Combined magnetic fields accelerate bone-tendon junction injury healing through osteogenesis

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The objective of this study was to explore the effect of combined magnetic fields (CMFs) on osteogenesis and the remodeling of newly formed bone at bone-tendon (BT) junction. Forty-eight mature rabbits in whom partial patellectomy was performed were used to establish a BT junction injury model at the patella-patellar tendon (PPT) complex and were then allocated to CMF treatment group (CMF group) or placebo treatment group (control group). Daily CMF therapy was delivered continuously from post-operative day 3 to weeks 4, 8, and 16. At each time point, the animals were sacrificed, and the PPT complexes were harvested for radiographic, histological, peripheral quantitative computed tomography, and micro-computed tomography (micro-CT) evaluation. The area, length, and bone mineral density of the newly formed bone in the CMF group were significantly greater than the control group at post-operative weeks 8 and 16. The micro-CT results showed that the newly formed bone in the CMF group contained more and thicker trabeculae than the control group at weeks 8 and 16. Histologically, the CMF group showed better remodeling of the BT junction. In conclusion, CMF treatment was able to accelerate osteogenesis during BT junction repair, thus facilitating the healing of BT junction injury.

An injury at the bone-tendon (BT) junction is common in orthopedics and sports medicine, and it often involves different ligaments, such as the anterior cruciate ligament, patellar tendon, rotator cuff insertion, plantaris muscle-tendon, and Achilles tendon (Wong & Leung, 2009; Cheung et al., 2010; Witt & Hyer, 2012). However, because the BT junction is a transitional region composed of a complex mixture of hard, bony, and soft connective tissues, its repair is more difficult than tendon-to-tendon or bone-to-bone healing (Lu et al., 2008; Wang et al., 2010). It is commonly believed that perfect restoration of the specific morphological construct and physiological function after a severe injury to the BT junction would be almost impossible (Hope & Saxby, 2007).

Recently, in addition to the improvements in surgical repair techniques and post-operative rehabilitation, two adjunct favorable treatments, including biological factors or biological materials and biophysical stimulations, may promote connective tissue healing. Allogenic chondrocytes, platelet-derived growth factor, bone marrow matrix cells with bone morphogenetic protein, and platelet-rich plasma have been reported to facilitate BT junction healing (Wang et al., 2002; Ouyang et al., 2003; Wong et al., 2004; Hannemann et al., 2012). However, the clinical application of biological augmentation factors is limited owing to difficulties involved in drug production and delivery technology, high treatment costs, unknown and potential short- and long-term side effects, and related ethical issues. Alternatively, biophysical stimulation modalities, such as low-intensity pulsed ultrasound stimulation and electromagnetic fields, have been studied in clinical trials and have been applied to patients with appropriate indications to enhance fracture healing, rehabilitation, and soft tissue repair (Lu et al., 2006, 2008; Bachl et al., 2008).

As a noninvasive treatment, electromagnetic fields were proved to promote the healing process of delayed unions and nonunions, and the U.S. Food and Drug Administration approved its clinical use in 1979. Many previous investigations also confirmed that magnetic fields facilitated the repair of the musculoskeletal system, especially during osteogenesis and bone formation (Lu et al., 2006; Bachl et al., 2008). The combined magnetic field (CMF), a unique electromagnetic field that includes...
a dynamic sinusoidal magnetic field and a magnetostatic field, has been used to promote bone healing and spinal fusion clinically by simulating the endogenous production of bone growth factors (Fitzsimmons et al., 1994; Hanft et al., 1998; Linovitz et al., 2002). Osteogenesis at the healing interface is known to be beneficial to the healing quality of the BT junction (Saltzman et al., 1990; Wang et al., 2006). Thus, we hypothesized that CMF stimulation can promote BT junction repair by accelerating osteogenesis.

Our study was based on an established partial patellectomy model in rabbits (Qin et al., 1999), and our aim was to evaluate CMF’s effects on osteogenesis by evaluating quantitative radiographic imaging, multilayer peripheral quantitative computed tomography (pQCT), micro-computed tomography (micro-CT), and histology.

Materials and methods

The study was approved by the local Animal Research Ethics Committee (No. 20070218).

Surgery procedure and experimental design

Forty-eight mature female New Zealand white rabbits with a body weight of 3.4 ± 0.3 kg were housed in cages, fed commercially available rabbit food, and given water. Partial patellectomy was performed at the left hind legs of these animals according to previously established experimental protocols (Qin et al., 1999; Qiu et al., 2012), while the right hind legs were preserved. Each rabbit was anesthetized intravenously with 30 mg/kg of 3% pentobarbital (Shanghai New Asia Pharmaceutical Co., Ltd., Shanghai, China), and the left patella-patellar tendon (PPT) complex was exposed through an anterolateral skin incision under aseptic condition. A transverse osteotomy was performed between the proximal two thirds and the distal one third of the patella, and the distal one third of the patella was excised at the tip. The patellar tendon was then sutured to the proximal two thirds of the patella through two drilled holes with a polydioxanone suture. A figure-of-eight tension band wire (wire diameter = 1 mm) was used around the superior pole of the patella and the proximal tibia to preserve the surgical reconstruction. After suturing the skin, lateral radiographs of the knee on the operated side were taken to examine the quality of the surgery and wire fixation. The knee was immobilized in a long leg cast at 120° knee flexion, which was the approximate resting position for rabbits’ hind limbs. Immobilization was performed for week, and then the cast was removed to allow cage activity. The rabbits that had undergone surgery were injected with an analgesic (intramuscularly 1 mg/kg of Tramadol; Grünenthal-GmbH, Aachen, Germany) and an antibiotic (penicillin sodium; North China Pharmaceutical Co., Shijiazhuang, China) for 3 days post-operatively.

After partial patellectomy, the rabbits were randomized to either the CMF treatment group (CMF group, n = 24) or the placebo treatment group (control group, n = 24). The post-operative stimulation and placebo treatments of both groups were performed in custom-made cages (Fig. 1) covered by the CMF therapy coils (DJO LLC, Vista, California, USA), which were preprogrammed for the therapeutic and placebo (without the magnetic field) instruments that appeared identical to meet the blinded requirement of the study. All experimental personnel, including the principal investigator, were blinded to the randomization. The parameters of the CMF were as follows: dynamic sinusoidal magnetic field strength: 400 mG; frequency: 76.6 Hz; amphi-magnetic field strength: ± 200 mG; magnetostatic field: ± 600 mG. The treatments were started on post-operative day 3 for 30 min/day and continued through post-operative weeks 4, 8, and 16, when the rabbits were sacrificed for evaluation (8 animals/group/time point).

Tissue sample preparation

The animals were killed with intravenously using an overdose of sodium pentobarbital at each time point. After removing the fixation wiring, the PPT complex of the operated knees in both groups was harvested for comparative analysis of the newly formed bone size, bone mineral density (BMD), and the fine structure of the newly formed bone at the BT junction healing interface.

Radiographic measurement

High-resolution radiographs of the anteroposterior (AP) and lateral views of each specimen were taken using a microradiography machine (cabinet x-ray system, model 43855C; Faxitron X-ray Corporation, Lincolnshire, Illinois, USA) with exposure time at 3 s, tube voltage at 40 kVp, and current flow at 0.3 mA, and the x-ray source-object distance was set at 40 cm. After importing the AP and lateral radiographs into an image analysis system (Image-Pro Plus 5.0.2; Media Cybernetics Inc., Rockville, Maryland, USA), the area and length of the newly formed bone was measured using Qin and Mak’s measurement protocol (Qin et al., 1999).

BMD measurements

We measured the volumetric BMD of the newly formed bone using a multilayer high-resolution pQCT scanner (Scanco Medical AG, Bassersdorf, Switzerland) with a spatial resolution of 0.3 mm and a CT slice thickness of 1 mm.

Three-dimensional morphologic reconstruction and calculation

A micro-CT scanner (viva40; Scanco Medical AG) was used to scan the PPT complex and reconstruct its three-dimensional structure with a scanning resolution of 28 μm. Then the patella’s overall shaping status was observed, and the microstructure data of...
the newly formed bone, which included the trabecular number (Tb.N) and the trabecular thickness (Tb.Th), were calculated.

Descriptive histology
After micro-CT scanning, the specimens were prepared for decalcified histological assessment stained with hematoxylin and eosin (H&E) (Qiu et al., 2012). First, specimens were fixed in 10% neutral buffered formalin for 48–72 h and then placed in 90% formic acid decalcification for 3 days, which was followed by dehydration, dipping wax, and paraffin-embedding techniques sequentially. Second, the histological sections from the midsagittal plane of each specimen were cut at 7 μm thickness using a rotary microtome (RM2165; Leica Microsystems, Nussloch, Germany). Third, the specimens were stained with H&E for observation under transmitted light microscopy (Olympus CX31; Olympus Inc., Tokyo, Japan).

Statistical methods
Data were given as means and standard deviations, and all statistical analyses were performed using SPSS software program, version 13.0 (SPSS Inc, Chicago, Illinois, USA). Except for the histological data, the radiographic data, pQCT, and micro-CT results were analyzed using independent samples t-test to measure the effect of the CMF intervention on BT junction healing. The significant level was set at P < 0.05.

Results
Radiographs measurement
Regardless of the group of the specimens, postoperatively, bone outgrowth from the patellar osteotomy site and morphologic reshaping enlarged as time passed in our study. The area and length of the newly formed bone increased gradually from week 4 to weeks 8 and 16. Compared with the control group, the newly formed bone was more significant in the CMF group at week 8 (area: 5.20 ± 1.62 mm² vs 2.52 ± 0.73 mm², respectively; P < 0.05; length: 1.43 ± 0.29 mm vs 1.10 ± 0.27 mm, respectively; P < 0.05) and at week 16 (2.47 ± 0.42 mm vs 1.74 ± 0.37 mm, respectively; P < 0.05). However, there was no significant difference at week 4 (area: 2.85 ± 0.90 mm² vs 1.72 ± 0.69 mm², respectively; P < 0.05; length: 0.88 ± 0.32 mm vs 0.67 ± 0.25 mm, respectively; P > 0.05) (Figs. 2 and 3).

Measurement of the pQCT
The CMF accelerated mineralization of the newly formed bone at the healing interface of the BT junction. The BMD of newly formed bone obtained by the pQCT was higher in the CMF group than in the control group at week 8 (0.56 ± 0.07 g/cm³ vs 0.46 ± 0.04 g/cm³, respectively; P < 0.05) and at week 16 (0.64 ± 0.03 g/cm³ vs 0.58 ± 0.02 g/cm³, respectively; P < 0.05). However, there was no significant difference at week 4 between the two groups (0.49 ± 0.08 g/cm³ vs 0.41 ± 0.07 g/cm³, respectively; P > 0.05) (Fig. 4).

Three-dimensional microarchitectural analysis
Using the scanning data from the micro-CT, we obtained the three-dimensional structure and microstructure of the newly formed bone at the BT junction as a region of interesting area (Fig. 5a). From the three-dimensional images, we found the new bone formation at the reconstructed patella increased and reshaped slowly in both groups. The CMF group showed more lamellar bones than the control group, which consisted of primarily woven bones. The microstructure data analysis also showed that bone formation and reconstruction in the CMF group was superior to the control group. At week 4, there was no significant difference in Tb.N between the control and CMF groups (0.49 ± 0.18 1/mm² vs 0.57 ± 0.16 1/mm², respectively; P > 0.05), but the difference became significant at week 8 (0.94 ± 0.28 1/mm² vs 1.34 ± 0.41 1/mm², respectively; P < 0.05) and at week 16 (2.13 ± 0.66 1/mm² vs 3.58 ± 0.89 1/mm², respectively; P < 0.01) (Fig. 5b). Compared with the control group, the Tb.Th of the newly formed bone in the CMF group was significantly thicker at week 16 (0.24 ± 0.05 mm vs 0.15 ± 0.06 mm, respectively; P < 0.05), while there was no difference at week 4 (0.07 ± 0.02 mm

Fig. 2. Measurement of the newly formed bone. (a) The anteroposterior digital radiographs of the patella. The encircled area represents the newly formed bone. (b) The lateral digital radiographs of the patella. The two short lines represent the distal end of the patella after osteotomy and the front of the newly formed bone. The distance between the two lines was calculated by the software marks of the newly formed bone length.
vs 0.07 ± 0.03 mm, respectively; \( P > 0.05 \) and at week 8 (0.11 ± 0.04 mm vs 0.09 ± 0.04 mm, respectively; \( P > 0.05 \)). In both groups, the Tb.N and Tb.Th gradually increased from week 4 to week 8, and from week 8 to week 16 (Fig. 5c).

Descriptive histology

Based on the H&E-stained decalcified sections, observation under bright light microscopy showed that the new bone and cartilage gradually formed and were structurally connected to the tendon and patella at the junction gap as the healing time progressed. At week 4, the BT interface was connected by disorganized fibrous tissue, and no apparent new bone was found in either group. It was not until week 8 that new bone formation could be found in both groups, and the marrow cavity started to form, which was more significant in the CMF group. At post-operative week 16, obvious fibrocartilage and new bone formation were identified around the reconstructed end of the patella in both groups. However, the CMF group specimens revealed more advanced remodeling from woven bone to lamellar bone with well-aligned collagen fibers. The BT interface healing quality significantly improved in the CMF group compared with that in the control group, which was primarily trabecular bone morphologically (Fig. 6).

Discussion

Electromagnetic field therapy has long been used to stimulate osteogenesis, bone fracture repair, and the maturation process, which involves the treatment of osteoporosis, bone necrosis, osteotomy, delayed union or nonunion, and bone transplanted and post-traumatic pseudarthrosis (Qin et al., 1999; Hibino et al., 2007; Barnaba et al., 2012). Bone formation is the primary step in the BT junction healing process (Ouyang et al., 2003; Huangfu & Zhao, 2007). Carcin et al. reported that the restoration of the BT junction’s mechanical strength was closely related with bone formation at the healing interface, and in some cases, the size and quality of new bone formation represented the degree of healing at the BT
Fig. 5. Three-dimensional morphology of the newly formed bone and the proximal patella reconstructed using micro-computed tomography. (a) The appearance of the reconstructed patella. The dotted straight line represents the surface of the osteotomy, and the arrow indicates the site of the newly formed bone. (b,c) The trabecular number (Tb.N) and the trabecular thickness (Tb.Th) histogram of the newly formed bone compared between the combined magnetic field (CMF) group and the control group (*P < 0.05, the difference between the CMF group and the control group at different time points; #P < 0.05, the difference among different time points for the CMF group and the control group; n = 8 for each group/time point).

Fig. 6. Sagittal hematoxylin and eosin-stained sections of the patella-patellar tendon after partial patellectomy. Both groups showed new bone formation at the proximal patella after partial patellectomy. The dotted straight line represents the surface of osteotomy (NB, newly formed bone; RP, residual patella; TF, tendon fiber; the arrowhead, directed at the regenerated fibrocartilage). The CMF group showed more trabecular bone, more marrow cavities, and more advanced remodeling from woven bone to trabecular lamellar bone than the control group. The scanned bar = 1000 μm for all.
Magnetic fields accelerate osteogenesis

In the present study, we demonstrated that CMF promotes BT junction healing by enhancing the ossification after partial patellectomy in rabbit models.

The rabbit PPT complex in our study served as a good model to investigate BT junction injury repair and remodeling process (Qin et al., 1999; Lu et al., 2006). The partial patellectomy often leads to an increase of the contact pressure at the patellofemoral joint, and the formation from the residual patella decreased the pressure (Marder et al., 1993). In this study, we observed that the CMF stimuli could accelerate the outgrowth of new bone. Thus, the increased contact stress of the patellofemoral joint may be reversed. The augment of bone formation was closely related to the restoration of the patella integrity, which played a great role in knee function (Sutton et al., 1976). The volume of the newly formed bone at the healing junction has been associated with better healing quality of the PPT complex healing (Qin et al., 1999). It seems that the new bone formation is conducive for the recovery of biological properties of the BT junction and the knee joint function in general. In the present study, the newly formed bone in the CMF group had a larger area, greater volume, and more trabeculae; therefore, we believe that the CMF treatment can enhance osteogenesis and subsequently play a positive role in the healing process of BT junction injuries.

Furthermore, we found that the newly formed bone during early time points was mostly woven bone with relatively uniform density in radiographic images. The newly formed bone was gradually shaped and remodeled into trabecular and lamellar bones, with the initiation of marrow cavity formation. Radiographs of both groups showed that the density of the newly formed bone was uneven where there was cortical bone mixed with cancellous bone at week 16. In the CMF group, bone regeneration and remodeling was faster than in the control group. There were more narrow cavities after 8 weeks of CMF treatment which may be why the rate of BMD was slower in the CMF group than in the control group. We postulated that during the first 8 weeks in the CMF group, the repair process of the BT junction would involve osteoid accumulation. After 8 weeks of CMF treatment, the repair process would enter into a period of reshaping and remodeling, where the woven bone would transform into trabecular lamellar bone and the newly formed bone would become more mature. Of course, the woven bone continued to augment in this period and was accompanied by reshaping and remodeling. However, because of the lower bone regeneration rate without CMF stimulation, the control group was still in the period of osteoid accumulation at week 8. This provided the evidence for the degree of bone formation at the organ level (i.e., the BMD that was calculated included the bulk bone volume during the bone mineralization phase, osteon canals, marrow spaces, and canalicular and lacunae walls) (Rauch & Schoenau, 2001). This finding conveyed that CMF appeared to facilitate the maturation of the newly formed bone.

In addition, as one type of electromagnetic field, the CMF greatly improved the patient compliance by decreasing the daily treatment time, which was only 30 min. Pulsed electromagnetic fields (PEMFs) have been widely used in the clinical setting, but it requires a treatment time of at least 4 h/day (Shi et al., 2013). Patients who had been treated with PEMF for less than 4 h daily showed no significant effect. The dropout rate of CMF in clinical trials was 17%, which was lower than that of PEMF (20%) (Mooney, 1990; Linovitz et al., 2002).

This study clearly demonstrates that CMF stimuli have an apparent positive effect on osteogenesis, thus promoting the repair of the BT junction. However, the molecular and cellular mechanisms involved remain unclear. As known, a changing biomechanical stimulus can modulate bone formation and remodeling (Kameo & Adachi, 2013; Schulte et al., 2013). Previous studies have proven electromagnetic therapy’s biological effects, which were based on inflammatory factors such as the down-regulation of interleukin-1, transforming growth factor (TGF)-α, and the up-regulation of gene expression in members of the TGF-β superfamily, which all played important roles in the restoration of BT injuries (Aaron et al., 2002, 2004; Benazzo et al., 2008). In vitro experiments on human mesenchymal stem cells, the electromagnetic therapy modulated the expressions of early osteogenic genes, including Runx2/Cbfa1 and alkaline phosphatase (Tsai et al., 2009). CMF also increased the insulin-like growth factor II production from bone cells promoting cell proliferation (Fitzsimmons et al., 1995) by up-regulating the calcium density and facilitating the intake of intracellular calcium (Fitzsimmons et al., 1994).

In this study, there are still some limitations. There are no biomechanical data to measure the healing quality of the BT junction, and we are planning to explore it in the future. Even BMD of the newly formed bone in the CMF group at week 16 was still lower than the proximal remaining patella. We believe the repair of BT junction was a lengthy process, and a longer treatment period may improve the BMD. We explored the bone formation from two-dimensional and three-dimensional angles, but osteogenesis is a necessary but not sufficient condition for the repair of BT junction injuries; there are still other necessary elements, such as cartilage, ligament, and extracellular matrix content. Lastly, the size of our samples was not large enough to avoid errors. More studies with larger sample sizes and longer follow-ups are required in the future.

In conclusion, CMF promoted osteogenesis at the BT junction interface in a partial patellectomy rabbit model, and it ultimately improved the healing quality of bone to tendon repair.
Perspective

The CMF has been used in clinical setting to improve the healing of nonunions and spinal fusions (Longo, 1997; Linovitz et al., 2002), but it is unknown whether it is appropriate for treating BT injuries. Our study offered a scientific basis for the clinical application of CMF treatment in BT injuries, as it may be a more effective and better tolerated therapeutic modality in the future. However, well-designed randomized controlled clinical trials are needed to establish CMF’s effectiveness and safety for the patients.

Key words: Physical therapy, joint injury, osteogenesis, bone-tendon junction.

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