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Extracorporeal shockwave therapy shows site-specific effects in osteoarthritis of the knee in rats

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ABSTRACT

Purpose: This study investigated the site-specific effects of extracorporeal shockwave therapy (ESWT) in osteoarthritis of the knee in rats.

Methods: Sixty SD rats were divided into five groups. Group I was the control and received sham surgery without anterior cruciate ligament transection (ACLT) and medial meniscectomy (MM) and no ESWT. Group II received ACLT + MM, but no ESWT. Group III received ACLT + MM and ESWT at distal femur. Group IV received ACLT + MM and ESWT at proximal tibia. Group V received ACLT + MM and ESWT at distal femur and proximal tibia. Each ESWT session consisted of 800 impulses at 14 kV (= 0.219 mJ/mm^2 energy flux density). The evaluations included radiograph, bone mineral density (BMD), histomorphologic examination, and immunohistochemical analysis.

Results: Radiographic appearance: Group II showed progressive osteoarthritis of the knee at 12 and 24 wk, whereas only subtle changes were noted in Groups I, III, VI, and V. BMD results: Group II showed significant decreases of BMD at 12 and 24 wk. The BMDs of Groups III, IV, and V were comparable to Group I. Cartilage degradation: Group II showed significant increases of Mankin score, Safranin O stain, and matrix metalloproteinase 13 and decrease of collagen II at 12 and 24 wk. The changes of Mankin score, Safranin O stain, matrix metalloproteinase 13, and collagen II in Groups III, IV, and V were comparable to Group I. Subchondral bone remodeling: Group II showed significant decreases of vascular endothelial growth factor, bone morphogenetic protein 2, and osteocalcin at 12 and 24 wk as compared to Group I. The changes of vascular endothelial growth factor, bone morphogenetic protein 2, and osteocalcin in Groups III, IV, and V were comparable to Group I.

Conclusion: ESWT shows site-specific effects at distal femur and proximal tibia in osteoarthritis of the knee in rats. The effects of ESWT are consistent at distal femur and proximal tibia, with no additive effects when both areas were simultaneously treated.

1. Introduction

Osteoarthritis (OA) of the knee is one of the most common degenerative joint disorders and often manifests with pain, deformity, and functional disability. Osteoarthritis of the knee has long been considered primarily a cartilage disease associated with cartilage loss and degradation [1–4]. The relationship between the subchondral bone changes and the

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initiation and progression of knee OA continues to be debated [5–8]. Some studies demonstrated increased subchondral bone turnover accompanied by microarchitectural changes in the subchondral trabecular bone in osteoarthritic joint [6,8,9]. Others reported that subchondral bone remodeling increases in OA changes and is associated with the disease progression [3,10,11]. These observations suggested a role of subchondral bone changes in the initiation and progression of OA changes of the knee, and that early intervention to the subchondral bone may ameliorate the initiation and progression of osteoarthritic changes [6–10]. Several studies reported positive effects of ESWT in osteoarthritis of various joints in animals [12–16]. A recent study demonstrated that application of extracorporeal shockwave therapy (ESWT) to the subchondral bone of the medial tibia condyle showed chondroprotective effects with decreased articular cartilage degradation and improved subchondral bone remodeling in the initiation of OA changes of the knee in rats [17]. Another study showed that ESWT is effective in the regression of established OA changes of the knee in rats [18]. In those studies, ESWT was applied only to the medial tibia condyle of the knee. However, the ideal location for ESWT application in the osteoarthritic knee is unknown. We hypothesized that the effects of ESWT in osteoarthritic knees may be related to the treatment site. The purpose of this study was to investigate the site-specific effects of ESWT in the osteoarthritic changes in rats.

2. Design and methods

Sixty male Sprague-Dawley rats were used in this study. The animals were divided into five groups, with 12 rats in each group. Group I was the control and received sham knee surgery without anterior cruciate ligament transection (ACLT) and medial meniscectomy (MM) or ESWT. Group II received ACLT + MM, but no ESWT, and was used for observation of OA changes of the knee. Group III underwent ACLT + MM and received ESWT to the distal medial femur condyle. Group IV underwent ACLT + MM and received ESWT to the medial proximal tibia condyle. Group V underwent ACLT + MM and received ESWT to the medial distal femoral condyle and medial proximal tibia condyle. Each session of shockwave treatment consisted of the application of 800 impulses of ESWT at 14 kV (equivalent to 0.219 mJ/mm^2) to the medial distal femoral condyle approximately 0.5 cm above the medial joint line and 0.5 cm from the medial skin, or to the medial proximal tibia condyle at 0.5 mm below the joint line and 0.5 mm from the medial skin edge. One-half of the animals received ESWT at 1 wk after knee surgery, whereas the other half received ESWT at 12 wk after knee surgery.

2.1. Arthrotomy and anterior cruciate ligament transection and medial meniscectomy

The right knee was prepared in a surgically sterile fashion. Through medial parapatellar mini-arthrotomy, the ACL was transected with a scalpel. Medial meniscectomy was performed by removing the entire medial meniscus. The ACL was not transected in the sham group. The knee joint was irrigated and the incision was closed. Prophylactic antibiotics with ampicillin 50 mg/kg every 6 h were given for 5 d after surgery. Postoperatively, the animals were cared for by a veterinarian. The surgical site and the activities of the animals were observed daily.

2.2. Shockwave application

ESWT was performed in Groups III, IV, and V. Groups I and II received no ESWT. The animals were sedated with phenobarbital while receiving ESWT. The source of the shockwave was an OssaTron (Saunwave, Alpharetta, GA). Each session consisted of the application of 800 impulses of shockwave at 0.219 mJ/mm^2 energy flux density. The ESWT dosage so chosen was based on the results of a pilot study that showed that 800 impulses at 14 kV (= 0.219 mJ/mm^2 energy flux density) is more effective and safe than 1200, 400, and 200 impulses in a rat model. In Group III, ESWT was applied to the medial distal femur condyle at 0.5 cm above the joint line and 0.5 cm from medial skin edge. One-half ($n = 6$) of animals received ESWT at 1 wk after knee surgery and the other half ($n = 6$) at 12 wk after knee surgery. In Group IV, ESWT was applied to the medial proximal tibia condyle at 0.5 cm below the joint line and 0.5 cm from medial skin edge. One-half ($n = 6$) of the cases were treated at 1 wk and the other half at 12 wk after knee surgery. In Group V, ESWT was applied to the medial distal femur condyle and medial proximal tibia condyle. One-half ($n = 6$) of the treatments were performed at 1 wk and the other half ($n = 6$) at 12 wk after knee surgery.

The evaluations included radiographs and bone mineral density (BMD) around the knee at 0, 12, and 24 wk. The animals that received ESWT at 1 wk after knee surgery were sacrificed at 12 wk, and the animals that received ESWT at 12 wk after knee surgery were sacrificed at 24 wk. The specimens were subjected to histomorphologic examination and immunohistochemical analysis.

2.3. Radiographs of the knee and bone mineral density around the knee

Radiographs of the knee in anteroposterior and lateral projections were obtained at 0, 12, and 24 wk after knee surgery. Radiographs were used to evaluate the bony appearance, osteoarthritic changes such as focal osteoporosis, narrowing of medial joint space, bone sclerosis, and spur formation.

BMD with region of interest around the knee joint was performed using dual-energy x-ray absorptionmetry scan at 0, 12, and 24 wk after knee surgery. BMD was used to assess the changes in bone density of the proximal tibia and the distal femur.

2.4. Histopathologic examination

One-half of the animals ($n = 6$) from each group that received ESWT at 1 wk after surgery were sacrificed at 12 wk, whereas the other half ($n = 6$) that received ESWT at 12 wk after knee surgery were sacrificed at 24 wk. The knee specimens were subjected to histopathologic examination for Mankin score and Safranin O stain to evaluate the articular cartilage degradation in OA changes.

The harvested specimens were fixed in 4% PBS-buffered formaldehyde at 4°C for 7 d and decalcified in 10%

PBS-buffered EDTA at 4°C for 14 d. Decalcified specimens were fixed and subjected to paraffin wax embedding and dissection into 5-μm-thick sections. The specimens were stained with hematoxylin-eosin and Safranin-O stains. The degenerative changes of the cartilage were graded histologically using Mankin scores for the assessments of cartilage structure, cartilage cells, and tidemark integrity [19]. In addition, Safranin O stain and tissue distributions including cortical bone, woven bone, and cartilagenous and fibrous tissues as well as the trabecular pattern of the subchondral bone were examined microscopically.

2.5. *Immunohistochemical analysis*

Immunohistochemical analyses of collagen II and matrix metalloproteinase (MMP)-13 for cartilage changes, and vascular endothelial growth factor (VEGF), bone morphogenetic protein 2 (BMP-2), and osteocalcin for subchondral remodeling, were performed with immunohistochemical stains. The harvested cartilage and bone specimens were fixed in 4% PBS-buffered formaldehyde for 48 h and decalcified in PBS-buffered 10% EDTA solution. Decalcified tissues were embedded in paraffin wax. The specimens were cut longitudinally into 5-μm-thick sections and transferred to poly-lysine-coated slides. Sections of the specimens were immunostained with specific reagents for collagen II and MMP-13 to identify cartilage degradation and VEGF, BMP-2, and osteocalcin (Santa Cruz Biotechnology Inc, Santa Cruz, CA) to identify subchondral bone remodeling including angiogenesis and osteogenesis. The immunoreactivity in specimens was demonstrated using a horseradish peroxidase-3′-, 3′-diaminobenzidine cell and tissue staining kit (R & D Systems, Inc, Minneapolis, MN). The immunoactivities were quantified from five areas in three sections of the same specimen using a Zeiss Axioskop 2 Plus microscope (Carl Zeiss, Gottingen, Germany). All the images of each specimen were captured using a Cool CCD camera (SNAP-Pro c.f. Digital kit; Media Cybernetics, Silver Spring, MD). Images were analyzed using Image-Pro Plus image-analysis software (Media Cybernetics, Silver Spring, MD). The percentage of immunolabeled positive cells over the total cells in each area was counted and the average of each specimen was used as the result.

2.6. *Statistical analysis*

The data of this study were expressed as mean ± SD. Group I data were used as the baseline for statistical comparison with other groups. The *P* values were obtained using ANOVA and *post hoc* test with Bonferroni correction among five groups, and Mann-Whitney *U* test between two groups. Statistical significance was set at $P < 0.05$.

3. Results

3.1. *Radiographic examination*

Radiographic changes of the knee on x-rays were shown in Figure 1. Radiographs of the knee taken at 12 wk showed gross OA changes in Group II, whereas only very subtle changes were noted in Groups I, III, IV, and V (Fig. 1, top row). Radiographs of the knee taken at 24 wk showed more advanced OA changes of the knee in Group II, whereas much less degenerative changes were noticed in Groups I, III, IV, and V (Fig. 1, bottom row).

3.2. *BMD results*

The BMD values were shown graphically in Figure 2. At 12 wk, the BMD values of distal femur and proximal tibia were significantly decreased in Group II as compared to Group I. This indicates that BMD decreased in the early stage of OA changes of the knee. The BMD values of Groups III, IV, and V were comparable as compared to Group I. It appears that ESWT reverses the BMD decrease after ACLT-induced OA changes. The BMD values showed no significant difference between Group III and Group IV, and no additive effects were noted in Group V.

At 24 wk, the BMD values of Group II were significantly decreased as compared to Group I, suggesting further decrease of BMD in progressive OA changes of the knee after ACLT. The BMD values of Groups III, IV, and V were comparable as compared to Group I. The BMD values showed no significant difference between Groups III and IV, and no additive effect was noted in Group V.

3.3. *Articular cartilage degradation*

The cartilage degradation biomarkers, including Mankin score, Safranin O stain, MMP-13, and collagen II, were shown graphically in Figure 3. At 12 wk, significant increases of Mankin score, Safranin O stain, and MMP-13 and decrease of collagen II were noted in Group II as compared to Group I. The changes of Mankin score, Safranin O stain, MMP-13, and collagen II in Groups III, IV, and V were comparable as compared to Group I. The changes were not significant between Group III and Group IV, and no additive effects were noted in Group V. The changes in cartilage degradation biomarkers suggested that ESWT shows chondroprotective effects in the initiation of ACLT-induced OA changes of the knee. The effects of ESWT were consistent when ESWT was delivered to the distal femur or the proximal tibia, but no additive effects were observed when both areas were treated simultaneously. At 24 wk, significant increases of Mankin score, Safranin O stain, and MMP-13 and decrease of collagen II were noted in Group II as compared to Group I. The changes of Mankin score, Safranin O stain, MMP-13, and collagen II in Groups III, IV, and V were comparable as compared to Group I. The changes between Group III and Group IV were not significant, and no additive effects were noted in Group V. The changes suggested that ESWT ameliorates the ACLT-induced OA changes of the knee. The effects of ESWT on the regression of established OA changes of the knee appeared consistent when ESWT was applied to the distal femur or the proximal tibia, with no additive effects when both areas were simultaneously treated.

3.4. *Subchondral bone remodeling*

The subchondral bone remodeling biomarkers, including VEGF, BMP-2, and osteocalcin, are shown graphically in Figure 4. At 12 wk, significant decreases of VEGF, BMP-2, and osteocalcin were noted in Group II as compared to Group I.

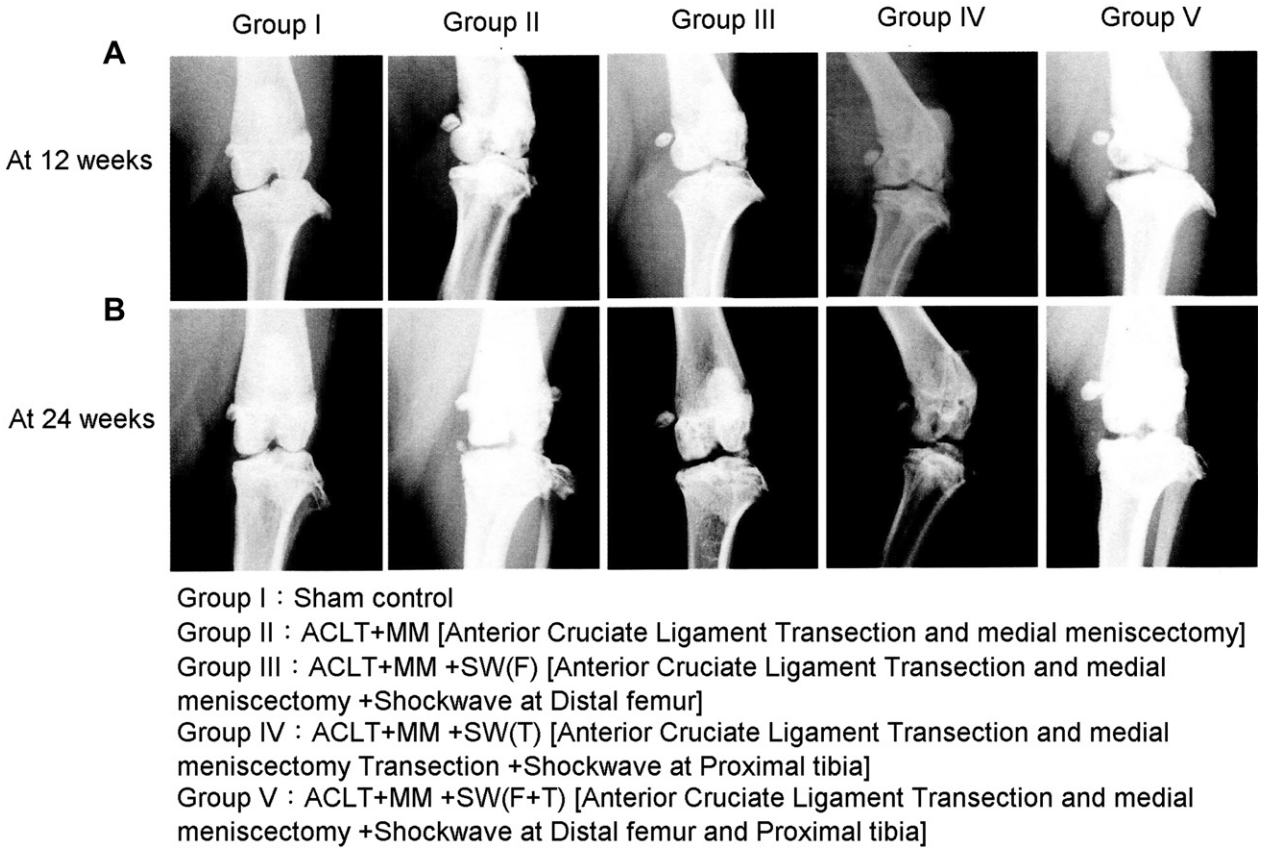


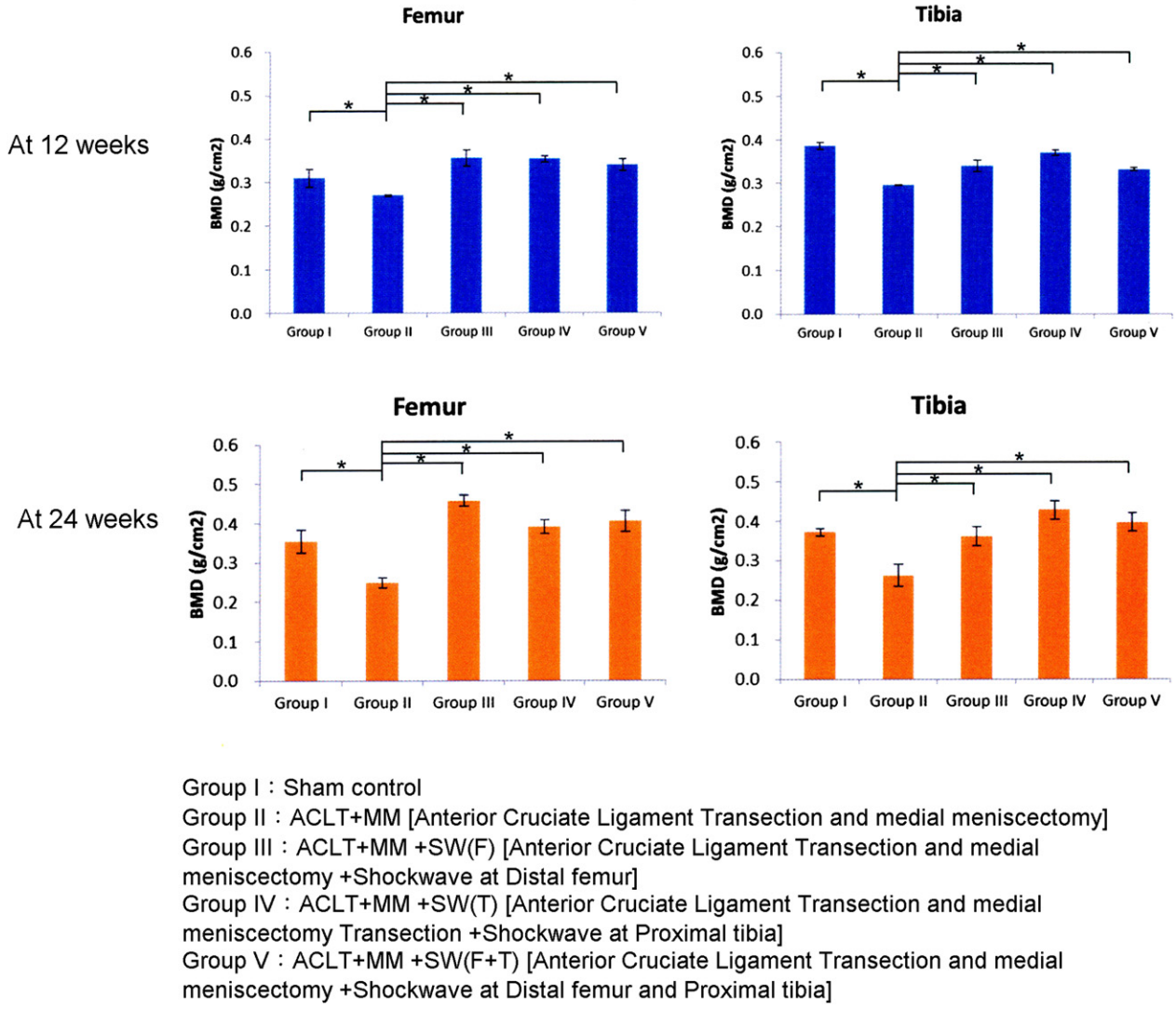
Fig. 1 – Radiographs of the knee taken at 12 wk (top row of images) showed gross osteoarthritis in Group II, but very subtle changes in Groups I, III, IV, and V. Radiographs of the knee taken at 24 wk (bottom row of images) showed progressive osteoarthritic changes of the knee in Group II, whereas the osteoarthritic changes were much less in Groups I, III, IV, and V.

The VEGF, BMP-2, and osteocalcin values of Groups III, IV, and V were comparable as compared to Group I. The data showed no difference between Group III and Group IV, with no additive effects noted in Group V. It appears that ESWT showed improvement in subchondral bone remodeling, including angiogenesis and osteogenesis, in ACLT-induced OA changes of the knee. The effects of ESWT were consistent when application was at distal femur or proximal tibia, but no additive effects were observed when both areas were treated at the same time. At 24 wk, Group II showed significant increases in VEGF, BMP-2, and osteocalcin as compared to Group I. The changes of VEGF, BMP-2, and osteocalcin were comparable among Groups III, IV, and V. The data showed no difference between Group III and Group IV, and no additive effects were noted in Group V. The data suggested that ESWT effectively ameliorates the established ACLT-induced OA changes of the knee. The effects of ESWT were consistent when ESWT was applied to the distal femur or the proximal tibia, but no additive effects were observed when both areas were treated simultaneously.

4. Discussion

The principal findings of the current study showed that ESWT is effective in the prevention and regression of osteoarthritis of the knee in rats. The effects of ESWT in OA of the knee are consistent when ESWT is applied to either the distal femur or the proximal tibia. However, no additive effects were observed when both areas were simultaneously treated. Some authors proposed the potential role of subchondral bone in the initiation and progression of OA changes [5,6,9]. Emerging evidence indicates that bone turnover increases in patients with early OA and increased bone volume and sclerosis in the late stage of OA changes in a dog model [9,10]. Therefore, the functional integrity of the articular cartilage depends on the mechanical properties of the subchondral bone. It appears that subchondral bone remodeling may precede the cartilage degradation in the initiation of OA changes of the knee. Application of ESWT to the subchondral bone results in improvement in cartilage degradation and subchondral bone remodeling that, in turn, prevents or retards the OA changes of the knee.

In this study, the effects of ESWT showed a similar trend when ESWT was applied to either distal femur or proximal tibia only. This may be explained by the close proximity between the distal femoral condyle and proximal tibia condyle in small animals. It appears that the effects of ESWT are site-specific in OA of the knee in rats. When ESWT was applied to both distal femur and proximal tibia, no additive effects were observed. This may be caused by overdose when both areas were treated at the same time. In clinical practice, application of ESWT may be performed at either the distal femoral or the proximal tibia, but not both areas at the same



Group I : Sham control
Group II : ACLT+MM [Anterior Cruciate Ligament Transection and medial meniscectomy]
Group III : ACLT+MM +SW(F) [Anterior Cruciate Ligament Transection and medial meniscectomy +Shockwave at Distal femur]
Group IV : ACLT+MM +SW(T) [Anterior Cruciate Ligament Transection and medial meniscectomy Transection +Shockwave at Proximal tibia]
Group V : ACLT+MM +SW(F+T) [Anterior Cruciate Ligament Transection and medial meniscectomy +Shockwave at Distal femur and Proximal tibia]

Fig. 2 – Bone mineral density around the knee showed significant decreases of BMD in Group II at 12 and 24 wk. BMD values of Groups III, IV, and V were comparable to Group I. The BMD values showed no difference between Group III and Group IV when compared to Group V.

time. The results of the current study may introduce a new concept in the management of early OA of the knee by shifting the primary focus from the articular cartilage to the subchondral bone. Furthermore, physical shockwave may play a role in the treatment of early OA of the knee.

The exact mechanism of ESWT remains unknown. Prior studies showed that ESWT enhances and induces the ingrowth of neovascularization associated with upregulation of angiogenetic growth factors at the tendon–bone interface [20,21]. Another study showed that ESWT enhances bone mass and bone strength after fracture of the femur in rabbits [22]. Overall, application of ESWT results in tissue repair and regeneration [21]. The results of the current study showed that ESWT ameliorates cartilage degradation and improves subchondral bone remodeling in osteoarthritis of the knee in rats. Additional studies are needed to verify the efficacy of ESWT in osteoarthritic knees in larger animals or human subjects.

4.1. *Limitations of the study*

There are weaknesses and limitations in this study. The radiographs of the knee in small animals are difficult to quantify in terms of the severity of osteoarthritic changes. The results of the current study were obtained from small animals that may differ from large animals or human subjects. In this study, ESWT was applied to the medial distal femur and/or the medial proximal tibia. The effects of ESWT on lateral femoral condyle and/or lateral tibia condyle are unknown. Additional studies are needed to compare the effects of ESWT in medial and lateral aspects of the knee. The effects of ESWT in distal femur and proximal tibia showed similar results when ESWT was applied only to either the distal femur or the proximal tibia. This was speculated because of the proximity between distal femur and proximal tibia in small animals. However, the actual reasons are

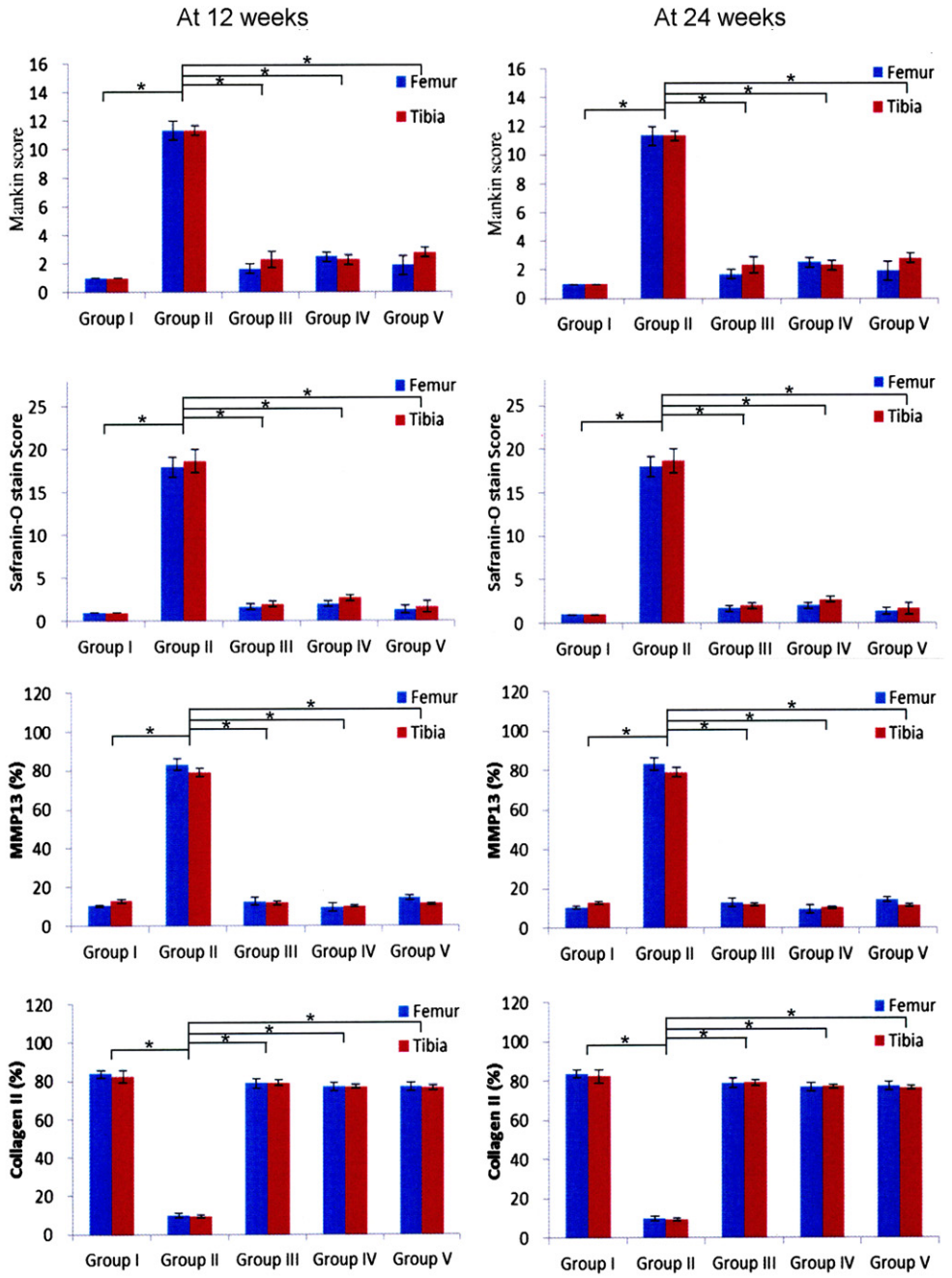


Fig. 3 – The cartilage degradation indices (Mankin score, Safranin O stain, MMP-13, and collagen II) showed significant increases of Mankin score, Safranin O stain, and MMP-13 and decrease of collagen II in Group II as compared to Group I. The changes of Mankin score, Safranin O stain, MMP-13, and collagen II in Groups III, IV, and V were comparable as compared to Group I. The changes were not significant between Group III and Group IV, and no additive effects were noted in Group V.

unknown. Simultaneous application of ESWT to distal femur and proximal tibia yielded no additive effects. The explanation of overdose of ESWT is speculative until proven otherwise. Nevertheless, future plans for additional studies with a more comprehensive approach, including clinical trials, are strongly recommended.

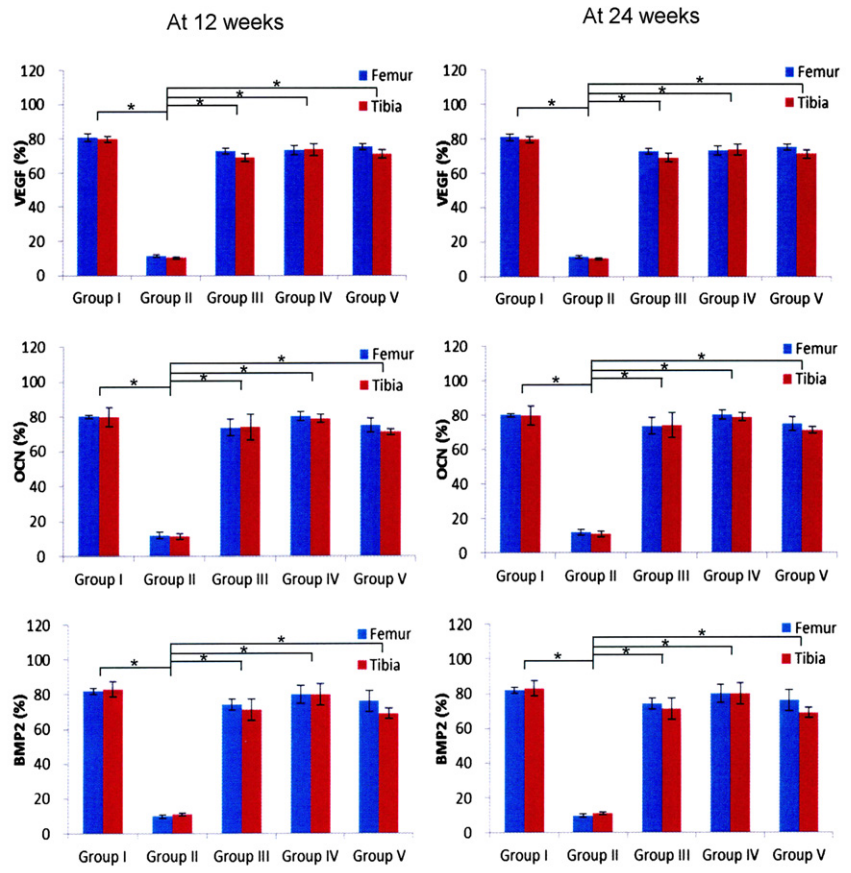


Fig. 4 – The subchondral bone remodeling indices (VEGF, BMP-2, and osteocalcin) at 12 and 24 wk showed significant decreases of VEGF, BMP-2, and osteocalcin in Group II as compared to Group I. The VEGF, BMP-2, and osteocalcin values of Groups III, IV, and V were comparable as compared to Group I. The data showed no difference between Group III and Group IV, without additive effects noted in Group V.

5. Conclusion

ESWT is effective in the prevention and regression of ACLT-induced OA of the knee in rats. The effects of ESWT in OA of the knee appear to be site-specific, with similar results when ESWT was applied to either the medial femur condyle or the medial tibia condyle. However, no additive effects were observed when both areas were simultaneously treated.

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REFERENCES

[1] Lane NE, Nevitt MC. Osteoarthritis, bone mass, and fractures: how are they related? Arthritis Rheum 2002;46:1.
[2] Oettmeier R, Abendroth K. Osteoarthritis and bone: osteologic types of osteoarthritis of the hip. Skeletal Radiol 1989;18:165.
[3] Ratcliffe A, Seibel MJ. Biochemical markers of osteoarthritis. Curr Opin Rheumatol 1990;277:21352.
[4] Hayami T, Funaki H, Yaoeda K, et al. Expression of the cartilage-derived anti-angiogenic factor chondromudulin-I decreases in the early stage of experimental osteoarthritis. J Rheumatol 2003;30:2207.

[5] Burr DM, Schaffler MB. The involvement of subchondral mineralized tissues in osteoarthrosis: quantitative microscopic evidence. Micros Res Tech 1997;37:343.
[6] Radin EL, Rose RM. Role of subchondral bone in the initiation and progression of cartilage damage. Clint Orthop 1986; 213:34.
[7] Hayami T, Pickarski M, Zhuo Y, Wesolowski GA, Rodan GA, Duong le T. Characterization of articular cartilage and subchondral bone changes in the rat anterior cruciate ligament transaction and meniscectomized models of osteoarthritis. Bone 2006;38:234.
[8] Burr DB. The importance of subchondral bone in osteoarthrosis. Curr Opin Rheumatol 1998;10:256.
[9] Dieppe P. Subchondral bone should be the main target for the treatment of pain and disease progression in osteoarthritis. Osteoarthritis Cartilage 1999;7:325.
[10] Dedrick DK, Goulet R, Huston L, Goldstein SA, Bole GG. Early bone changes in experimental osteoarthritis using microscopic computed tomography. J Rheumatol Suppl 1991; 27:44.
[11] Harada SI, Rodan GA. Control of osteoblast function and regulation of bone mass. Nature 2003;423:35.
[12] Frisbie DD, Kawcak CE, Mcllwraith CW. Evaluation of the effect of extracorporeal shock wave treatment on experimentally induced osteoarthritis in middle carpal joints of horses. Am J Veterinary Res 2009;70:449.
[13] Ochiai N, Ohtori S, Sasho T, et al. Extracorporeal shock wave therapy improves motor dysfunction and pain originating from knee osteoarthritis in rats. Arthritis Cartilage 2007; 15:1093.
[14] Mueller M, Bockstahler B, Skalicky M, Mlacnik E, Lorinson D. Effects of radial shockwave therapy on the limb function of dogs with hip osteoarthritis. Veterinary Record 2007;160:762.
[15] Dahlberg J, Fitch G, Evans RB, McClure SR, Conzemius M. The evaluation of extracorporeal shockwave therapy in naturally occurring osteoarthritis of the stifle joint in dogs. Vet Comp Orthop Traumatol 2005;18:147.
[16] Revenaugh MS. Extracorporeal shock wave therapy for treatment of osteoarthritis in the horse: clinical application. Vet Clin North Am Equine Pract 2005;21:609.
[17] Wang CJ, Weng LH, Ko JY, Sun YC, Yang YJ, Wang FS. Extracorporeal shockwave therapy shows chondroprotective effects in osteoarthritic rat knee. Arch Orthop Trauma Surg 2011;131:1153.
[18] Wang CJ, Ko JY, Weng LH, et al. Extracorporeal shockwave shows regression of osteoarthritis of the knee in rats. J Orthop Res 2011;171:601.
[19] Mankin HJ, Dorfman H, Lippiello L, Zarins A. Biochemical and metabolic abnormalities in articular cartilage from osteo-arthritic human hips: II. Correlation of morphology with biochemical and metabolic data. J Bone Joint Surg 1971;53 A:523.
[20] Wang CJ, Hung HY, Pai CH. Shock wave enhanced neovascularization at the tendon-bone junction. An experiment in dogs. J Foot Ankle Surg 2002;41:16.
[21] Wang CJ, Wang FS, Yang KD, Huang CS, Hsu CC. Shock wave therapy induces neovascularization at the tendon-bone junction. A study in rabbits. J Orthop Res 2003;21:984.
[22] Wang CJ, Yang KD, Wang FS, Chen HS, Chen HH, Hsu CC. Shock wave therapy enhances bone mass and bone strength after fracture of the femur. A study in rabbits. Bone 2004;34:225.