 3000 impulses were administered at an energy flux density of 0.25 mJ/mm² (approximately 3 bar) at a frequency of 8 Hz (Jhan et al., 2022; Hu et al., 2024). The probe was chosen effective treatment depth (5–20-mm focal depth). using a probe of 4 cm. No anesthesia was used, and patients were monitored for local adverse effects (37).
Group C (Exercise Only): Participants performed a standardized exercise program (9 exercises including treadmill warm-up, bridging, straight leg raising, knee extension, prone knee flexion, wall squat, and hip strengthening in various positions). Exercises were performed 3 times per week for 8 weeks, with 2 sets of 10 reps each. All three groups followed the same structured exercise program (38).

Phase 4: Post-Intervention Assessment and Texture Analysis Methodology:
One day after completing the 8-week intervention, all participants underwent a standardized post-treatment assessment. Clinical outcomes were reassessed using the Visual Analogue Scale (VAS) for pain and the Ar-WOMAC Index for functional evaluation. Radiological assessment included standardized weight-bearing AP knee radiographs, which were analyzed with the IB LAB TX Analyzer™ to examine subchondral bone microarchitecture.
All radiographs (n = 240; pre- and post-treatment) were anonymized and processed by a blind engineer. The software automatically adjusted brightness and contrast, excluded poor-quality scans, and consistently defined regions of interest (ROIs) beneath the tibial plateau in both medial and lateral compartments. Each ROI was segmented into a 3×8 grid (24 compartments) (Figure 1), further divided into subzones for localized trabecular evaluation (39). Automated quality control mechanisms within the software excluded radiographs exhibiting motion artifacts or malalignment, in accordance with criteria established by Bastos & Nogueira, (2025) (40).

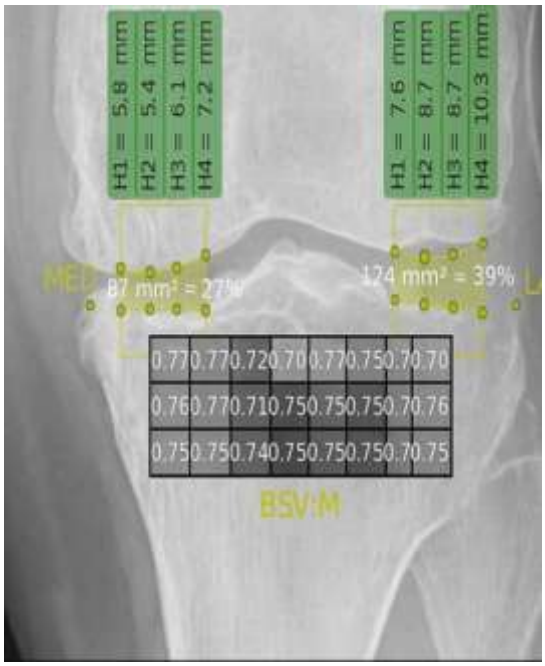

Figure 1. Automated segmentation of the tibial subchondral bone using the IB LAB Analyzer. A 3×8 grid divides the ROI into 24 compartments based on anatomical landmarks, with each compartment further split into three horizontal rows for detailed structural evaluation. Each compartment is automatically generated and analyzed by AI software.

Two key texture parameters were extracted. The BSV, ranging from 0 to 1, reflected the degree of trabecular integrity, with higher values indicating improved structural organization. The FD, also normalized to a 0–1 scale, characterized the complexity of the trabecular pattern. Together, these measures provided complementary insights into treatment-related bone adaptations. All data were exported as anonymized CSV files for blinded statistical analysis (41–43).

Statistical analysis

Statistical analysis was done by SPSS v27. Normality was assessed with the Shapiro–Wilks test. All participants completed the trial without missing data, and analyses followed the intention-to-treat principle (ITT). Parametric data were expressed as mean ± SD and compared using ANOVA with Tukey post hoc tests, with effect sizes (η^2) reported. Non-parametric data were expressed as median (IQR) and analyzed using the Kruskal–Wallis test with Bonferroni correction, with ε^2 effect sizes calculated. Categorical variables were presented as frequencies (%) and tested using Chi-square. Statistical significance was set at $p < 0.05$ (two-tailed).

RESULTS

Demographic Data:

In this study the three study groups (A, B, and C) were comparable at baseline, with no significant differences in demographic or clinical characteristics. Participants' mean ages were in the mid-fifties across groups ($p = 0.757$), with a predominance of females, particularly in Group B (65%; $p = 0.521$). BMI values were similar ($p = 0.829$), and the distribution of mild to moderate KOA severity was balanced ($p = 0.434$). Overall, the groups were well matched, ensuring the validity of treatment outcome comparisons (Table 1).

Table 1. The demographic and KOA severity of the studied groups.

Variable		Group A (n=40; 33.33%)	Group B (n=40; 33.33%)	Group C (n=40; 33.33%)	P
Age (years)	**Mean ± SD**	55.6 ± 6.47	55.4 ± 7.26	54.5 ± 6.64	0.757
	Range	42 – 65	41 – 65	42 – 65	
Sex	**Male**	19 (47.5%)	14 (35%)	17 (42.5%)	0.521
	Female	21 (52.5%)	26 (65%)	23 (57.5%)	
BMI (Kg/m^2)	**Mean ± SD**	28.2 ± 3.68	28.5 ± 4	28 ± 4.31	0.829
	Range	17.5 - 34.3	21.1 - 36.2	20.6 - 38.5	
KOA severity	**Mild**	24 (60%)	19 (47.5%)	19 (47.5%)	0.434
	Moderate	16 (40%)	21 (52.5%)	21 (52.5%)	

BMI. Body mass index, KOA severity. Knee osteoarthritis.

Within Group Analysis (Pre vs. Post Comparison for Each Group). and Between-Group Analysis (Treatment Effect Comparison):

A comparative analysis of clinical and texture outcomes across the three study groups before and after treatment. Clinical outcomes and texture metrics showed significant improvements post-treatment, particularly in Group A. VAS decreased from 5.7 to 3.15 in Group A, 5.7 to 4.25 in Group B, and 6.5 to 5.4 in Group C ($p < 0.001$, $\varepsilon^2 = 0.18$). WOMAC improved from 50.9 to 39.9 in Group A, 45.7 to 38.0 in Group B, and 52.2 to 46.7 in Group C ($p = 0.004$, $\eta^2 = 0.091$). Texture analysis showed BSV increased significantly in Group A (0.43 → 0.62, $p < 0.001$), but not in Group C ($p = 0.051$). FD improved in Group A (0.67 → 0.77, $p < 0.001$) with no significant changes in Group B ($p = 0.065$). Overall, Group A (ChNPs phonophoresis) showed the most significant improvements in pain intensity (VAS), functional status (WOMAC), and subchondral bone structure (BSV and FD) compared to Groups B and C. Group B (ECSWT) also demonstrated significant but lesser changes, while Group C (exercise only) showed the least improvement (Table 2).

Table 2. The clinical outcomes and the Texture metrics analysis across study groups (within and between groups).

Measure	Time	Group A (n=40)	Group B (n=40)	Group C (n=40)	Effect Size	P value	Post Hoc
VAS score	**Pre-treatment**	5.7 (5 – 6.83)	5.7 (4.9 – 6.53)	6.5 (5 – 7.2)	--	0.387	--
VAS Score	**Post-treatment**	3.15 (2.5 – 4.23)	4.25 (3.6 – 4.9)	5.4 (4.15 – 5.83)	$\varepsilon^2 = 0.18$	<0.001*	P1 = 0.018* P2 < 0.001* P3 = 0.031*
VAS Score	**P^ (within group)**	<0.001*	<0.001*	<0.001*	--	--	--
WOMAC Score	**Pre-treatment**	50.91 ± 11.76	45.68 ± 10.96	52.17 ± 12.34	$\eta^2 = 0.072$	0.034*	P1 = 0.116 P2 = 0.881 P3 = 0.038*
WOMAC Score	**Post-treatment**	39.91 ± 11.92	38.02 ± 11.27	46.7 ± 12.5	$\eta^2 = 0.091$	0.004*	P1 = 0.758 P2 = 0.032* P3 = 0.004*
WOMAC Score	**P^ (within group)**	<0.001*	<0.001*	<0.001*	--	--	--
BSV	**Pre-**	0.43 ±	0.49 ± 0.24	0.57 ± 0.25	--	0.632	--

	treatment	0.23					
BSV	**Post-treatment**	0.62 ± 0.240	0.58 ± 0.24	0.6 ± 0.25	η^2 = 0.081	0.007*	P1 = 0.935 P2 = 0.026* P3 = 0.060
BSV	**P^ (within group)**	<0.001*	<0.001*	0.051	--	--	--
FD	**Pre-treatment**	0.67 ± 0.11	0.68 ± 0.12	0.71 ± 0.67	--	0.776	--
FD	**Post-treatment**	0.77 ± 0.13	0.68 ± 0.13	0.69 ± 0.67	η^2 = 0.114	<0.001*	P1 = 0.005* P2 = 0.041* P3 = 0.618
FD	**P^ (within group)**	<0.001*	0.065	<0.001*	--	--	--

Data are presented as follows: VAS scores are shown as median (IQR). WOMAC, BSV, and FD values are Presented as mean (± SD). *: Statistically significant at P ≤ 0.05. P^: Within-group comparison between Pre- and Post-treatment. P1: Comparison between Group A and Group B. P2: Comparison between Group A and Group C. P3: Comparison between Group B and Group C.

DISCUSSION

Knee osteoarthritis is a progressive, multifactorial disease characterized by pain, functional decline, and structural deterioration. Traditional management has largely focused on articular cartilage and synovial inflammation, with less emphasis on subchondral bone, despite its central role in disease progression. Moreover, the integration of AI-based imaging biomarkers for monitoring treatment-related changes remains limited. To address these gaps, the present study evaluated two distinct non-invasive strategies, ChNPs gel-phonophoresis and ECSWT while employing AI-driven TX to assess microarchitectural subchondral bone changes.

Pain Reduction Across Treatment Modalities

All groups demonstrated significant pain reduction post-intervention (P < 0.001), with Group A (ChNPs-phonophoresis) achieving the most pronounced analgesia, followed by ECSWT and exercise. Intergroup analysis confirmed superior outcomes for ChNPs phonophoresis over ECSWT (P = 0.018) and exercise (P < 0.001), while ECSWT also outperformed exercise (P = 0.031).

These findings are consistent with recent evidence highlighting the benefits of phonophoresis. Yang et al. (2022) (44) reported significant pain relief with NSAID phonophoresis, while Mehrotra & Tripathi (2020) (45) showed dexamethasone phonophoresis provided superior VAS improvements compared to conventional ultrasound. Similarly, ECSWT demonstrated clinically meaningful pain reduction in prior studies (46). Mechanistically, ChNPs enhance drug retention and local bioavailability, supported by preclinical work showing that celecoxib- and kartogenin-loaded ChNPs suppressed inflammatory mediators (47). Together, these results support the analgesic superiority of nanoparticle-mediated phonophoresis in KOA.

Impact on Functional Outcomes

All groups exhibited significant functional improvements on the Ar-WOMAC (P < 0.001). Post-treatment analysis revealed both ChNPs-phonophoresis and ECSWT outperformed exercise alone, with no significant difference between Groups A and B.

The observed gains are supported by Abed et al. (2024) (48), who showed enhanced functional recovery with metformin phonophoresis, and by Yang et al. (2022) (44), who reported significant WOMAC improvement using NSAID gels. Similarly, ECSWT has demonstrated sustained functional benefits (49). These findings underscore the potential of both modalities to improve joint function, though variability in ultrasound parameters and drug formulations across studies necessitates standardized protocols.

Subchondral Bone Remodeling: AI TX Assessment

AI-based TX revealed significant post-treatment structural gains, with Group A showing the greatest improvement in BSV and FD, ECSWT yielding moderate effects, and exercise showing minimal or negative changes. These findings align with prior work linking fractal texture to microarchitectural integrity (50) and confirming ECSWT-induced osteogenesis (51).

Importantly, TX metrics outperformed conventional grading in sensitivity, consistent with Almhdie-Imjabbar et al. (2022) (52), who reported FD and BSV as reliable predictors of OA progression. However, variability in anatomical landmarks and imaging acquisition remains a limitation, emphasizing the need for standardized imaging protocols.

Clinical Implications: Toward Structure-Targeted Care

The findings highlight the therapeutic value of biologically active, non-invasive strategies for KOA. ChNPs gel phonophoresis combines chitosan's anti-inflammatory and regenerative potential with ultrasound-enhanced delivery, while ECSWT provides mechanical stimulation that promotes angiogenesis and bone remodeling. Supporting evidence demonstrates ChNPs' ability to suppress pro-inflammatory cytokines (53) and enhance cartilage and bone regeneration (54). Together, these effects extend treatment beyond symptom relief to structural modification, a paradigm shift in OA management.

Diagnostic Value of AI-Based Texture Analysis

TX offers quantitative, reproducible assessment of microstructural changes. Jang et al. (2022) (41) showed BSV detected treatment effects undetected by K-L grading, while Almhdie-Imjabbar et al. (2022) (52) confirmed FD's prognostic utility. In the current study, significant BSV and FD improvements, especially in the ChNPs group, demonstrated the superior diagnostic sensitivity of TX over conventional radiography.

Recent evidence also supports the role of AI in radiographic KOA assessment. Zhao et al. (2025) (55) reported that deep learning models achieved high sensitivity for advanced K–L grades, but only moderate performance for early stages. This highlights that while DL can improve grading consistency, texture-based biomarkers such as BSV and FD may offer a more sensitive framework for detecting early treatment-related structural changes.

RECOMMENDATIONS

This study highlights ChNPs-phonophoresis as a safe, minimally invasive, and effective adjunct for early-to-moderate KOA, particularly for patients unsuitable for invasive therapies. By addressing both symptoms and structural pathology, it supports a shift toward integrative, structure-targeted management. Parallel improvements in BSV and FD further validate AI-driven texture analysis as a sensitive adjunct for monitoring treatment response and guiding clinical decision-making.

LIMITATIONS

Nevertheless, limitations must be acknowledged. Outcomes were assessed only in the short term, without long–term follow–up to establish the durability of treatment effects. Also, the 8–week intervention period, though sufficient for early clinical and imaging responses, may have been too brief to capture the full extent of subchondral bone remodeling, which typically requires longer observation.

While our findings and those of prior literature strongly advocate for the integration of ChNPs and ECSWT into early KOA management, further research is warranted. Specifically, larger–scale, longer–duration human trials are essential to validate structural outcomes and clarify the relative contributions of inflammatory and mechanical mechanisms. Until then, these therapies should be viewed as promising adjuncts, particularly for structure–targeted, non–invasive intervention rather than definitive disease–modifying solutions.

CONCLUSION

This study demonstrates that ChNPs-phonophoresis provides superior pain relief, functional improvement, and subchondral bone remodeling in KOA compared to ECSWT or exercise alone. AI–based texture analysis offered sensitive detection of structural changes, outperforming conventional radiographic grading. These findings support shifting KOA management toward non–invasive, structure–targeted strategies that address both symptoms and underlying pathology. While results are promising, longer–term and larger trials are needed

to confirm durability, optimize protocols, and standardize imaging biomarkers. Integrating nanotechnology, ultrasound delivery, and AI–driven imaging offers a transformative model for personalized, disease–modifying KOA treatment.

Clinical Trial Registration Code: NCT06567301

Conflicts of interest. The authors declare no conflict of interest.

Data Availability: The dataset Presented in the study is available on request from the corresponding author after Publication.

Ethical Approval. This study was approved by Health Research Ethics Committee of Faculty of Physical Therapy, Cairo University with Ethical clearance number P.T.REC/012/005026.

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Informed Consent: Informed consent was obtained from each patient included in this study.

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