

# Potential diagnostic role of diffusion tensor imaging in early-stage osteonecrosis of the femoral head

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**Abstract.** The present study aimed to explore the potential diagnostic role of diffusion tensor magnetic resonance imaging (DTI) in the early stage of modified corticosteroid-induced osteonecrosis of the femoral head (ONFH). A total of 20 beagles were randomly classified (1:1) into either an experimental group (LM), which were intramuscularly injected with lipopolysaccharide (LPS) and methylprednisolone (MPS) on three consecutive days, or control (CON) group, which were injected with saline. Magnetic resonance imaging (MRI) and DTI were performed at pre-induction and 8 and 12 weeks post-induction. Apparent diffusion coefficient (ADC) values in the range of interest in the femoral head were quantified using DTI. Proximal femora were examined for ONFH at 8 and 12 weeks. The results demonstrated that ONFH developed in four beagles at 8 weeks and in six beagles at 12 weeks, whereas no ONFH was detected in the CON group. No abnormalities were detected by MRI and DTI, and no mortality occurred. In beagles with ONFH in the LM group, the ADC values were  $4.7 \pm 0.2 \times 10^{-4}$  and  $4.8 \pm 0.3 \times 10^{-4}$  mm<sup>2</sup>/sec at 8 and 12 weeks, respectively, which were significantly increased compared with the CON group ( $2.5 \pm 0.3 \times 10^{-4}$  and  $2.4 \pm 0.3 \times 10^{-4}$  mm<sup>2</sup>, respectively) and the LM group without ONFH ( $2.6 \pm 0.4 \times 10^{-4}$  and  $2.4 \pm 0.3 \times 10^{-4}$  mm<sup>2</sup>, respectively) ( $P < 0.05$ ). The results of the present study indicated that intramuscular injection of LPS and MPS may lead to early-stage ONFH in beagles. As such, the detection of locally elevated ADC values in the femoral head may aid in the early diagnosis of ONFH.

## Introduction

Osteonecrosis (ON) of the hip, which predominantly affects young adults, often induces a series of unrelenting symptoms that culminate in hip pain and loss of function (1). It is estimated that 20,000 to 30,000 patients are diagnosed with ON annually accounting for 10% of the 25,000 total hip arthroplasties performed annually in the United States (2). The disease has also been termed 'the coronary disease of the hip' by Chandler (3) as the disease simulates the ischemic condition in the heart. Osteonecrosis of the femoral head (ONFH) frequently progresses to a subchondral fracture of the femoral head, eventually leading to complete joint destruction. Joint-preserving surgical interventions are generally more successful at earlier stages of bone involvement compared with those after the occurrence of a subchondral fracture. Therefore, the optimal time to evaluate and treat osteonecrosis of the femoral head is prior to the occurrence of a subchondral fracture (4). Treatment algorithms for osteonecrosis of the femoral head are based on the staging of the lesion. Based on clinical and laboratory observations, there is typically a  $\geq 3$  months delay between the occurrence of hormone-related ONFH and abnormal magnetic resonance imaging (MRI) results (5,6), which is defined as the 0-stage of the Association Research Circulation Osseous or Steinberg classification systems (7).

To date, there is no noninvasive technique to accurately diagnose 0-stage ONFH. If early stage ONFH was diagnosed with noninvasive techniques, extracorporeal shock wave or autologous bone marrow stem cell transplantation may be used to limit the progression of ONFH, which would be of great clinical value (8). In recent years, MRI technology has developed rapidly, and the emergence of functional MRI (fMRI) has facilitated the elucidation of novel information and an in-depth understanding of various bone diseases (9), including craniofacial fibrous dysplasia, bone marrow abnormalities in multiple myeloma, systemic sclerosis, sclerosing osteomyelitis as well as metastasis of different cancers to the bone (10).

The present study aimed to explore the potential diagnostic role of diffusion tensor magnetic resonance imaging (DTI) in the early stages of ONFH in an animal model. The results of the present study may provide a theoretical basis for the clinical application of DTI for the early diagnosis of ONFH.

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**Key words:** osteonecrosis of the femoral head, diffusion tensor magnetic resonance imaging, apparent diffusion coefficient, early stage

## Materials and methods

**Animals, grouping and treatment.** A total of 20 male beagles (age, 12-14 months; weight, 5.5-6.5 kg) were obtained from the Animal Center of Capital Medical University (Beijing, China) and randomly classified into one of two equal groups: Control (CON) group or experimental (LM) group. Beagles were tagged and housed in cages ( $n=1/\text{cage}$ ) under standard laboratory conditions at 20°C (humidity, 48%) with a 12-h dark/light cycle. A standard diet and water were provided *ad libitum*. All experimental procedures adhered to the recommendations outlined by the Chinese Department of Health for the Care and Use of Laboratory Animals and were approved by the Ethics Committee of the Chinese Rehabilitation Research Center at Beijing Charity Hospital (Beijing, China). Beagles in the LM group were intramuscularly injected with 10  $\mu\text{g}/\text{kg}$  lipopolysaccharide (LPS; Sigma-Aldrich, St. Louis, MO, USA) and 20 mg/kg methylprednisolone (MPS; Pfizer, Inc., New York, NY, USA) on three consecutive days. Beagles in the CON group were injected with normal saline. Following the daily injection, the beagles were permitted free activity.

**MRI protocols.** MRI and DTI were performed on the bilateral proximal femora prior to drug injection and at 8 and 12 weeks following the last injection using a 1.5 T superconducting magnet system (Achieva; Philips Healthcare, Best, The Netherlands). Following anesthetization via initial intramuscular injection of 25 mg/kg ketamine hydrochloride and intraperitoneal maintenance with 5 mg/kg sodium pentobarbital and blood pressure monitoring, the beagles were placed in a supine position with the lower limb flexed and fixed with adhesive tape. An extremity coil was used on the target site. MRI investigations were performed using an 1.5 T MRI system. All magnetic resonance pulse sequences and scan parameters used in the MRI and DTI protocols are listed in Table I. Two radiologists (independent and blinded to the investigations) assessed the MRI and DTI scans to evaluate morphologic and signal alterations in the cartilage and subchondral bone of the femoral head.

To measure the apparent diffusion coefficient (ADC) of the femoral head, a circular area (diameter, 5-mm) was selected to be the region of interest (ROI). The ROI was automatically transposed onto two maps (ADC values) generated by the image analysis software (version 17.0 SPSS, Inc., Chicago, IL, USA) (Fig. 1). ADC values of the femoral head were obtained by averaging the values obtained from the three slices selected over the target site beneath the joint space in the mid-coronal T1-weighted images (Table II).

**Histological examination.** Five beagles in each group were sacrificed via an overdose of sodium pentobarbital at 8 and 12 weeks following the initiation of the experiment. Tissue samples were harvested from the femoral head. Specimens (1.0-mm thick) were cut along the coronal plane and fixed in 10% formalin solution for 2 weeks. Following treatment with 10% nitric acid and decalcification overnight, according to conventional methods (11), the specimens were stained with hematoxylin and eosin (Shanghai Xiangjian Medical Equipment Co., Ltd., Shanghai, China). ONFH was considered present when there were empty lacunae, accumulation of bone marrow

cell debris, and an increase in fat cells in the bone marrow (12). Histological analysis was performed to observe the osteonecrotic changes and repair processes in the femoral head 8 and 12 weeks post-treatment. Two pathologists (independent and blinded to the investigations of the present study) examined the tissue sections according to the criteria outlined by Arlet (13). The presence of degeneration and necrosis, the disappearance of marrow cells and nuclei and hypochromasia of trabecular osteocytes were regarded as early signs of ON (13). Sporadic empty lacunae, which may have been induced by sectioning through the edge of a lacuna, were not considered as a sign of ON.

**Statistical analysis.** Statistical analysis was performed using SPSS 17.0 software (SPSS, Inc., Chicago, IL, USA). Data are presented as the mean  $\pm$  standard deviation. Differences between the LM and CON groups were compared using two-sided Student's t-test.  $P<0.05$  was considered to indicate a statistically significant difference.

## Results

**Histopathological findings.** No changes in form, weight, abdominal distension or tapering limbs were observed in the LM or CON groups, and no mortality occurred during the experimental period. In the CON group, no pathological alterations were observed at 8 or 12 weeks post-treatment. The articular cartilage was rich in blood vessels and intramedullary hematopoietic cells, and the trabeculae were arranged neatly and clearly. Trabecular bone cells, which were surrounded by many osteoblasts, were clearly visible, whereas empty lacunae were rare (Fig. 1). In the LM group, ONFH occurred in four beagles 8 weeks after treatment, which was detected via fat cell hypertrophy, decreased marrow hematopoietic cells, trabecular bone thinning and increasing spaces, structural disorder, partial trabecular breakage and trabecular karyopyknosis of the bone. The nuclei were small, with increasing numbers of empty lacunae detected (Fig. 2). At 12 weeks post-treatment, ONFH was detected in six animals in the LM group. The bone marrow was saturated with fat cells, bone trabecular interruption and empty lacunae; increased trabecular bone necrosis was detected around small osteoblasts, and necrotic inflammatory cells were visible. There were minimal nascent blood vessels and necrosis was detected around the areas of fibrovascular tissue repair (Fig. 3). These results demonstrate that corticosteroid treatment results in the development of ONFH in 60% of the animals.

**Radiographical findings.** T1-weighted images showed a high signal and T2-weighted images showed a low or intermediate signal for beagles in the CON group. No abnormal signal alterations were observed in the femoral head via MRI or DTI in any of the animals in the CON group at 8 and 12 weeks post-treatment (Fig. 4). In the LM group, the results of MRI and DTI were consistent with the CON group (Fig. 5). In the LM group, mean ADC values in the ROI of beagles with ONFH were significantly increased, as compared with the LM group without ONFH or the CON group ( $P<0.05$ ; Table II). These results further confirm that corticosteroid treatment leads to ONFH.

Table I. Sequences and scan parameters used for magnetic resonance imaging and DTI.

Purpose	Pulse sequence	TE/TR (mm)	FOV (mm)	Matrix	Thickness (mm)	NEX	Specific parameters
Anatomical sequence	TSE/coronal	35/520	160x160	256x256	4	1	
	TSE//coronal	100/2000	160x160	256x256	4	1	
DTI protocol	SE.EPI	60/2100	160x160	256x256	4	4	VOI: 25x25x2.5 mm b-value: 500 sec/mm

DTI, diffusion tensor magnetic resonance imaging; TE, echo time; TR, repetition time; FOV, field of view; matrix, image matrix size; NEX, number of excitations; TSE, turbo spin echo; VOI, volume of interest; SE, spin echo.

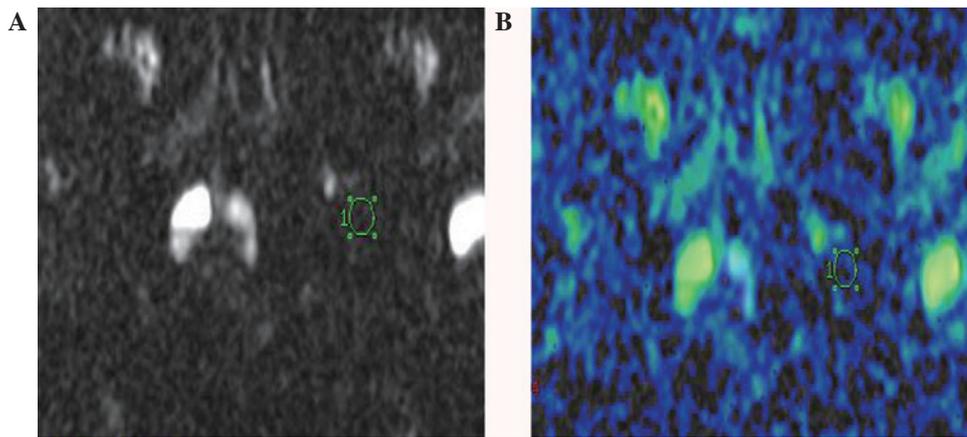


Figure 1. Diffusion tensor magnetic resonance imaging of the region of interest in the femoral head. (A) Diffusion tensor magnetic resonance imaging of the femoral head. (B) The DTI image after computer software processing in order to calculate the ADC value.

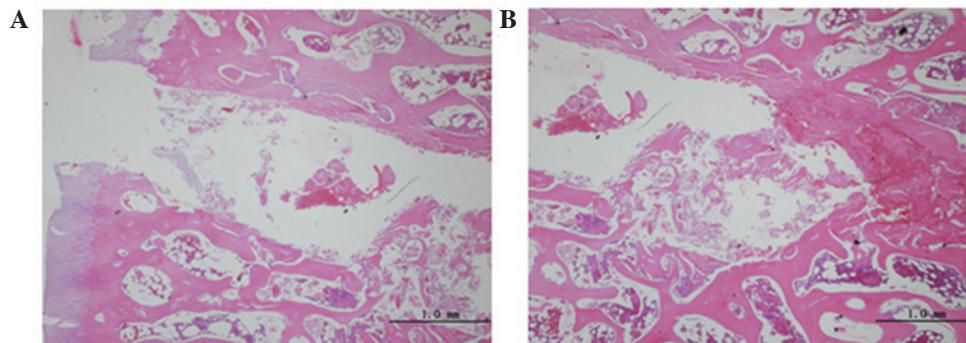


Figure 2. (A) Osteonecrosis in the subchondral zone (B) Broken trabecular bone and bone matrix dissolution in the experimental group (magnification, x40).

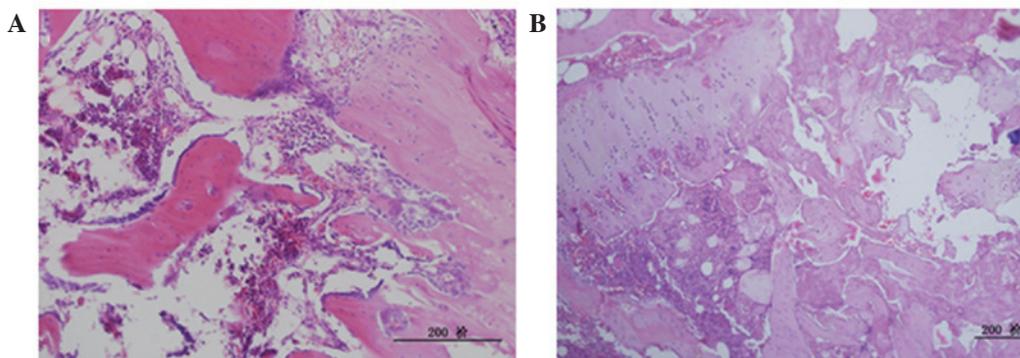


Figure 3. (A) Osteoblasts, osteoclasts (magnification, x40) and (B) fibrous tissue repair (magnification, x100) were detected in the experimental group.

Table II. Apparent diffusion coefficient values in the proximal femur ( $\times 10^{-4}$  mm<sup>2</sup>/sec).

Animal group	Prior to administration	8 weeks post-administration	12 weeks post-administration	P-value
Beagle with ON of LM group	2.7 $\pm$ 0.3	4.7 $\pm$ 0.2 <sup>a</sup>	4.8 $\pm$ 0.3 <sup>a</sup>	<0.05
Beagle without ON of LM group	2.5 $\pm$ 0.4 <sup>b</sup>	2.6 $\pm$ 0.4 <sup>a,b</sup>	2.4 $\pm$ 0.3 <sup>a,b</sup>	>0.05
Control group	2.6 $\pm$ 0.3 <sup>b</sup>	2.5 $\pm$ 0.3 <sup>a,b</sup>	2.4 $\pm$ 0.3 <sup>a,b</sup>	>0.05

<sup>a</sup>P>0.05 vs. pre-administration in LM group; <sup>b</sup>P<0.05 vs. control group post-administration.

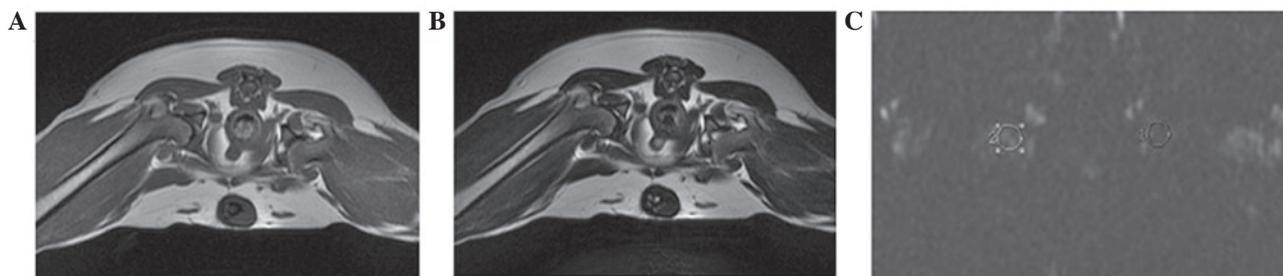


Figure 4. (A) T1- and (B) T2-weighted, and (C) diffusion tensor magnetic resonance imaging demonstrated no abnormal signal changes in the femoral head of beagles in the control group, which were treated with saline.

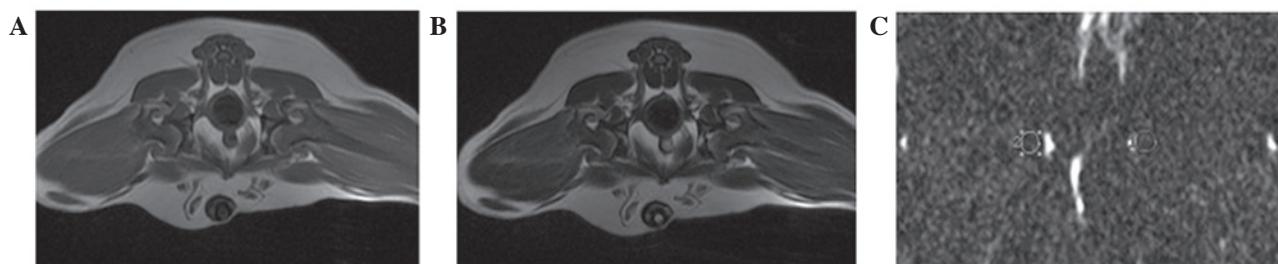


Figure 5. (A) T1- and (B) T2-weighted, and (C) diffusion tensor magnetic resonance imaging demonstrated no abnormal signal changes in the femoral head of beagles in the experimental group, which were intramuscularly injected with lipopolysaccharide and methylprednisolone for three consecutive days.

## Discussion

Since the etiology of ON remains unknown, there is no standard method for the establishment of an animal model for experimental studies. Corticosteroid medication is a pivotal risk factor for the development of ON (14). Previous clinical and experimental studies have confirmed that long- or short-term intermittent use of high-dose corticosteroids may induce ON (15), and the response of both humans and animals to glucocorticoids is consistent (16).

Climcher and Kenzora (17) determined that steroids do not cause ONFH unless the patient has a disease that predisposes them to ONFH. The characteristics of ON induced by horse serum or endotoxin combined with steroids are similar to those of clinical ON, and are more stable than those induced by corticosteroids alone. In previous studies, a combination of low-dose LPS and high-dose MPS was used to induce ON, resulting in a high rate of ON and low animal mortality (6.2%) (18-23). Steroid injection combined with intravenous injection of LPS 24 h later has been demonstrated to induce a local and systemic Shwartzman reaction (shw-r), which is

characterized by disseminated intravascular coagulation and results in blood coagulation disorders, blood clotting and microthrombosis formation (24).

It has previously been demonstrated that shw-r is capable of causing vasculitis, endothelial cell necrosis, hemorrhage and thrombosis, which result in tissue damage (25). As the mortality of animals with shw-r is high, a modified shw-r was elicited with a single injection of LPS combined with MPS in the large animals used in the present study. Histopathological analysis was performed 8 and 12 weeks post-treatment, which demonstrated that 4 and 6 beagles, respectively, developed ONFH. No mortality occurred. These results showed that the experimental protocol of low-dose LPS and subsequent pulsed high-dose MPS injections used in the present study is an effective method for inducing ON in beagles, with a high incidence of ONFH and low mortality. This animal model may be useful for subsequent studies investigating imaging alterations in the early stages of ONFH.

MRI signal intensity is predominantly correlated with the hydrogen density of the scanned organ (26); however, the pathological changes detected in ON are mainly due to

alterations in fat and water content. MRI, which has a high sensitivity and specificity in the diagnosis of ON, began to be used in clinical exploration of avascular necrosis in 1983 (27). In recent years, technology has advanced to the point that MRI can be used for the early diagnosis of ONFH and the determination of pathophysiological changes in the femoral head according to imaging alterations (28). Different pathological stages of avascular necrosis exhibit differing MRI variations (29). Nevertheless, it is important to note that MRI can only detect alterations after the ON has progressed to a certain degree; therefore, even if the results of MRI are normal, ON cannot be completely ruled out. Notably, Beltran *et al* (30) have reported on cases of biopsy-proven ON in which the MRI scans of five patients appeared normal.

fMRI, which is an imaging technology based on conventional MRI, is a novel approach for examining patients at risk of developing ONFH. Exploratory research into the early diagnosis of ONFH with fMRI, including magnetic resonance spectroscopy, controlled perfusion MRI and diffusion MRI, have previously been reported (31-33).

DTI is an MRI technique that has been employed to microimage cartilage and skeletal muscle (34). DTI has been demonstrated to be extremely sensitive to the morphology of the tissue examined and precise to the scale of tens of microns (35). DTI has also been used to study the changes in collagen fiber orientation under mechanical compression.

DTI facilitates the noninvasive microarchitectural characterization of heterogeneous tissue. DTI parameters of ADC of water in the bone marrow can be quantified, which provides a useful tool for the noninvasive investigation of human tissues (36,37). ADC values reflect the association between the direction of the diffusion of water molecules and the organizational structure (38). These results may have been induced by increased free water in the surrounding tissue caused by acute ischemia of the femoral head and cell necrosis. MRI and DTI analysis demonstrated that the local signal strength was not significantly altered in the experimental beagles with ONFH, as compared with the beagles without. This may be due to the fact that the spatial resolution of DTI remains low, and the osteonecrotic lesions and water content of bone tissue are limited.

The results of the present study had certain limitations. Firstly, the statistical analyses are limited by the relatively small sample size. Secondly, the observation period was relatively short, which may have limited the observation of consecutive pathological and radiological changes that may occur in ON. Prolonging the observation period and establishing various time points would be of value in future studies. Furthermore, DTI also has limitations, including low resolution.

In conclusion, the results of the present study demonstrated a good correlation between the histological alterations and the DTI findings. These data may enable future studies to explore the role of fMRI in the early diagnosis of ONFH. Improvements in the hardware, image signal-to-noise ratio, spatial resolution and image post-processing software of DTI may enable the application of this technique to clinical screening, particularly in patients who exhibit at high risk for ONFH and whom conventional MRI does not show any abnormalities. As negative MRI scan cannot completely rule out ONFH, a method of diagnosing early-stage ONFH

may enable the prevention or reversal of the progression of ON. Diffusion analysis with ADC may allow physicians to obtain more detailed information on the structure of cancellous tissue, changes in bone marrow composition and bone metabolism. Further investigation and hardware improvements are required to investigate the advantages of DTI for the diagnosis of ONFH.

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