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# Treatment of early stage osteonecrosis of the femoral head with autologous implantation of bone marrow-derived and cultured mesenchymal stem cells

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ABSTRACT

*Background:* Treatment of early-stage osteonecrosis of the femoral head (ONFH) with autologous implantation of iliac crest bone marrow-derived mononuclear cells, which contain tens of thousands of bone marrow mesenchymal stem cells (BMMSCs), recently achieved a promising outcome.
*Methods:* One hundred patients with early-stage ONFH were recruited and randomly assigned to BMMSC treatment or core decompression (CD) treatment. Each BMMSC-treated hip received femoral head (FH) implantation of $2\times10^6$ autologous subtrochanteric bone marrow-derived and *ex vivo* expanded BMMSCs. The radiographic stage of ONFH according to the Association Research Circulation Osseous classification, Harris hip score (HHS), and the volume of the necrotic lesion or the low signal intensity zone (LowSIZ) in the FH were assessed before and 6, 12, 24, and 60 months after the initial operation.
*Results:* Sixty months after the operation, only 2 of the 53 BMMSC-treated hips progressed and underwent vascularized bone grafting. In CD group, 7 hips lost follow-up, and 10 of the rest 44 hips progressed and underwent vascularized bone grafting (5 hips) or total hip replacement (5 hips). Compared with the CD group, BMMSC treatment significantly improved the HHS as well as decreased the volume of femoral head LowSIZ of the hips preoperatively classified at stage IC, IIB, and IIC ($P<0.05$, respectively; stage IIA, $P=0.06$, respectively). No complication was observed in both treatment groups.
*Conclusions: Ex vivo* expansion of autologous BMMSCs can reliably provide a greater number of BMMSCs for FH implantation. This intervention is safe and effective in delaying or avoiding FH collapse, which may necessitate total hip replacement.



## Introduction

Osteonecrosis of the femoral head (ONFH) is a disease in which necrotic bone lesions usually progress to femoral head collapse and symptomatic hip arthritis; the disease mainly affects individuals in their thirty to sixty years of age [1,2]. ONFH is always associated with one or more risk factors, such as trauma to the hips, alcohol abuse, excessive use of corticosteroid, hemoglobinopathy, Gaucher's disease, pregnancy, coagulopathies, Caisson disease, organ transplantation, hyperbaric exposure, inflammatory or autoimmune diseases, and other idiopathic mechanisms. However, the pathophysiology of ONFH remains uncertain [3–6].

Core decompression (CD) has been widely used to delay the progress of osteonecrotic lesions destroying the femoral head. However, a number of factors may influence the prognosis of such treatment, including alcohol abuse and corticosteroid use, as well as the size and location of the necrotic lesion [6–10]. Although vascularized or nonvascularized autologous bone grafts and osteotomies have also been employed in treating ONFH [4,6,8,9], these procedures remain complicated, expensive, and not widely reproducible.

Recent pioneer studies by Hernigou et al. and Gangji et al. have demonstrated the efficacy of autologous bone marrow cell implantation into the femoral head during early-stage ONFH [11–13]. In such procedures, several tens of thousands of bone marrow stem cells, which were isolated and concentrated from anterior iliac crest-aspirated bone marrow, were implanted into the osteonecrotic zone in the femoral head right after CD. A novel protocol has been developed in which subtrochanteric bone marrow was directly aspirated through the CD tunnel and bone marrow-derived mesenchymal stem cells (BMMSCs) were cultured *ex vitro* for about two weeks to obtain millions of cultured BMMSCs for femoral head implantation. The concentration of BMMSCs in harvested autologous bone marrow is relatively lower than that in the *ex vivo* cultured MSC suspension. To obtain a larger number of BMMSCs without *ex vivo* expansion, a higher volume of autologous bone marrow must be aspirated. In

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the current study, about 10 mL of bone marrow were harvested and about 2 mL of concentrated BMMSC suspension were obtained by *ex vivo* expansion. Transplanted BMMSCs are believed to directly differentiate into osteoblasts or into vascular endothelial cells to promote the repair process *in vivo* [7,11]. The present study aims to assess the safety and efficacy of the above-mentioned novel procedures in the treatment of early-stage ONFH.

## Methods

### *Study design*

This single-center randomized clinical trial was conducted in a university-affiliated hospital in China between May 2004 and July 2006. The objective of this study was to assess the efficacy of cultured bone marrow-derived mesenchymal stem cell implantation into the femoral head as treatment against early stage osteonecrosis of the femoral head. The protocol of the present study was approved by the Institutional Review Board of Dalian University and the Ethics Committee of the City of Dalian under the authorization of the Ministry of Public Health of China. Written informed consent was obtained from each patient before enrollment.

### *Participants and randomization*

Patients with ONFH were recruited at the Dalian University Zhongshan Hospital. The inclusion criteria were age between 18 and 55 years, presence of osteonecrotic stages from IC to IIC according to the Association Research Circulation Osseous (ARCO) classification [14], and risk factors, such as trauma, corticosteroid use, alcohol abuse, Caisson disease, and other idiopathic mechanisms. The exclusion criteria were pregnancy, current and previous infections, skeletal immaturity, immunosuppressive drug therapy, a history of inflammatory arthritis, cardiovascular diseases, prior systemic corticosteroid treatment, and mental health problems. The patients who met the inclusion criteria were randomly divided into two groups following the randomization sequence created by a third party not involved in this study at the time of patient admission (Fig. 1). Patients in one group were treated with core decompression (CD treatment group) and patients in the other group were treated with femoral head autologous implantation of cultured BMMSCs (BMMSC treatment group).

### *Procedures*

#### *BMMSC treatment*

With the aid of a Stryker's Navigation System, a decompression tunnel was made using a trephine through the trochanter and femoral neck into the necrotic region in the femoral head, 2–3 mm away from the cartilage (Fig. 2A). The medial part of the bone core withdrawn from the trephine was sent for pathological examination (Fig. 2B) and the lateral part was bored with a 1 mm diameter Kirschner wire along its central axis (Fig. 2C). After 10 mL of subtrochanteric bone marrow was aspirated through the decompression tunnel (Fig. 2D), the necrotic segment was removed by a custom-made trephine with a collapsible scraping end (Fig. 2E). Next, the bored bone core was plugged into the decompression tunnel (Fig. 2F) before the outlet of the decompression tunnel was sealed with bone wax followed by layer closure. The subtrochanteric bone marrow-derived BMMSCs were subjected to proliferation *in vitro* for two weeks, after which about $2\times10^6$ BMMSCs were harvested and prepared in 2 ml normal saline solution later injected into the osteonecrotic site in

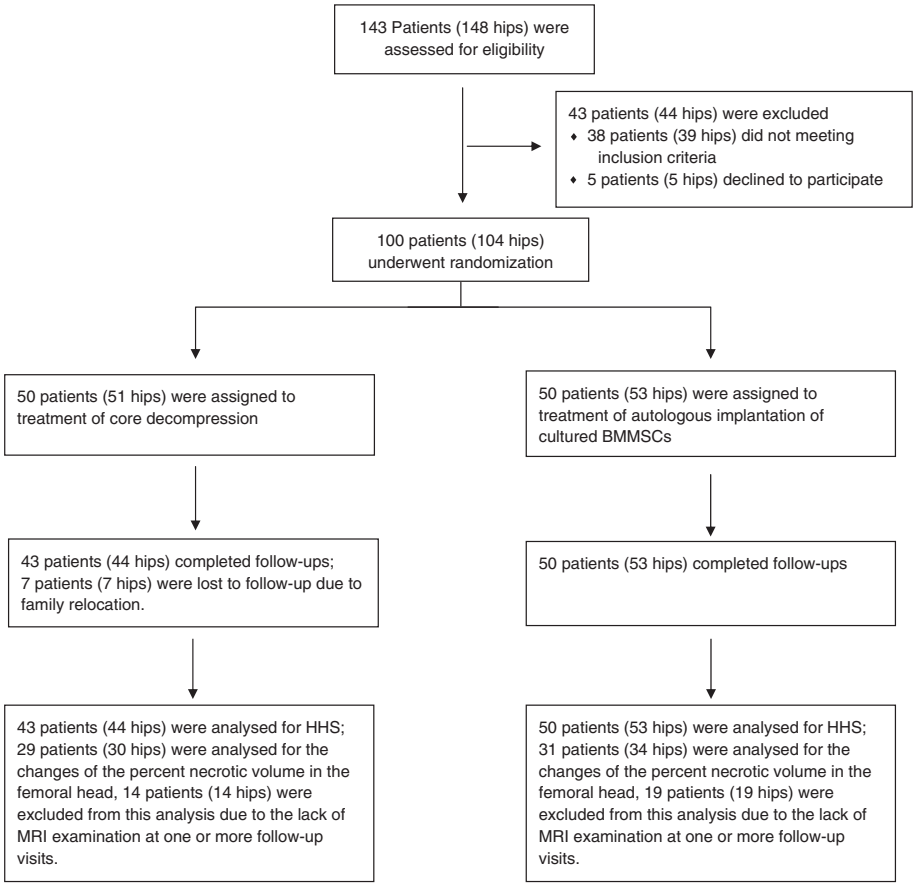


**Fig. 1.** Enrollment, randomization, and follow-up.

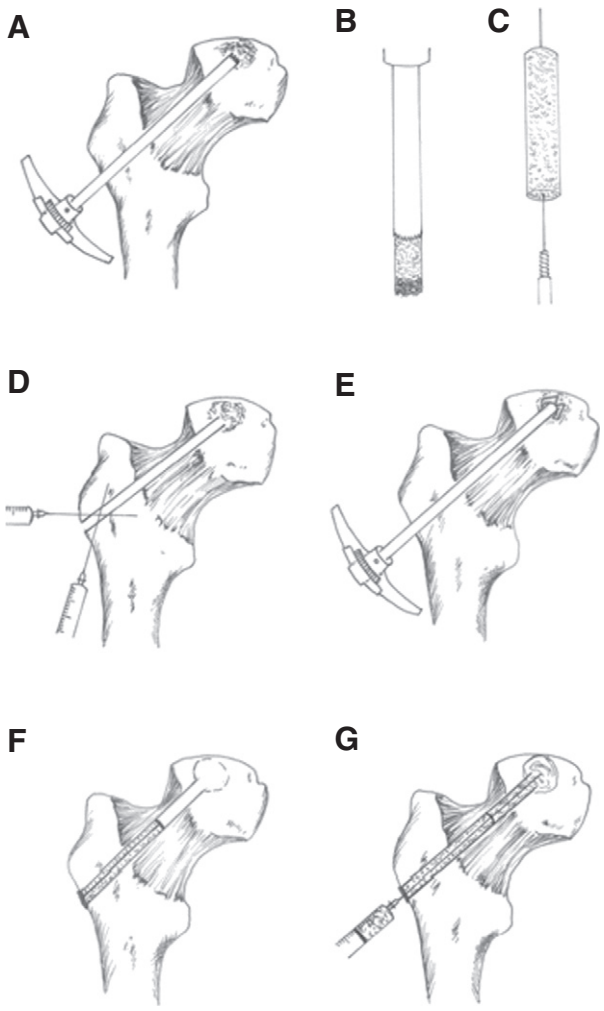


**Fig. 2.** Illustration of the surgical procedures. (A) Establishing the core decompression tunnel; (B) withdrawing the bone core from the trephine; (C) boring the lateral segment of the bone core; (D) aspirating bone marrow from the subtrochanteric regions; (E) removing necrotic bone from the femoral head; (F) plugging the decompression tunnel with the bored bone core and sealing the outlet of the tunnel with bone wax; (G) implanting BMMSCs into the femoral head.

the femoral head with a puncture needle through the bored plug and the decompression tunnel (Fig. 2G). Detailed surgical procedures and BMMSCs culture protocol are described in the online Supplementary data.

*CD treatment*

The procedures for CD treatment including establishment of the decompression tunnel and removal of the necrotic segment from the femoral head were identical to the BMMSC treatment as described above; however, some steps including bone marrow aspiration from the iliac crest, bone core plug preparation, and BMMSC implantation were skipped. Please see detailed procedures described in the online Supplemental data.

*Postoperative care*

After surgeries, all patients were treated prophylactically with an intravenous infusion of cefazolin for 3–5 days. Patients were prohibited from bearing full bodyweight for six weeks. Postoperative rehabilitation followed postoperative care, where all patients followed a strict rehabilitation and training program. Quadriceps muscle and passive range of motion exercises began the first day after surgery. All patients had bed rest with light skin traction for 3 weeks. Patients were allowed assisted weight bearing with two crutches within 3 weeks following the operation. Patients were then instructed to practice weight bearing with a maximum of 30% body weight 4 weeks post-operation. Full weight bearing was permitted at the beginning of the 6th week post-operation.

*Outcome assessments*

Patients were assessed before and 6, 12, 24, and 60 months after the treatments. Primary outcomes were assessed by radiographic progression in the osteonecrotic stage, as well as pain, function, activity, and motion of the hip, which were measured and recorded with Harris hip score (HHS) [15]; secondary outcomes were evaluated by assessing the size of the osteonecrotic lesion in the femoral head. The study by Hernigou and Lambotte demonstrated a close correlation between the measurements of the necrotic volume in the femoral head based on the pathologic specimens and the necrotic volume (low signal intensity zone) in magnetic resonance images (MRIs) [16]; therefore, following the methods described by Steinberg et al. and Gangji et al. [12,17] in determining the osteonecrotic volume in the femoral head, we used an ImageJ image analysis software to measure the actual sizes of the necrotic lesion and the non-affected zone in the femoral head on each of the 20 transverse T1-weighted MRI slices with 3 mm slice thickness acquired with a 1.5 T PHILIPS Intera Achieva MRI Scanner, and then calculated the percent volume of the necrotic lesion (before the surgery) or the low signal intensity zone (LowSIZ [after surgical removal of the necrotic lesion]) of the femora head. All the preoperative and postoperative assessments were done by the authors who were unaware of the group assignment.

*Statistical analysis*

Data are presented as "mean" or "mean ± SEM". The significance of differences between the two treatment groups in terms of patient characteristics was examined using the $\chi^2$ test or the Fisher's exact test for categorical variables. Within each treatment group, significance of difference in the changes of HHS or percent osteonecrotic volume over the entire follow-up period between the groups divided by osteonecrotic stages was assessed using a one-way analysis of variance (ANOVA) followed by Tukey–Kramer multiple comparisons test. The significance of difference in the changes of HHS or the percent osteonecrotic volume in the femoral head over the entire follow-up period between two treatment groups with hips at the same ARCO stage or two groups of hips at different stages but within the same treatment was tested with two-way ANOVA. An unpaired *t* test was used to examine the difference in HHS or percent volume of necrotic lesion/LowSIZ of the femoral head, or in the percent change against the preoperative baseline level between the two treatment groups, a *P*-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using GraphPad Prism software (Version 5.0).

## Results

*Patients*

Between May 2004 and July 2006, 100 patients with 104 hips affected by ONFH enrolled in the current study. These patients were randomly assigned to the CD (50 patients/51 hips) and BMMSC (50 patients/53 hips) treatment groups. Follow-up assessments were performed 6, 12, 24, and 60 months post-operation. Seven patients (7 hips) in the CD treatment group did not complete the follow-up examinations because of family relocation, whereas all patients in the BMMSC treatment group completed their follow-ups (Fig. 1). The demographic data of the patients were recorded during the preoperative visit. Patients in the two treatment groups were statistically comparable in age, sex, and osteonecrotic stages (Table 1).

**Table 1**
Baseline characteristics of the patients.

| | CD group | BMMSC group | *P* value |
|---|---|---|---|
| Age — yr | | | |
| Range | 18–53 | 18–53 | N/A |
| Mean | 33.8 ± 7.70 | 32.7 ± 10.5 | 0.552 |
| Female sex — no. (%) | 24 (48%) | 23 (46%) | 1.000 |
| Risk factors — patients/hips | | | |
| Trauma | 12/12 | 8/8 | 0.469 |
| Corticosteroid use | 13/13 | 10/11 | 0.647 |
| Alcohol abuse | 7/8 | 11/11 | 0.449 |
| Caisson disease | 5/5 | 5/6 | 1.258 |
| Idiopathic | 13/13 | 16/17 | 0.677 |
| ARCO stage — patients/hips | | | |
| IC | 2/2† | 3/3* | 1.000 |
| IIA | 15/15 | 15/15 | 1.165 |
| IIB | 22/22 | 23/24 | 1.000 |
| IIC | 12/12† | 10/11* | 0.815 |

* or †, Two hips of the same patient were preoperatively classified as stage IC and IIC, respectively.

*Primary outcomes*

Sixty months after the initial surgeries, 10 of the 44 CD-treated hips had progressed to stage III or IV ONFH, whereas only 2 of the 53 BMMSC-treated hips had progressed to stage III, demonstrating that BMMSC treatment significantly protected the treated hips from progressing to higher osteonecrotic stages ($P<0.05$, as examined by Fisher's Exact Test). Of the ten CD-treated hips, 5 hips that progressed to ARCO stage III or IV underwent total hip replacement, including 1 case before 36 months post-operation, 2 cases between 36 and 48 months, and 2 cases between the 48 and 60 months post-operation; the other five hips that progressed to ARCO stage III had vascularized bone grafting, including 3 cases before 36 months, 1 case between 36 and 48 months, and 1 case between 48 and 60 months post-operation. In contrast, no total hip replacement was needed in BMMSC-treated hips, wherein the two hips, which progressed from IIA to IIIA or IIC to IIIC, respectively, underwent vascularized bone grafting between 24 and 36 months after the initial surgeries (Fig. 3, survivorship curves). Over the 60-month postoperative period, statistically improved HHS was found in CD- and BMMSC-treated hips except for the CD-treated hips that were preoperatively classified as stage IC (Fig. 4, upper panel), demonstrating the efficacy of both treatments against early stage ONFH. Compared with CD treatment, BMMSC treatment contributed to greater improvement of HHS in hips of Stages IC ($P<0.01$), IIA ($P=0.06$), IIB ($P<0.01$), and IIC ($P=0.02$) (Fig. 4). As results, the mean HHS of BMMSC-treated hips of each stage, which was assessed 60 months after the initial surgery, was statistically higher than that of CD-treated hips (Fig. 4, upper panel). Specifically, the percent increase in HHS assessed at the 60-month follow-up against the preoperative baseline (identified as "0 month" in Fig. 4) in BMMSC-treated hips preoperatively classified as stage IIB or IIC was statistically greater than that of the corresponding CD-treated hips (Stage IIB, 129.0% *vs.* 104.1%, $P<0.05$; Stage IIC, 109.9% *vs.* 79.1%, $P<0.05$, tested by unpaired *t* tests).

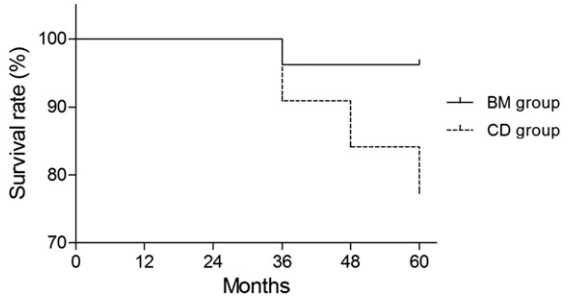


**Fig. 3.** Survivorship curve for the BMMSC treatment group (solid line) and the CD treatment group (dashed line).

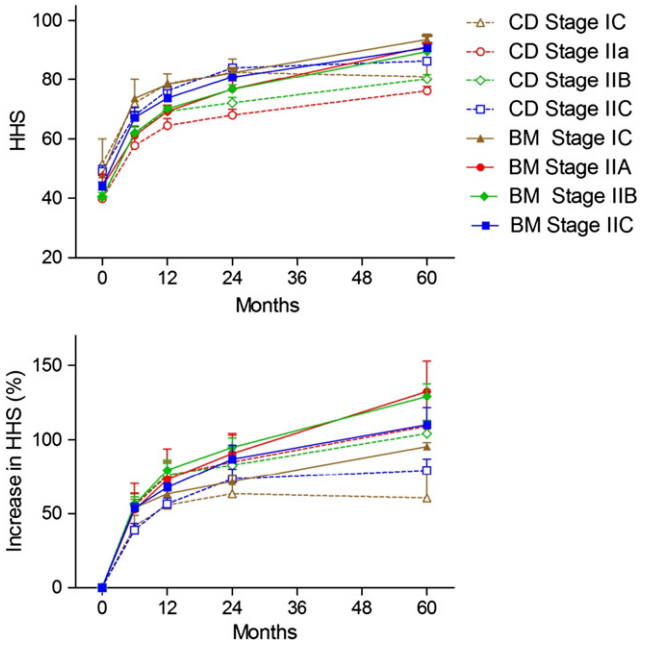


**Fig. 4.** Changes of HHS (top panel) and the percent increase of HHS (lower panel) in each treatment group over the entire postoperative period.

*Secondary outcomes*

Quantitative volumetric measurements remain the most reliable method to determine the true size of a three-dimensional osteonecrotic lesion in the femoral head [18].In the present study, MRI examination was performed before and 6, 12, 24, and 60 months after the surgery, and the volume of the necrotic lesion or LowSIZ in the femoral head was measured following the methods described by Steinberg et al. and Gangji et al. [12,17] and expressed as the percent necrotic volume of the femoral head (before the surgery) or percent LowSIZ volume of the femoral head (after the surgical removal of the necrotic lesion). Sixty months after the initial surgery, statistically decreased LowSIZ volumes in the femoral head were found in both treatment groups, except the CD-treated hips preoperatively classified as stage IIA. Over this postoperative period, BMMSC treatment greatly decreased LowSIZ volume in the femoral head of the hips at each preoperative stage, compared with CD treatment (Fig. 4C, stage IC, $P=0.014$; stage IIA, $P=0.06$; stage IIB, $P<0.001$; and stage IIC, $P<0.001$). Among the hips at advanced osteonecrotic stages such as IIB and IIC, statistically greater percent decrease in the LowSIZ volume was found in the BMMSC-treated hips compared with CD-treated hips (Fig. 5, lower panel, $P<0.001$, respectively). Accordingly, the remaining volume of LowSIZ in BMMSC-treated hips was significantly smaller than that of the CD-treated hips at stage IIB (6.5% *versus* 13.3%, $P<0.001$) or IIC (13.8% *versus* 29.3%, $P<0.001$). Within the BMMSC treatment group, the percent decrease in the volume of LowSIZ in the femoral head was greater in the hips of stage IIB or IIC than that of the hips at stage IIA (Fig. 5, lower panel, $P<0.001$ or $P=0.046$, respectively). As shown in the left panels of Figs. 6A, C, E, and G, BMMSC treatment constantly decreased the volume of LowSIZ in the femoral head. In contrast, in many CD-treated hips, apparent decreases in the LowSIZ volume were found only during the first 24 months post-operation, after which the LowSIZ remained no change or increased over time (Fig. 6, right panels).

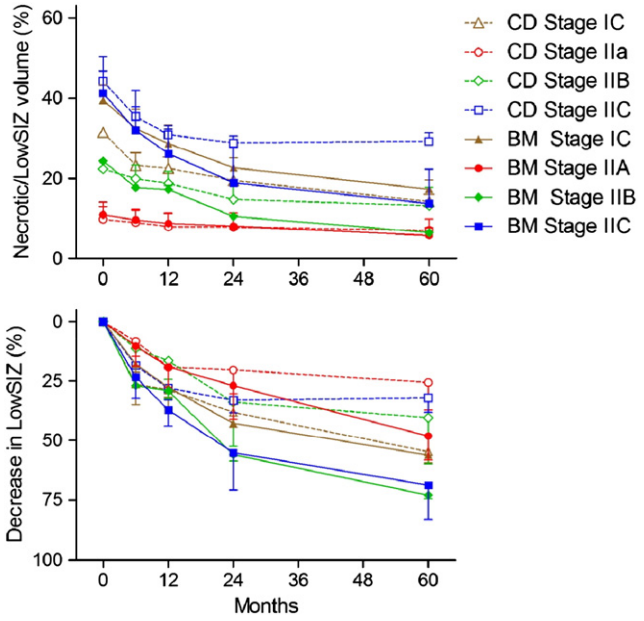


**Fig. 5.** Changes of the percent volume of the low signal intensity zone (LowSIZ) in the femoral head and percent decrease in the LowSIZ volume in each treatment group.

*Complications*

No complications were observed during the administration of anesthesia or after the operation in patients from the two treatment groups.

## Discussion

The current study demonstrates that autologous implantation of cultured BMMSCs into the femoral head is a safe and effective treatment against early-stage ONFH. Compared with CD treatment, BMMSC implantation can significantly decrease the pain and other joint symptoms caused by osteonecrosis and delay or avoid the progress of this disease towards higher osteonecrotic stages or collapse of the femoral head, which may necessitate additional surgeries including total hip replacement.

Theoretically, the necrotic bone can be repaired by the bone progenitor cells in the femoral head. However, osteonecrotic changes in the femoral head can decrease the number of bone progenitor cells in the uninvolved part in the femoral head [19]. Based on the fact that the stromal component of the red bone marrow is the source of osteogenic precursor cells [20], promising results have been achieved in a number of studies undertaken to assess the efficacy and safety of autologous implantation of bone marrow mononuclear cells into the necrotic zone in the femoral head [11,12,21]. According to their protocols, surgical procedures were performed to aspirate several hundred milliliters of bone marrow from the anterior iliac crest. Subsequently, the bone marrow mononuclear cells were isolated and concentrated into a final volume of about 50 mL containing several tens of thousands of stem cells in terms of fibroblast colony-forming units for implantation in to the femoral head [11,12,21]. In the present study, about 10 mL of bone marrow from the subtrochanteric region were directly aspirated once the decompression tunnel was established in the surgery, abandoning the procedures for bone marrow aspiration from the iliac crest. Expansion of autologous BMMSCs *ex vivo* allowed the harvesting of sufficient amounts of cultured BMMSCs within two weeks and preparation about $2\times10^6$ BMMSCs for FH implantation, which was much greater than the number of implanted bone marrow stem cells per FH reported by other researchers [11,12,21]. Recent findings demonstrated an increase in the level of vascular endothelial growth factor in hematoma [22],

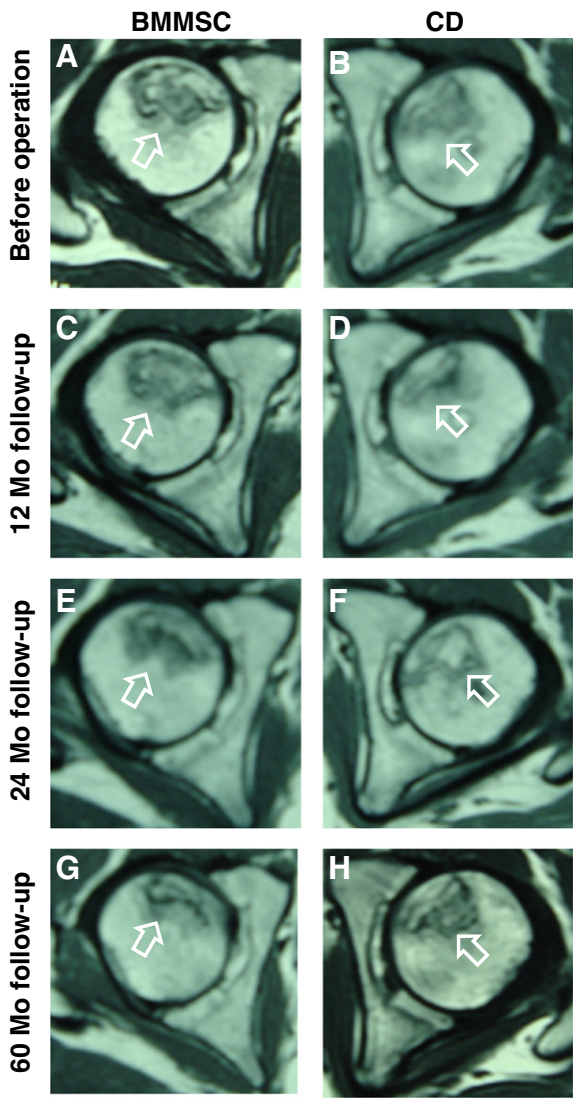


**Fig. 6.** Transversal T1-weighted magnetic resonance images of two femoral heads. The left panels (A, C, E, and G) were from a hip treated with BMMSC transplantation, the right panels (B, D, F, and H) were from a hip treated with core decompression. Arrows indicate the necrotic lesions.

which could promote angiogenesis and osteogenesis of mesenchymal stem cells [22,23]. Therefore, we speculate that the organization of hematoma in the plugged decompression tunnel and the cavity of the cleaned necrotic site provides not only an ideal reservoir with which to retain the implanted BMMSCs, but also an optical microenvironment to promote the differentiation of the BMMSCs, which contributes to the repair and revascularization of the femoral head. Recent findings by Feng et al. also associated decreased number of circulating endothelial progenitor cells with osteonecrosis of the femoral head [24], suggesting a negative influence in angiogenesis and vascular repair in the affected femoral head; however, such condition could be compensated by the implantation of BMMSCs into the femoral head since bone marrow mesenchymal stem cells were found to differentiate into endothelial cells both *in vitro* and *in vivo* [25,26].

The size and location of the necrotic lesion are considered to be the most important prognostic factors [6–10]. According to our experience, a navigation system can offer the surgeons not only 3-dimensional mapping of the anatomical features but also virtual real-time imaging, guiding the trephine on the way towards the necrotic lesion without malpositions, and simultaneously reducing

intraoperative fluoroscopic time. However, a number of problems exist with the navigation system, including a relatively low level of image resolution as well as a relatively high acquisition cost. Therefore, MRI examination remains an effective way in determining the size and location of a necrotic lesion in the femoral head with a relatively high resolution, ensuring a thorough curettage and evacuation of the necrotic lesion. We propose since successful repair of the necrotic damage in the femoral head can result in constant alleviation of pain and amelioration of the function, activity, and motion of the hip, as well as a constant decrease in the volume of the LowSIZ crucially, it should be considered a factor that predicts the clinical outcomes of this disease. Such a proposal could be supported by the most recent findings of Hernigou and colleagues, who had followed up 342 patients with 534 hips at osteonecrotic stage I or II according to the Steinberg classification [17] for 8 to 18 years after autologous bone marrow grafting [13]. During the most recent follow-up, a mean HHS of 88 points (improved from a mean preoperative HHS of 70 points) was exhibited in 440 hips that did not need total hip replacement, of which 69 hips preoperatively classified as stage I exhibited total resolution of osteonecrosis and the other 371 hips only exhibited a mean volume of 12 $cm^3$ (decreased from a mean preoperative volume of 26 $cm^3$) of LowSIZ without a marginal band-like pattern on T1-weighted MRIs [13]. Given the fact that the femoral head has an average volume of 60 $cm^3$, the 12 $cm^3$ LowSIZ could be estimated to be 20% in volume of the femoral head [11]. Therefore, this large sample study suggests that the reconstructive repair is a slow process, taking at least 8 years to improve the HHS to a mean of 88 points and to decrease the percent volume of LowSIZ to a mean of 20% of the femoral head. In the present study, the mean HHS of the BMMSC-treated hips was increased to 88 points and the percent LowSIZ volume of the femoral head was decreased to a mean of 15% at 60 months post-operation, suggesting a rapid reconstructive repair process promoted by BMMSC implantation, which predicts an optimistic outcome. As demonstrated in Fig. 3, for example, LowSIZ remains in the BMMSC-treated hip 60 months after the initial surgery (Fig. 6G); therefore, follow-up examination will be continued and updates especially about the complete healing of the affected hips in the BMMSC treatment group will be reported in the future.

## Conclusions

In summary, obtaining a significantly larger number of BMMSCs through *ex vivo* expansion of autologous BMMSCs from a relatively small volume of subtrochanteric bone marrow aspirated through the core decompression tunnel is a safe, reliable, and highly effective procedure. The present study demonstrates the efficacy and safety of autologous implantation of *ex vivo* expanded BMMSCs into the femoral head for the treatment of early-stage ONFH.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.bone.2011.11.002.

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