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ORIGINAL ARTICLE

Treatment of experimental osteonecrosis of the hip in adult rabbits with a single local injection of recombinant human FGF-2 microspheres

Yutaka Kuroda · Haruhiko Akiyama · Keiichi Kawanabe · Yasuhiko Tabata · Takashi Nakamura

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Abstract Basic fibroblast growth factor (FGF-2) exerts anabolic actions on bone formation. Here we investigated the potential effects of recombinant human FGF-2 (rhFGF-2) on the repair process of osteonecrosis of the femoral head (ONFH) and the development of secondary osteoarthritis (OA) in adult rabbits. ONFH was induced by intramuscular injection with methylprednisolone, and vascular occlusion of the capital femoral epiphysis by electrocoagulation, in adult Japanese white rabbits. Animals were randomized into two groups: treatment and control. The treatment group was given a single local injection into the femoral head of 100 μg rhFGF-2 in 100 μl gelatin hydrogel microspheres 8 weeks after the ONFH procedure, and the control group was given phosphate-buffered saline in 100 μl gelatin hydrogel microspheres. Morphological, histopathological, and radiologic analyses, including micro-computed tomography scans and magnetic resonance imaging, showed collapse of the femoral head and progression of articular cartilage degeneration in the control group at 16 weeks after the single local injection of rhFGF-2. In contrast, rhFGF-2 treatment resulted in new bone formation in the femoral head and prevented the femoral head from collapsing. In addition, the changes in OA, assessed by the modified Mankin score, was significantly lower in the treatment group. Our results indicate that a single local injection of rhFGF-2 microspheres promoted the repair of the osteonecrotic femoral head and inhibited femoral head collapse and OA progression. rhFGF-2 may be a promising strategy for the treatment of ONFH.

Keywords FGF-2 · Single local injection · Osteonecrosis · Osteoarthritis · Femoral head

Y. Kuroda (✉) · H. Akiyama · K. Kawanabe · T. Nakamura
Department of Orthopaedic Surgery, Graduate School of Medicine, Kyoto University, Shogoin, Kawahara-cho 54, Sakyo-ku, Kyoto 606-8507, Japan
e-mail: ykuromd@kuhp.kyoto-u.ac.jp

Y. Tabata
Department of Biomaterials, Field of Tissue Engineering, Institute for Frontier, Medical Sciences, Kyoto University, Kyoto, Japan

Introduction

Osteonecrosis of the femoral head (ONFH) is caused by impairment of blood supply in the femoral head. ONFH is initially asymptomatic, and if left untreated, more than 70% of instances of ONFH lead to collapse of the femoral head with subsequent hip joint destruction [1]. Most cases advance to secondary osteoarthritis (OA), and the patient eventually requires total hip arthroplasty (THA). Therefore, early intervention before collapse would be a better strategy for treatment [2, 3]. Surgical alternatives for preservation include core decompression, osteotomy, and nonvascularized and vascularized bone grafting, but their efficacy remains controversial, and the complications are of concern. The ultimate goal is to treat ONFH at the early stage to preserve the femoral head. Several treatment options including injection of growth and differentiation factors [4, 5], autologous bone marrow cell or stem cell transplantation [6, 7], and administration of bisphosphonates or statins have been reported recently, and these have been shown to be effective in animal models or in patients [8–11].

During the repair process of ONFH, hematopoietic and multipotent progenitor cells are mobilized from the bone marrow, and these cells differentiate into several types of cells, including vascular endothelial cells, osteoclasts, and

osteoblasts, which contribute to neovascularization, resorption of necrotic bone, and subsequent new bone formation, respectively. Accelerating the repair process could delay or prevent collapse of the femoral head. Basic fibroblast growth factor (FGF-2) is a pleiotropic regulator of the proliferation, migration, and differentiation of the cells in vasculature and bone tissues, and it has anabolic effects on angiogenesis and bone formation [12–17]. We have reported that FGF-2 administered in a gelatin hydrogel provides continuous release of recombinant human FGF-2 (rhFGF-2) at a relatively low concentration for about 2 weeks [18, 19]. Because FGF-2 administered in solution in vivo is eliminated rapidly at the applied site by diffusion, proteolysis, or antibody neutralization, a controlled-release system is a promising strategy to optimize the effect of rhFGF-2 in tissue regeneration in vivo [20]. The therapeutic potential of rhFGF-2 delivered through a gelatin hydrogel has been reported for the revascularization of the myocardium and ischemic limb and bone formation of fracture repair [20–25], suggesting that rhFGF-2 in a gelatin hydrogel is a promising candidate for the treatment of ONFH.

In this study, we investigated the potential clinical application of rhFGF-2 in a gelatin hydrogel by a single local injection on the repair process of ONFH and the development of secondary OA using an adult rabbit model.

Materials and methods

Materials

The gelatin hydrogel was prepared by chemical cross-linking of acidic gelatin and was then incubated with rhFGF-2 (Kaken Pharmaceutical, Tokyo, Japan) at 4°C for 12 h, as described previously [18].

Animal ONFH model and rhFGF-2 injection

Adult male Japanese white rabbits (Kitayama Labs, Nagano, Japan) with body weight of 3.0–4.0 kg and older than 30 weeks, whose femoral head growth plates have closed, were housed in single cages and fed a standard laboratory diet and water. All experiments were reviewed by the Ethics Animal Research Committee, Graduate School of Medicine, Kyoto University, Japan.

The animal model of ONFH was developed by administration of high-dose corticosteroids (40 mg/kg methylprednisolone) and vascular occlusion of the capital femoral epiphysis by electrocoagulation of the femoral surgical neck and capsule, as described previously [26, 27]. Briefly, the animals were anesthetized using intravenous injections of pentobarbital sodium (25 mg/kg), intramuscular injection of ketamine hydrochloride (10 mg/kg), and local administration of 0.5% lidocaine solution. Under aseptic conditions, a 3-cm longitudinal skin incision was made over the left greater trochanteric area. To expose the hip joint, the tensor fascia lata muscle was split along the length of its bundles, and the gluteus medius muscle was detached partially from the anterior greater trochanter. The hip joint capsule was removed, and electrocoagulation of soft tissue attachments at the femoral surgical neck was performed circumferentially to interrupt the extraosseous blood supply to the femoral head through the medial and lateral circumflex arteries. The ligamentum teres was not ligated. After closure of the muscles and skin, all rabbits were injected once with 40 mg/kg methylprednisolone (Solu-Medrol; Pfizer, Tokyo, Japan) into the right gluteus muscle. Eight weeks after the ONFH procedure, a hole (1 mm diameter, 5 mm depth) was drilled from the basicervical region into the medial border of the femoral head using an electric bar, and gelatin hydrogel microspheres containing 100 μg rhFGF-2 (treatment group) or phosphate-buffered saline (PBS) (control group) were implanted. The rabbits were then returned to their cages, where they were permitted unrestrained mobility.

Assessment of the femoral head

The rabbits for the experimental ONFH model were killed at preoperation and at 4, 8, 12, or 24 weeks after the ONFH procedure ($n = 5$ in each group). Animals after the rhFGF-2 treatment or the control injection were killed at 24 weeks after the ONFH procedure ($n = 5$ in each group), and the proximal femora were dissected. To assess the gross appearance of the femoral head deformity, microphotographs were taken and used to measure the roundness index [28]. The size of the area of articular surface of the femoral head involved in OA change was quantified with digital photography by measuring the percentage of the surface involved as described previously [29].

Radiographic evaluation of the femoral head was graded according to modified Ficat and Arlet staging of ONFH (Table 1) [30].

Table 1 Modified Arlet and Ficat staging of osteonecrosis of the femoral head

Stage	Radiographic appearance of femoral head
1	Normal
2	Cystic and/or osteonecrotic lesions, normal contour of femoral head, no subchondral fracture
3	Crescent sign or subchondral fracture
4	Collapse and/or secondary osteoarthritis (cysts, marginal osteophytes, and destruction of the cartilage)

Micro-computed tomography (μCT) scans (SMX-100CT-SV3; Shimadzu, Kyoto, Japan) were used to evaluate the irregularity of the subchondral bone and the bone regeneration rate (BRR) at the implanted area. The coronal and horizontal plane images of the central implant area were converted into binary format data by Image J (U.S. National Institutes of Health, Bethesda, MD, USA). Thresholds for each specimen were chosen to separate bone from marrow by determining the HU value that maximized the between class variance of water and bone values in the μCT scans [31]. Irregularity was defined as the percentage of irregular articular surface in the central coronal plane, and BRR was defined as the average percentage of the bone area to the total area.

Magnetic resonance images (MRI) of the femoral heads were obtained in the coronal and sagittal planes using a 0.3 T magnetic resonance imaging system (AIRIS; Hitachi, Tokyo, Japan). Before MRIs, the rabbits were anesthetized using intravenous injections of pentobarbital sodium (25 mg/kg). The imaging parameters were as follows: T_1-weighted spin-echo MRIs [repetition time (TR)/echo time (TE) = 300/15.7 ms], T_2-weighted fast spin-echo MRIs (TR/TE = 3400/15.7 ms), 2.0 mm slice thickness, 1 mm intersection gap, and 256 × 134 imaging matrix.

For the histological examination, the femora obtained were fixed in 4% paraformaldehyde for 1 week, decalcified with Morse's solution (10% sodium citrate and 22.5% formic acid), and cut along the coronal plane for observation of the trabecular bone and articular cartilage. These specimens were embedded in paraffin, cut into 5-μm-thick sections, and stained with hematoxylin, eosin, and Safranin O. The degree of degeneration of the articular cartilage was graded using a semiquantitative modified Mankin score [32].

Statistical analysis

Data are presented as mean ± standard deviation. Student's *t* test was used to compare BRR in the control and rhFGF-2 treatment groups. The modified Mankin scores were compared between groups using the nonparametric Kruskal–Wallis test. One-way analysis of variance (ANOVA) was used to compare the control and rhFGF-2-treatment groups for the other variables. P values <0.05 were considered significant.

Results

Macroscopic and histopathological features of ONFH development after the ONFH procedure

We applied a rabbit model of experimental ONFH induced by a combination of methylprednisolone administration and vascular occlusion of the capital femoral epiphysis by electrocoagulation. The rabbits started to develop ONFH around 4 weeks after the ONFH procedure and established ONFH within 8 weeks (Table 2). The femoral heads showed progression of osteonecrosis from early to end stage that progressed with time (Fig. 1a–c). At 8 weeks after the surgery, osteonecrotic femoral heads were observed macroscopically as yellowish and flat, and many creases and fissures on the articular surface and loss of sphericity and flattening of the femoral head were detected (Fig. 1b). The loss of the spherical shape of the femoral head was detected in 4 animals at 12 weeks after the ONFH procedure, and collapse of the femoral head was detected in 2 animals. At 24 weeks after the surgery, all specimens showed secondary OA changes such as increased contour of the bone ends, bony spur formation at the periphery of the femoral head, erosion, and fibrillation (Fig. 1c). CT images of the femoral head 8 weeks after the surgery showed reduced femoral sphericity, absorption of the trabecular bone, and thinning of the subchondral bone. At 24 weeks after the surgery, collapsed femoral head and irregularity of the subchondral bone were detected (Fig. 1d–f).

Table 2 Results of an experimental osteonecrosis of the femoral head (ONFH) model

After the ONFH procedure	Preoperation ($n = 5$)	4 weeks ($n = 5$)	8 weeks ($n = 5$)	12 weeks ($n = 5$)	24 weeks ($n = 5$)
Roundness index (%)	46.5 ± 0.4	47.1 ± 1.5	51.9 ± 3.5	54.2 ± 4.2	56.9 ± 1.2
Area of articular surface involved in OA change (%)	0	1.8 ± 0.9	25.6 ± 21.0	44.2 ± 3.7	53.1 ± 10.5
Irregularity of subchondral bone (%)	0	0 ± 0	16.7 ± 12.3	20.6 ± 3.6	54.2 ± 10.7
Modified Ficat and Arlet staging of osteonecrosis of the femoral head	Stage 1 = 5	Stage 1 = 2			
		Stage 2 = 2	Stage 2 = 1	Stage 2 = 1	
		Stage 3 = 1	Stage 3 = 3	Stage 3 = 2	
			Stage 4 = 1	Stage 4 = 2	Stage 4 = 5
Modified Mankin score (0–13 points)	0	3.2 ± 1.0	6.2 ± 0.4	7.8 ± 0.4	7.8 ± 0.4

Data are expressed as average ± standard deviation (SD)

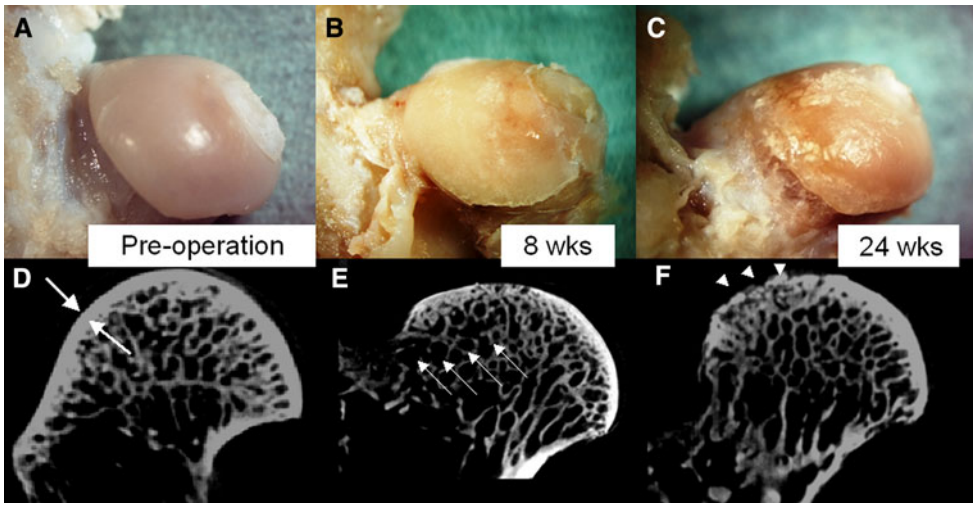

Fig. 1 Macrophotographs and representative micro-computed tomography (μCT) images of the femoral heads before the operation (**a**, **d**) at 8 weeks after the surgery (**b**, **e**). The *arrows* in **d** denote normal subchondral bone. Irregular resorption of bony trabeculae (*thin arrows*) at 8 weeks after surgery is seen in **e**. At 24 weeks after surgery, the subchondral bone has deteriorated partially (*arrowheads*) in **f**. *wks*, weeks

At 4 weeks after the surgery, macroscopic findings showed a torn surface of the femoral head in three zones (Fig. 2a, b). Histopathological studies showed three zones comprising a necrotic zone, reparative interface zone, and normal zone in the femoral head (Fig. 2c–e). In the necrotic zone, necrotic trabeculae characterized by empty lacunae of pyknotic nuclei of osteocytes with necrotic marrow fat tissues were detected (Fig. 2c). In the reparative interface zone between the necrotic zone and adjacent normal tissues, new appositional bone formation occurred on the surface of dead trabecular bone (Fig. 2d). MRIs showed a homogeneous low signal on T_1-weighted images in the femoral head (Fig. 2f).

Induction of bone formation and prevention of collapse of the femoral head by a single local injection of rhFGF-2

Eight weeks after the ONFH procedure, a single local injection of gelatin hydrogel microspheres containing 100 μg rhFGF-2 or PBS was given, and the outcome of the treatment was evaluated 16 weeks after injection. Macroscopic findings showed that controlled release of rhFGF-2 inhibited collapse of the femoral head, compared with segmental collapse in the control (Fig. 3a, b). MRI showed homogeneous low signal areas of the femoral heads in T_1- and T_2-weighted images in the control group (Fig. 3c, e). In contrast, in the rhFGF-2-treated group, homogeneous isointensity in the femoral head was shown in T_1- and T_2-weighted images (Fig. 3d, f). In the control group, μCT showed absorption of the trabecular bones, segmental collapse, and no trabecular bone regeneration in the implanted region of the femoral head (Fig. 4a, b). In contrast, μCT showed apparent regeneration of the trabecular bones in the implanted region of the femoral head in the rhFGF-2-treated group (Fig. 4c, d). BRR at and around the implanted region was significantly greater in the rhFGF-2 treatment group (37.9% ± 11.5% and 71.2% ± 3.3%, respectively) compared with the control group (11.5% ± 4.2% and 47.8% ± 8.6%, respectively; $P < 0.01$) (Fig. 4e). Histopathological analyses of the controls showed complete necrosis with dense medullary fibrosis around the implanted region (Fig. 5a, b). In contrast, in the rhFGF-2-treated group, normal living trabeculae and bone marrow were seen (Fig. 5c, d), the trabecular structures in the femoral head were restored, and collapse of the femoral head was not observed.

Inhibition of secondary OA changes by a single local injection of rhFGF-2

The results of the control group and rhFGF-2 group are summarized in Table 3. Macroscopically, in all the samples of the rhFGF-2 group collapse was not seen (stage 2 = 5), whereas the control group showed segmental collapse and severe OA changes (stage 3 = 1; stage 4 = 4). The macroscopic findings showed that the area of the articular surface of the femoral head involved in OA changes was significantly less in the rhFGF-2-treated group (14.1% ± 9.0%) than in the control group (42.1% ± 5.4%; $P < 0.01$) (Fig. 6). μCT findings also showed that the roundness index of the femoral head, which increases with OA progression, was significantly lower in the rhFGF-2-treated group (52.4% ± 4.9%) than in the control group (62.2% ± 4.3%; $P < 0.01$) (Fig. 6). The irregularity of the subchondral bone of the femoral head was markedly lower in the rhFGF-2-treated group (17.5 ± 6.6%) than in the control group (59.1% ± 13.6%; $P < 0.01$). Histopathological findings showed the irregular articular surface of the femoral head and degradation of the cartilage matrix in the control group. In contrast, the full-thickness cartilage and subchondral bones were

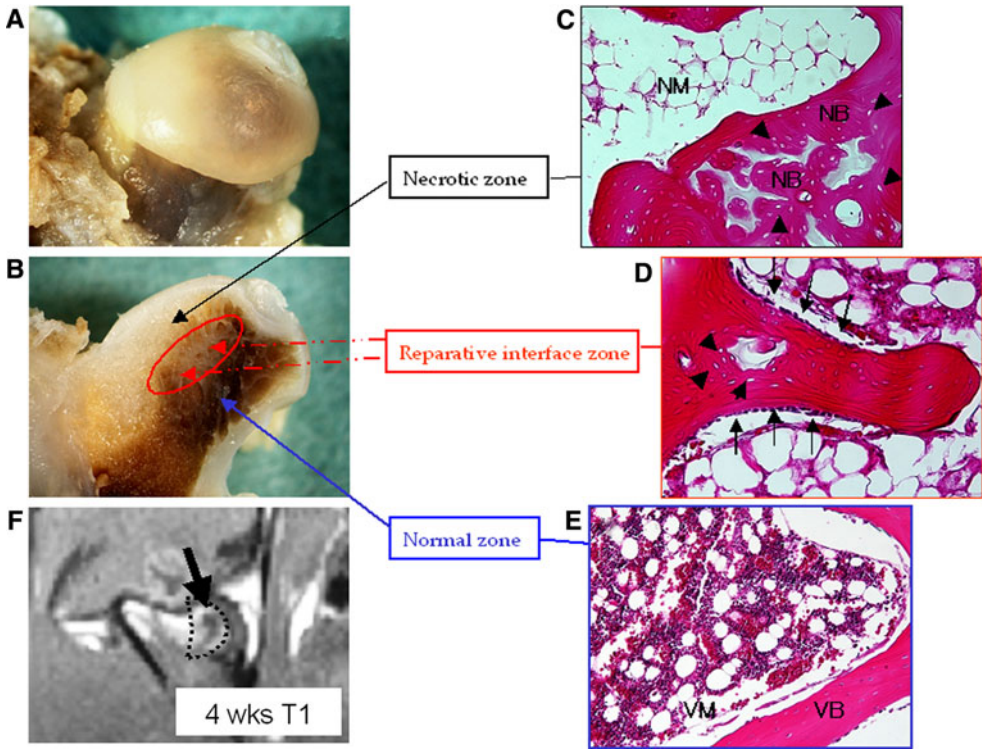

Fig. 2 A representative macrophotograph (**a**) and torn surface of the femoral head (**b**) at 4 weeks after surgery. Osteonecrosis of the femoral head (ONFH) comprises three zones (necrotic zone, reparative interface zone, and normal zone). **c** Histological findings of the necrotic zone. Empty osteocyte lacunae (*arrowheads*) around a resorption cavity and bone marrow necrosis are detected. *NB*, necrotic bone; *NM*, necrotic marrow. (H&E) staining. ×200). **d** In the *reparative interface zone*, empty osteocyte lacunae (*arrowheads*) around a resorption cavity and bone marrow edema are detected. Appositional bone formation (*arrows*) is detected on the surface of necrotic trabeculae. The marrow spaces are filled with granulation tissue. H&E. ×200. **e** In the normal zone, living bone cells (viable bone, *VB*) and bone marrow (viable marrow, *VM*) are detected. H&E. ×200). **f** Representative magnetic resonance imaging (MRI) of the femoral head (*dashed line*). A bandlike pattern with low signal intensity (*arrow*) is shown in the T_1-weighted image 4 weeks after the ONFH procedure

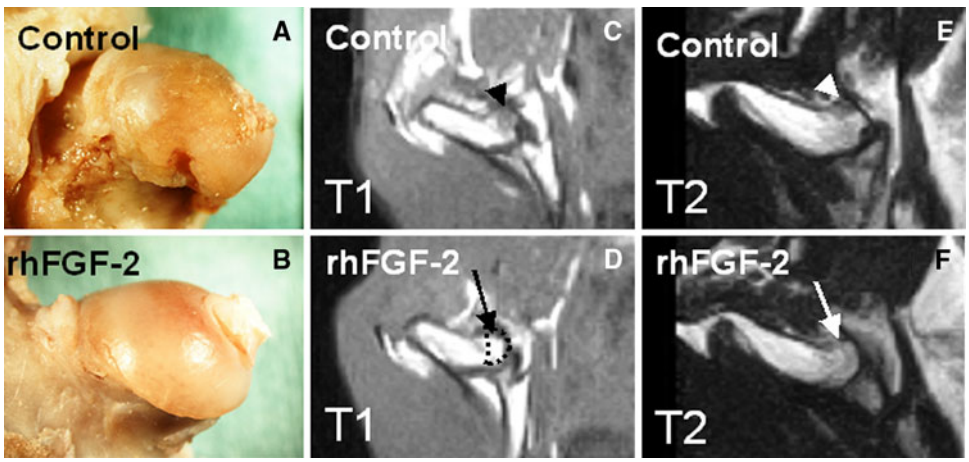

Fig. 3 Representative macrophotographs and MRI of each group. **a** Macrophotograph of the femoral head in the control group shows broken contours with segmental defects and an irregular surface of the femoral head. **b** In the recombinant human FGF-2 fibroblast growth factor-2 (*rhFGF-2*)-treated group, the normal contour of the femoral head is maintained. MRI show low signal intensity of the femoral head (*arrowheads*) in both T_1- and T_2-weighted images in the control group (**c**, **e**) and isointensity of the femoral head (*arrows*) in the rhFGF-2-treated group (**d**, **f**)

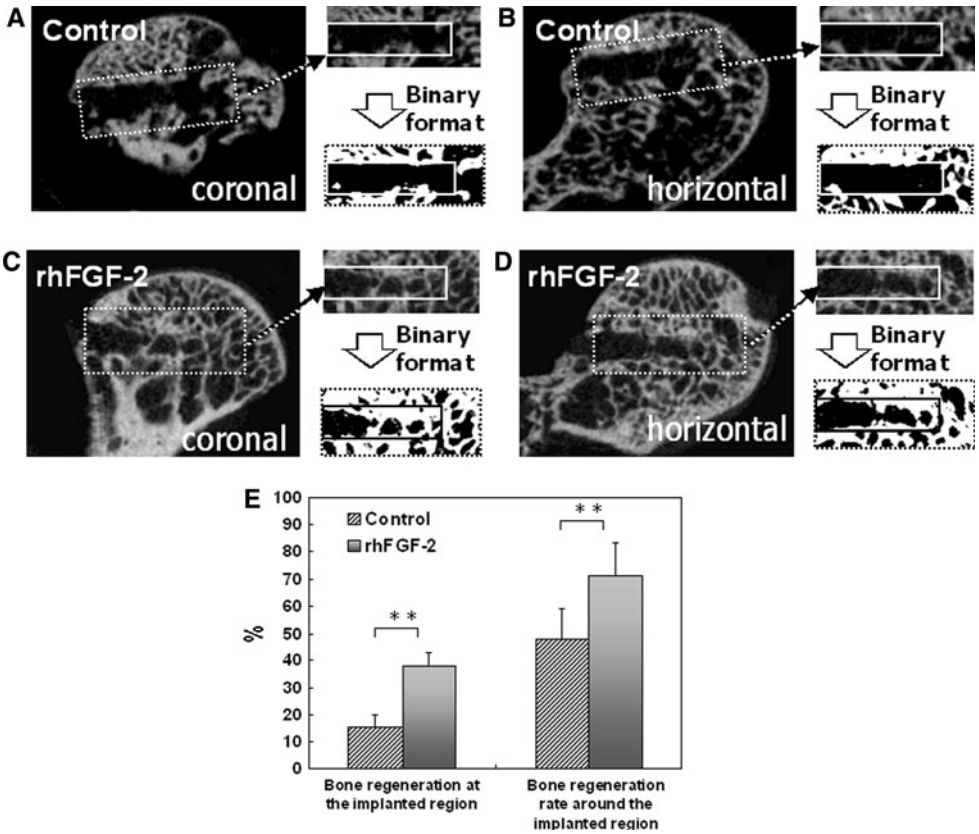

Fig. 4 Representative μCT images of the implanted region and binary format data. **a**, **b** μCT images show bone defect at the implanted region in the control group. **c**, **d** In contrast, apparent bone regeneration is observed in the rhFGF-2-treated group. **a**–**d** The μCT images were converted into binary format data to calculate the bone regeneration rate (*BRR*) at the implanted area (*solid line rectangle*) and BRR around the implanted area (*dashed line rectangle*). The two selected μCT images of the central implant area were converted to a binary format data. BRR of the implant area (1 × 5 mm) and around the implant area (2 × 6 mm) was defined as the average percentage of the bone area to the total area of the binary format images. **e** The BRR was significantly higher in the rhFGF-2-treated group than in the control group. Data are expressed as the average ± standard deviation (SD). $^{**}P < 0.01$

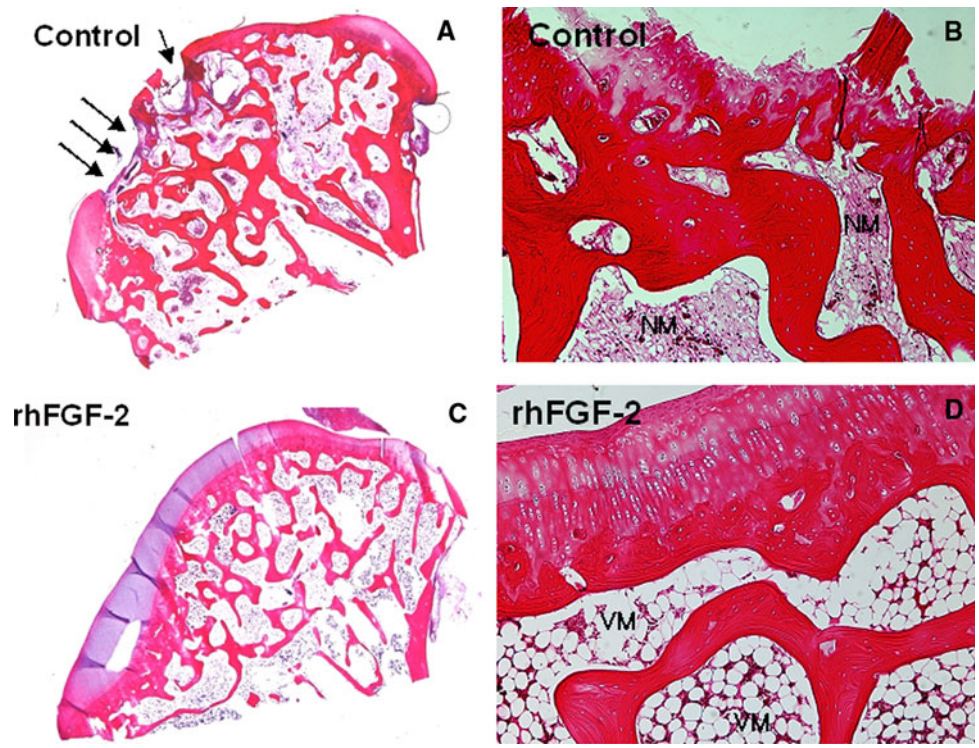

Fig. 5 Histopathological analyses at low magnification of the femoral head. **a** H&E staining shows the broken contour of the femoral head and segmental defect (*arrows*) in the control group (×10). **c** In contrast, the femoral head has a normal contour in the rhFGF-2-treated group. **b** At higher magnification (×100), complete necrosis with dense medullary fibrosis around the subchondral region is seen in the control group and bone resorption cavities are observed. **d** In contrast, normal living trabeculae and bone marrow are seen in the rhFGF-2-treated group. *NM*, necrotic marrow

maintained in the rhFGF-2-treated group (Fig. 7a). Histological grading using the modified Mankin score of the femoral articular cartilage showed significantly less severe OA in the rhFGF-2 treated group (3.4 ± 1.6 points) than that in the control (8.8 ± 2.6 points; $P < 0.05$) (Fig. 7b). These results indicate that the single local injection of

Table 3 Results of control and recombinant human FGF-2 fibroblast growth factor-2 (rhFGF-2) groups

After ONFH procedure	Control group ($n = 5$)	rhFGF-2-treated group ($n = 5$)	P value
Roundness index (%)	62.2 ± 4.3	52.4 ± 4.9	<0.01
Area of articular surface involved in osteoarthritis (OA) change (%)	42.1 ± 5.4	14.1 ± 9.0	<0.01
Irregularity of subchondral bone (%)	59.1 ± 13.6	17.5 ± 6.6	<0.01
Modified Ficat and Arlet staging of osteonecrosis of the femoral head	Stage 3 = 1 Stage 4 = 4	Stage 2 = 5	
Modified Mankin score (0–13 points)	8.8 ± 2.6	3.4 ± 1.6	<0.05

Data are expressed as average ± standard deviation (SD)

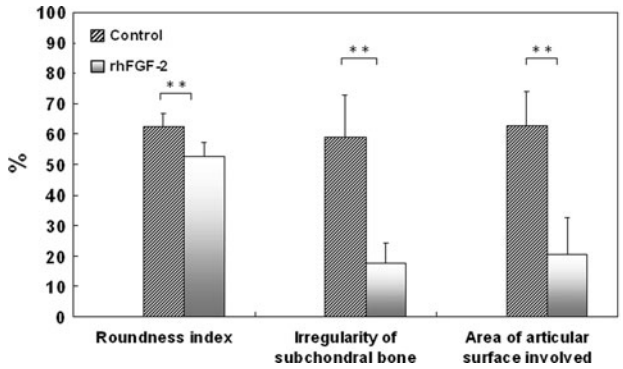

Fig. 6 Preservation of the femoral head and minimal osteoarthritis (OA) changes in the rhFGF-2-treated group. The area of articular surface of the femoral head involved in OA changes measured by macroscopic images and the roundness index and the irregularity of the subchondral bone by μCT images were significantly lower in the rhFGF-2-treated group than in the control group ($P < 0.01$). The values of these indexes increase with OA progression

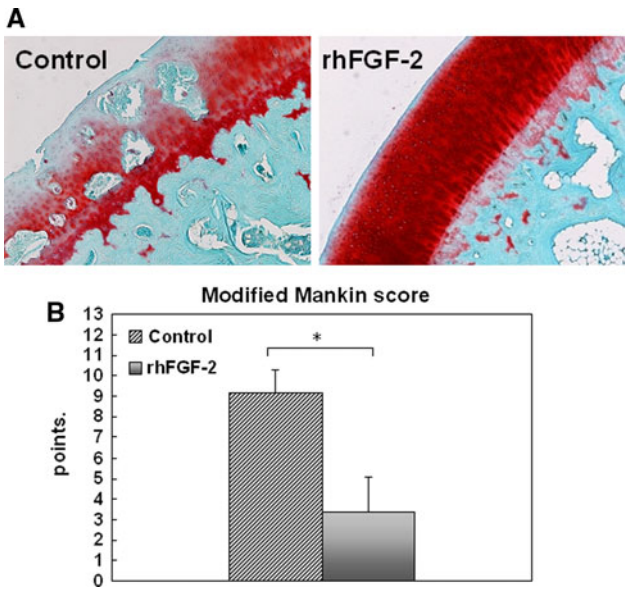

Fig. 7 Representative histological findings of the articular cartilage of the femoral head. **a** Broken contour and segmental defects in the articular cartilage are seen in the control group. Normal contour and full thickness of the cartilage layers are seen in the rhFGF-2-treated group. Safranin O staining. ×40. **b** The histological score of each group based on the modified Mankin score shows significant inhibitory effect of rhFGF-2 on OA progression. *$P < 0.05$

rhFGF-2 inhibited the progression of the secondary OA changes of the femoral head.

Discussion

We evaluated whether a single local injection of rhFGF-2 microspheres would have therapeutic effects on the repair of ONFH in an experimental model of osteonecrosis in adult rabbits. The rhFGF-2 treatment inhibited the progression of ONFH and OA changes, as evidenced by new bone formation in the trabeculae of the osteonecrotic femoral head and prevention of femoral head collapse.

FGF-2 is recognized as a pleiotropic regulator of the proliferation, migration, and differentiation of cells in bone tissues and the vasculature and has anabolic effects on angiogenesis and bone formation [12–17]. One of the problems in the clinical application of rhFGF-2 is its poor in vivo stability unless a drug delivery system is contrived. We have reported on a controlled-release system involving rhFGF-2 in acidic gelatin with an isoelectric point of 5.0, which forms a polyionic complex with FGF-2 [18, 19]. Release of rhFGF-2 from the hydrogel at the site of implantation was measurable for more than 2 weeks, a time frame that correlates strongly with the patterns of in vivo FGF-2 release and hydrogel degradation. Previous studies have also shown that rhFGF-2 microspheres are effective in accelerating bone repair using a fracture model in animals [20, 21] and in treating high tibial osteotomy in humans [24]. In addition, rhFGF-2 microspheres induced complete regeneration at the defect in a monkey skull 21 weeks after implantation [25]. In contrast, treatment with rhFGF-2-free gelatin hydrogels or the soluble form of rhFGF-2 resulted

in no bone regeneration. Other reports show that FGF-2 might stimulate the local production of other factors such as transforming growth factor-β, bone morphogenetic proteins, prostaglandins, insulin-like growth factor, and endogenous FGFs, all of which are involved in the serial cascade of bone formation [33–36]. Overall, the potential for FGF-2 to coinduce angiogenesis, bone resorption, and bone formation makes it an attractive target for therapeutic use in local bone regeneration including reconstructive surgery, bone fracture repair, and the treatment of ONFH [2–5]. In this study, a single local injection of rhFGF-2 microspheres induced bone formation at the osteonecrotic femoral head in our rabbit model, providing evidence that rhFGF-2 is effective for treating ONFH. Hydroxyapatite ceramic and β-tricalcium phosphate are other promising carriers of rhFGF-2, systems that can release rhFGF-2 at adequate concentrations to induce bone formation [37, 38]. However, because these materials are solid or granules, more invasive surgical procedures are needed for application of these rhFGF-2 composites into the osteonecrotic femoral head, compared with a local injection of rhFGF-2 microspheres.

Our data show that the application of rhFGF-2 microspheres has a promoting effect both on new bone formation and on preserving the contour of the femoral head. Resorption of dead trabeculae of the femoral head during the repair process may weaken the structural support of the femoral head and may be partly responsible for collapse in the late stages of ONFH, leading to secondary OA [27]. In this study, 80% (stage $3 = 1$; stage $4 = 4$) of the osteonecrotic femoral heads from the control group were collapsed, whereas no collapse was seen in the rhFGF-2-treated group. In addition, the OA score was significantly lower in the rhFGF-2-treated group than in the control group. These results indicate that a single local injection of rhFGF-2 suppresses OA progression by accelerating bone regeneration at the necrotic region and providing mechanical support to prevent the femoral head from collapse and OA progression.

Several studies have reported preventing collapse of the femoral head and avoiding joint replacement by using other growth factors, including bone morphogenetic proteins (BMPs) and vascular endothelial growth factor (VEGF) [2, 4, 39]. BMPs are a family of proteins with demonstrated osteogenic potential that may be useful in the treatment of ONFH because of their pleiotropic effects. Although VEGF is also another kind of angiogenic growth factor, FGF-2 may have several therapeutic advantages for ONFH. FGF-2 is a powerful mitogen that stimulates migration and proliferation of various vascular cell types such as endothelial cells, fibroblasts, and smooth muscle cells, whereas VEGF is specific for endothelial cells [40, 41]. Basic and clinical research studies show that FGF-2 also functions as an important regulator of bone development, bone formation, and bone remodeling, and indeed rhFGF-2 is now used clinically as a therapeutic strategy for the treatment of orthopedic fields [12–17]. In future studies, appropriate combination of these growth factors for the treatment of ONFH might be determined.

We conclude that a single local injection of rhFGF-2 microspheres induces repair of the osteonecrotic femoral head and inhibits femoral head collapse and OA progression. A single local injection of rhFGF-2 microspheres is a promising strategy for promoting functional repair of ONFH.

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