Original Article Clinics in Orthopedic Surgery 2024;16:702-710 • https://doi.org/10.4055/cios23344

Tissue-Engineered Bone Regeneration for Medium-to-Large Osteonecrosis of the Femoral Head in the Weight-Bearing Portion: An Observational Study

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Background: Stem cell therapy for the treatment of osteonecrosis of the femoral head (ONFH) showed promising outcomes. However, ONFH with a large lesion in the weight-bearing portion is a poor prognostic factor and still challenging issue to be solved. We aimed to evaluate the effect of tissue-engineered bone regeneration for this challenging condition to preserve the femoral head.

Methods: A total of 7 patients (9 hips) with ONFH who received osteoblasts expanded *ex vivo* from bone marrow-derived mesenchymal stem cells (BMdMSCs) and calcium metaphosphate (CMP) as scaffolds from March 2002 to March 2004 were retrospectively reviewed. The median age was 27.0 years (interquartile range [IQR], 23.0–34.0 years), and the median follow-up period was 20.0 years (IQR, 11.0–20.0 years). After culture and expansion of stem cells, we performed core decompression with BMdMSC implantation at a median number of 10.1 $\times 10^7$ (IQR, 9.9–10.9 $\times 10^7$). To evaluate radiographic outcomes, the Association Research Circulation Osseous (ARCO) classifications, the Japanese Investigation Committee (JIC) classification, and modified Kerboul combined necrotic angle (mKCNA) were evaluated preoperatively and during follow-up. Clinical outcomes were evaluated by a visual analog scale (VAS) and Harris Hip Score (HHS).

Results: The preoperative stage of ONFH was ARCO 2 in 5 hips and ARCO 3a in 4 hips. The ARCO staging was maintained in 3 hips of ARCO 2 and 4 hips of ARCO 3a. Two hips of ARCO 2 with radiographic progression underwent total hip arthroplasty. According to mKCNA, 2 hips showed medium lesions, and 7 hips showed large lesions. The size of necrotic lesion was decreased in 4 hips (2 were ARCO 2 and 2 were ARCO 3a). There were no significant changes in JIC classification in all hips (type C1: 3 hips and type C2: 6 hips) ($p = 0.655$). Clinically, there were no significant changes in the VAS and HHS between preoperative and last follow-up ($p = 0.072$ and $p = 0.635$, respectively).

Conclusions: Tissue engineering technique using osteoblasts expanded *ex vivo* from BMdMSC and CMP showed promising outcomes for the treatment of pre-collapsed and early-collapsed stage ONFH with medium-to-large size, mainly located in weight-bearing areas.

Keywords: *Femoral head, Osteonecrosis, Osteoblast, Stem cell, Tissue engineered*

Received November 1, 2023; Revised March 30, 2024; Accepted May 17, 2024
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Osteonecrosis of the femoral head (ONFH) involves blood supply disruption, which can lead to subchondral bone fracture, subsequent collapse of the femoral head, and painful disabling arthrosis.[1,2] Although total hip arthroplasty (THA) shows promising results, various complications including osteolysis or bearing-related complications have been reported.[3,4] Most affected patients are young and a long-term follow-up is required.[5] Therefore, the preservation of the native hip articulation is important.

There have been various surgical options introduced that focus on early interventions for ONFH to preserve the femoral head.[2,6-8] The joint preserving procedures include core decompression (CD) with or without autologous bone marrow-derived mesenchymal stem cell (BMdMSC) implantation, vascularized bone graft, and osteotomy. However, the prognosis of ONFH is usually influenced by the stage, size, and location of the necrotic lesion regardless of the various treatment methods.[1,2,9-11] In general, large and lateral-located in the weight-bearing portion and post-collapsed lesions are poor prognostic factors of ONFH and remain still challenging for surgeons worldwide. CD alone is only indicated for the treatment of small- to medium-sized pre-collapsed stage of ONFH.[12] Vascularized fibular or iliac bone graft had been reported to have a successful outcome in patients with advanced ONFH.[13-15] However, it requires long operation time and is technically demanding. Furthermore, it has several complications such as donor site morbidities. Trans-trochanteric curved varus osteotomy or trans-trochanteric anterior or posterior rotational osteotomy revealed similar results compared with vascularized bone graft.[16] However, these procedures have a limited indication and are difficult to perform. Therefore, the importance of procedures to prevent femoral head collapse less invasively and time-efficiently with a low complication rate and a short rehabilitation period is emphasized.

Currently, an increasing number of studies have focused on stem cell therapy for the treatment of ONFH.[17-23] Hernigou et al.[24] demonstrated that the number of MSCs in the bone marrow of the ONFH patients decreased and suggested that ONFH may involve the MSC. Another study also study showed that the capacity of osteoblasts decreased in ONFH patients.[25] These findings were the basis for the idea that implantation of MSCs into necrotic lesions could be a useful treatment option for the treatment of ONFH. Since the first application of CD combined with autologous bone marrow aspirate injection for treating ONFH in 1993, many clinical studies have reported promising results of various kinds of stem cell therapy for the early stage ONFH.[19,26,27] On the other hand, some studies reported the effect of stem cell therapy for the early stage ONFH is uncertain.[28-30] These various results may be due to high heterogeneity among studies, and there is no consensus as to the ideal patient and efficacy of stem cell therapy. Furthermore, the long-term outcomes of stem cell therapy for large and lateral-located ONFH lesions have not been investigated.

Therefore, we tried the tissue engineering technique using osteoblasts expanded *ex vivo* from BMdMSCs and calcium metaphosphate (CMP) as a scaffold to regenerate bone to prevent collapse of pre-collapsed (Association Research Circulation Osseous [ARCO] 2) and early stage (ARCO 3a) ONFH with medium-to-large size, mainly located in weight-bearing areas.

METHODS

The Institutional Review Board of Kyungpook National University Hospital approved this study (IRB No. KNUH-2022-06-009-001), and informed consent was obtained from all patients.

Patients

We retrospectively reviewed patients with ONFH who received osteoblasts expanded *ex vivo* from BMdMSCs and CMP from March 2002 to March 2004. The diagnosis of ONFH was based on anteroposterior and frog-leg lateral x-rays of the bilateral hip, computed tomography, and magnetic resonance imaging (MRI) for each case. The inclusion criteria were as follows: (1) patients aged 18 years or older and (2) voluntary agreement to participate in this study. The following exclusion criteria were applied: (1)

contraindication to undergoing an MRI, (2) positive serological test for human immunodeficiency virus, hepatitis B, or hepatitis C, and (3) incomplete follow-up data. Eventually, a total of 7 consecutive patients (9 hips) were prospectively enrolled in this study and retrospectively reviewed. Five patients (5 hips) had unilateral procedures and 2 patients (4 hips) had bilateral procedures. The median age was 27.0 years (interquartile range [IQR], 23.0–34.0 years), and the median follow-up period was 20.0 years (IQR, 11.0–20.0 years).

Bone Marrow Collection and Autologous Osteoblast Culture

All patients who participated in the study had their first visit to collect bone marrow before main operation. Approximately 10 mL of bone marrow was aspirated from the anterosuperior iliac spine and mononuclear cells were collected. The bone marrow was spun through Histopaque (Sigma) gradient centrifugation. After centrifugation, bone marrow mononuclear cells were collected and then washed twice with phosphate-buffered saline, pH 7.4. The bone marrow mononuclear cells were suspended in α-minimum essential medium (MEM) containing 10% fetal bovine serum (FBS) (Invitrogen) and incubated at 37 ℃ in a humidified atmosphere of 5% CO_2 for 12 hours. Non-adherent cells were removed and adherent cells were cultured and expanded for further experiments. The BMdMSCs under the passage 3 were used in the following experiments. To induce osteoblastic differentiation, the BMdMSCs were cultured in an osteogenic medium (α-MEM supplemented with 10% FBS, 50 μg/mL α-ascorbic acid, 10 mm β-glycerophosphate and 100 nm dexamethasone, and antibiotics) for 7 days. The culture medium was changed every other day. These cells were expanded and differentiated to osteoblasts for totally 2–4 weeks *ex vivo*. Porous bead-form scaffolds were made of CMP and cells were seeded in an average density of 1.2 million/mL^3 into 20 to 30 beads for 1 hour in a clean bench room. The median value of final obtained stem cell count was 10.1 $\times 10^7$ (IQR, 9.9–10.9 $\times 10^7$). CMP was used as a scaffold for the following rationales: (1) adherence of osteoblast with osteoconductive effect has been proven to be excellent, (2) support the differentiation of BMdMSCs to osteoblast, (3) induction of osteoblast-related genes, and (4) prevention of systemic adverse effects of osteoblasts. Schematic drawings of the process are shown in Fig. 1 and details are described in our previous study.[31]

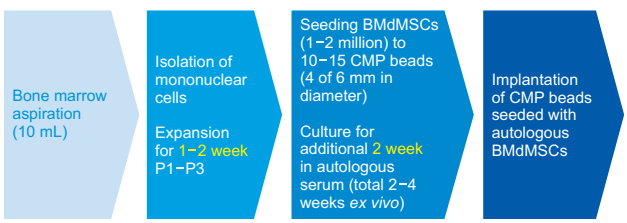

Fig. 1. Schematic drawing of preparation for autologous bone marrow-derived osteoblast implantation. BMdMSC: bone marrow-derived mesenchymal stem cell, CMP: calcium metaphosphate.

CD with Autologous Bone Marrow-Derived Osteoblast Implantation

Patients were placed on a table with image intensifiers with a C-arm after anesthesia. First, we determined the size and location of the necrotic lesion. Preoperative MRI images were used together with the image intensifier views to confirm the site of the necrotic lesion. Then, under the fluoroscopic guidance, a skin incision was made and a guide pin was inserted for CD. A 10- to 12-mm diameter core tract was made from the lateral cortex at the distal portion of the greater trochanteric ridge into the center of the necrotic lesion. Under the control of the C-arm image intensifier, images from various angles were obtained and compared with MRI images to improve targeting accuracy. The necrotic area was curetted using a low-speed burr and a curved curette. Curettage was performed for necrotic bone removal and the area was cleaned. Curettage was performed as much as possible until about 0.5 cm of subchondral bone remained on the C-arm. We proceeded slowly and carefully to avoid penetration of the femoral head; as a result, a mushroom-like empty space was created. Next, the CMP beads with adhering osteoblasts were implanted through the core tract and the tract was blocked

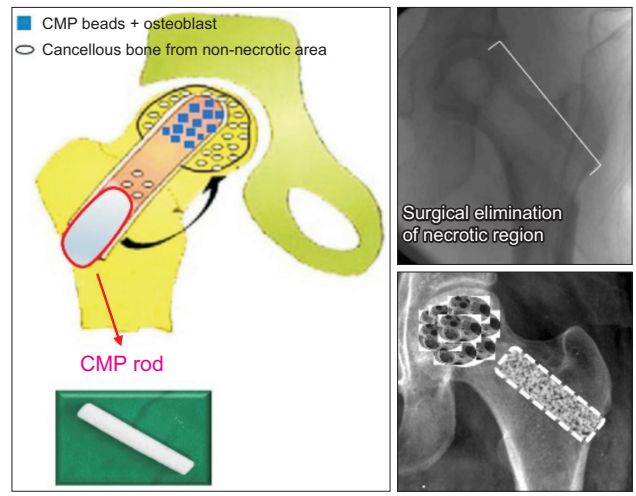

Fig. 2. A mixture of cancellous bone from a non-necrotic area, osteoblast, and calcium metaphosphate (CMP) was implanted into the lesion and in the distal portion of the tunnel. A CMP rod was inserted.

with a same diameter CMP rod (Fig. 2). No prophylaxis for deep vein thrombosis was done in any patients. Partial weight-bearing with a walker or crutches was performed after 3 weeks and full weight-bearing was permitted after 6 weeks postoperatively.

Radiological and Clinical Evaluation

For radiological evaluation, anteroposterior and frog-leg lateral view radiographs were taken at baseline and each follow-up (at every 3 months until 1 year, every 6 months until 3 years, and every year after 3 years). MRI follow-up studies were performed at intervals of at least 3 years, depending on the patient's circumstances. Radiological progression of ONFH was measured by reference to the 2019 revised ARCO staging system.[32] Regarding the location of the necrotic lesion, we used Japanese Investigation Committee (JIC) classification, which is based on the mid-coronal T1-weighted MRI of the femoral head.[11] In the JIC classification, necrotic lesions were classified into 4 types: (1) type A (< medial 1/3 of the weight-bearing portion), (2) type B (< medial 2/3 of the weight-bearing portion), (3) type C1 (> medial 2/3 of the weight-bearing portion but not extending laterally to the acetabular edge), and (4) type C2 (extending laterally to the acetabular edge). In addition, the modified Kerboul combined necrotic angle (mKCNA) that measures the necrotic arc on the mid-coronal and mid-sagittal MRI was used to evaluate the size of the necrotic lesion.[9] The necrotic lesions are classified into 3 categories: (1) small lesion (mKCNA < 190°), (2) medium lesion (mKCNA between 190° and 240°), and (3) large lesion (mKCNA > 240°). All radiographic parameters were measured and recorded by 2 authors not involved in demographic data acquisition (SYK and SHB). Regarding mKCNA, the intraclass correlation coefficient was 0.92 for interobserver reliability and 0.88 for interobserver reliability. Regarding ARCO staging and JIC classification, there were perfect intra- and interobserver agreements. For clinical evaluation, patients were asked regarding pain or disability or adverse events at each follow-up. A visual analog scale (VAS) and modified Harris Hip Score (HHS) were evaluated preoperatively and at the last follow-up. When the treatment had been insufficient in controlling pain or disability, we discussed with the patient about THA conversion. The final decision was made according to the patient's own wishes.

Statistical Analysis

We did nonparametric test and compared the pre- and postoperative variables that included ARCO staging, JIC classification, mKCNA, VAS, and HHS using Wilcoxon signed-rank tests. The p-values < 0.05 were considered statistically significant. Statistical analyses were conducted using the IBM SPSS version 26.0 software (IBM Corp.).

RESULTS

Table 1 shows descriptive data of 9 hips. The preoperative stage of ONFH was ARCO 2 in 5 hips and ARCO 3a in 4 hips. The ARCO staging was maintained in 3 of 5 hips with ARCO 2 (60%) and 4 of 5 hips with ARCO 3a (80%).

Table 1. Characteristics and Descriptive Data of 9 Hips

Case	Age/sex	Cell count ($\times 10^7$)	Follow-up period (yr)	Preoperative			Last follow-up			Conversion to arthroplasty
				ARCO stage	JIC classification	mKCNA	ARCO stage	JIC classification	mKCNA	
1	16/F	10.2	20	3a	C1	200	3a	C1	175	No
2	37/M	10.1	6	2	C2	320	3b	C2	360	Yes
3	23/M	11.4	20	3a	C2	290	3a	C2	285	No
4	23/M	9.9	20	3a	C2	300	3a	C2	290	No
5	35/M	11.0	4	2	C2	320	3b	C2	350	Yes
6	23/F	10.9	16	3a	C2	310	3a	C2	300	No
7	33/M	9.6	16	2	C1	250	2	C1	220	No
8	27/M	9.8	20	2	C2	250	2	C2	220	No
9	27/M	10.0	20	2	C1	230	2	C1	200	No

ARCO: Association Research Circulation Osseous, JIC: Japanese Investigation Committee, mKCNA: modified Kerboul combined necrotic angle.

The femoral head collapse was progressed in 2 of 9 hips (22%). In those with ARCO 2, 2 of 5 hips collapsed while no hip collapsed in those with ARCO 3a. There were no significant changes in JIC classification in all hips (type C1: 3 hips and type C2: 6 hips) (p = 0.655). Three hips with JIC type C1 maintained their preoperative ARCO stage at the final follow-up. Among the 6 hips with JIC type C2, 4 hips maintained their preoperative ARCO stage, 2 hips progressed to ARCO stage 3b, which were converted to THA.

According to the mKCNA, 2 hips showed medium lesions, and 7 hips showed large lesions. The median mKCNA was 290.0° (IQR, 240.0°–315.0°) preoperatively and 285.0° (IQR, 210.0°–325.0°) at the last follow-up. These changes showed no significant differences (p = 0.402). The mKCNA decreased more than 20° in 4 hips, among which 2 were ARCO 2 and 2 were ARCO 3a. Of the 7 hips with large necrotic lesions, necrotic size was decreased in 2 hips, maintained in 3 hips, and increased in 2 hips.

Regarding clinical outcomes, the VAS changed from 4 (IQR, 2.75–7) at baseline to 2 (IQR, 1–3) at the final follow-up without significant change (p = 0.072). The HHS changed from 83.0 (IQR, 76.0–87.0) preoperatively to 88.0 (IQR, 76.0–90.0) at the final follow-up. However, no significant change was found (p = 0.635). THA conversion was performed in 2 hips with increased mKCNA and intolerable pain by the request of the patients. All cases of THA conversion had large lesions with JIC type C2. No surgery-related complications were documented.

Illustrative Case 1

A 16-year-old female patient had a femoral neck fracture in the left hip 3 years ago and underwent conventional hip screw fixation. Two years ago, she underwent removal of an internal device. At the initial visit of our hospital, March 2002, she complained of left hip joint pain. The patient was evaluated with MRI, and ARCO stage 3a and JIC type C1 of ONFH was diagnosed. The mKCNA was 200°. Surgery was performed by our own method under general anesthesia. At the 20-year follow-up, the patient showed satisfactory outcomes of decreased mKCNA of 175° without any evidence of collapse (Fig. 3).

Illustrative Case 2

A 23-year-old male patient complained of bilateral hip joint pain that was noticed 6 months before first visit. the symptom was aggravated during motion and relieved

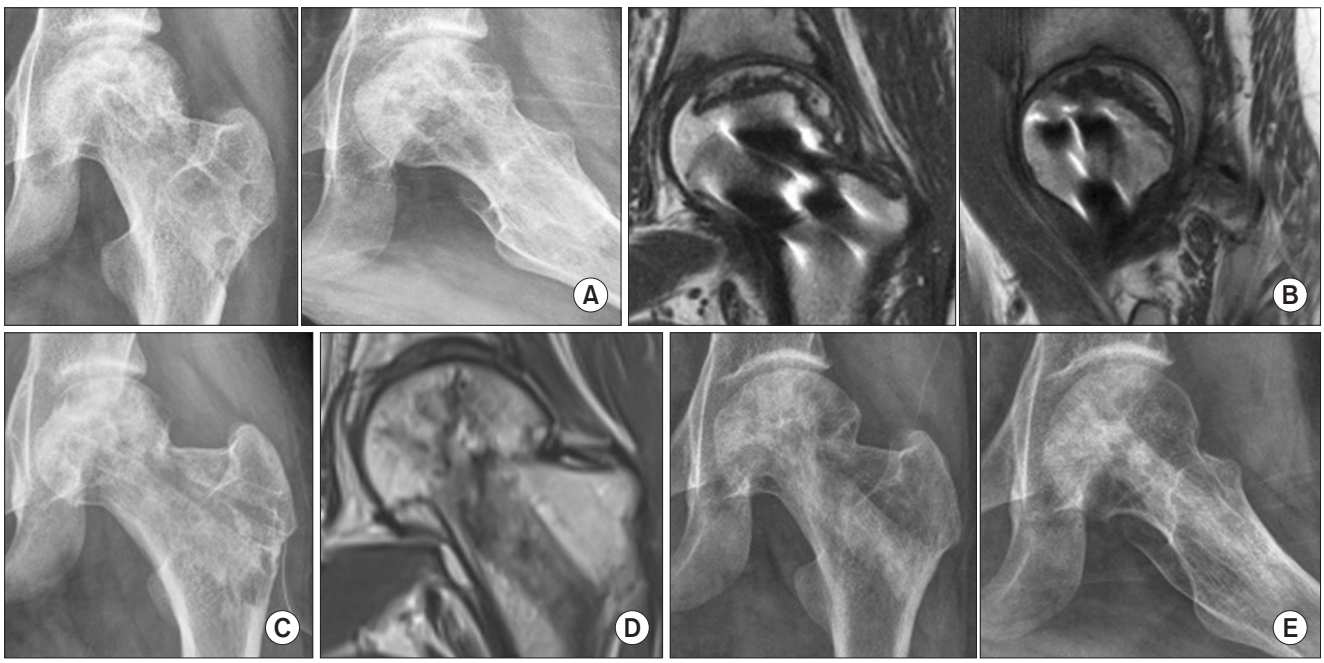

Fig. 3. Illustrative case 1. (A) Anteroposterior and frog-leg lateral radiographs showed a necrotic lesion in the left femoral head. (B) Mid-coronal and mid-sagittal views of T1-weighted magnetic resonance imaging (MRI) suggested osteonecrosis of the femoral head with Association Research Circulation Osseous (ARCO) stage 3a, Japanese Investigation Committee type C1, and the modified Kerboul combined necrotic angle of 200°. (C) Immediate postoperative radiographs. (D) At 20-year follow-up, T1-weighted MRI showed decreased size of the necrotic lesion and maintained ARCO staging. (E) At 20-year follow-up, satisfying radiographic results were obtained with partial regeneration of the femoral head.

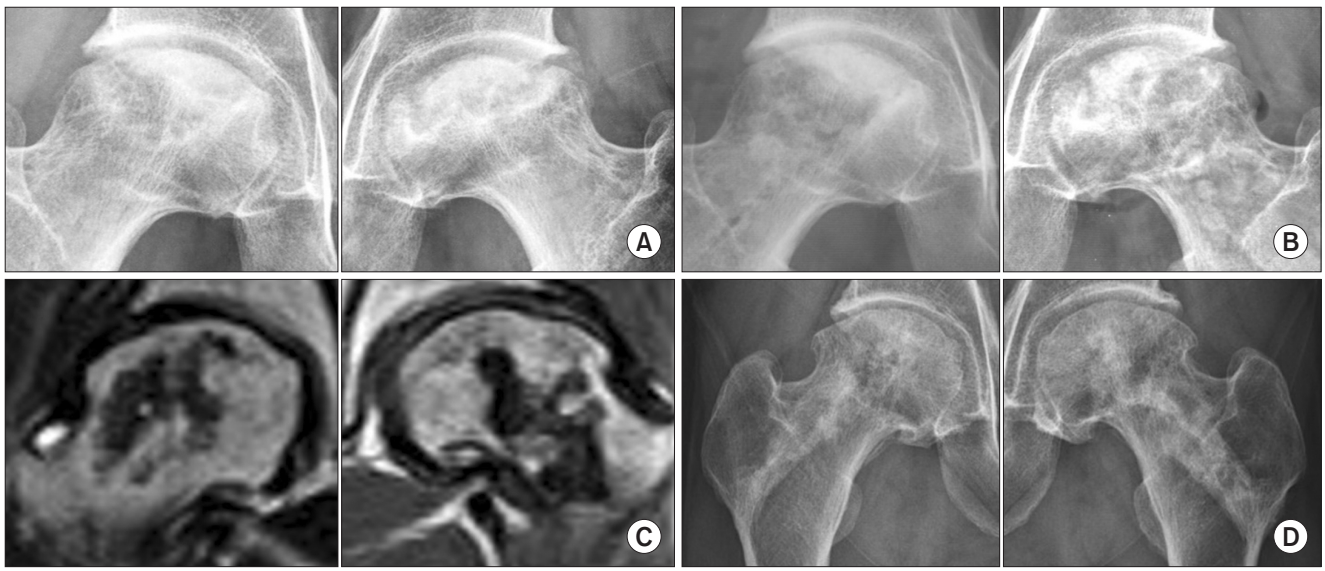

Fig. 4. Illustrative case 2. (A) Anteroposterior radiographs showed necrotic lesions in the bilateral femoral heads and suggested osteonecrosis of the femoral head with Association Research Circulation Osseous (ARCO) stage 3a and Japanese Investigation Committee type C2. (B) Immediate postoperative radiographs of the bilateral femoral heads. (C) At 12 years postoperatively, the mid-coronal view of T1-weighted magnetic resonance imaging showed maintained ARCO staging without further progression of the subchondral fracture or femoral head depression. (D) At 20-year follow-up, satisfying radiographic results were obtained without clinical discomfort.

at rest. He had a long-term history of steroid use for the treatment of ulcerative colitis. He underwent multiple drilling on the right hip and CD on the left hip 2 years ago. Radiographs of the hip joints were checked and osteolytic lesions of the femoral head were observed. The patient was evaluated with MRI and the T1-weighted images showed the characteristic necrotic lesions in the both femoral heads. Based on these findings, he was diagnosed with ARCO stage 3a and JIC type C2 of bilateral ONFH. The mKCNA was 290° on the right side and 300° on the left side. Surgery was performed by our own method under general anesthesia. In MRI performed 12 years after surgery, it was observed that the necrotic lesions and the collapse of subchondral bone did not progress. At the 20-year follow-up, ARCO staging, JIC classification, and mKCNA were maintained with satisfactory clinical outcomes (Fig. 4).

DISCUSSION

The current study demonstrated that the tissue engineering technique using osteoblasts expanded *ex vivo* from BMdMSC and CMP showed reliable outcomes for the treatment of pre-collapsed and early-collapsed stage ONFH with medium-to-large size, mainly located in weight-bearing areas. However, ONFH with large and JIC type C2 lesions still has been challenging to treat and needs to have close attention.

Recently, there have been several studies that focused on stem cell therapies as a strategy for the treatment of ONFH, and promising results have been reported.[17-22] However, long-term clinical and radiologic outcomes are not clear and remain controversial.[28-30,33] As of yet, there was no large-scale prospective randomized control trial to investigate the effect of stem cells on the treatment of ONFH with a long-term follow-up. Furthermore, due to the high heterogeneity among the studies, it is difficult to standardize the stem cell implantation procedure and to determine optimal indications.

It is well known that the size and location of necrotic lesions are considered major determinants in the treatment of ONFH, predicting the prognosis of ONFH.[1,2,9,10] Various classification systems that characterize the size and location of the necrotic lesions have been introduced to predict the risk of collapse. In general, most large and lateral-located lesions have more progressive courses of femoral head collapse. Therefore, the treatment options should be determined according to the size and location of the necrotic lesions. Ha et al.[9] reported that there was a strong correlation between the mKCNA and the risk of femoral head collapse. Their study showed that 50% of medium lesions and all large lesions collapsed within 3 years from the diagnosis of ONFH. Compared with previous reports of Ha et al.,[9] the current study showed

promising outcomes of stem cell therapy. In our study, even with large and lateral-located necrotic lesions, effective outcomes were shown in 5 out of 7 hips. In addition, our study showed that the median mKCNA was decreased in 4 hips (2 hips with medium lesions and 2 hips with large lesions) and was maintained in 3 hips with large lesions. THA conversion was done only in 2 hips and these had mKCNA of 320°, which were expected to have a poor prognosis. Therefore, our tissue engineering technique performed for the treatment of ONFH with medium-to-large necrotic lesions demonstrated a collapse rate that was lower than that of natural course, and thus it can be considered to be effective.

JIC classification has shown a promising prognostic value in ONFH.[11] Several previous studies have reported the collapse rate of ONFH using the JIC classification system: JIC type C1 and C2 showed a high rate of femoral head collapse, especially JIC type C2.[10,34] Nishii et al.[10] reported that the collapse rate of JIC type B was 50% and that of JIC type C was 76%. In our study, all 2 hips that underwent THA had JIC type C2. Compared with Nishii et al.'s study,[10] the current study showed promising results of a stem cell therapy. However, care should be taken in interpreting our results as various factors such as age or ARCO staging that could affect the results were not controlled.

In this study, we could not observe differences between the preoperative and postoperative VAS and HHS outcome scores over the long-term follow-up. The patients included in our study were only ARCO 2 and 3a patients, and in most cases, our procedures were aimed to prevent the progression of the disease. Although immediate postoperative pain scores were increased, final follow-up scores were not significantly increased. We believe that the disease stage had not progressed in most cases and as a result, there was no significant difference in the clinical results. However, a relatively small patient pool could have masked the results; therefore, a large-scale study is needed.

The optimal number of transplanted stem cells is a major concern of stem cell therapy and needs to be investigated further. Although it is desirable to have a large number of transplanted MSCs due to their repair capacity, the maximum safe dose and optimal dose have not been determined. According to recent studies, the number of MSCs used ranges from 10^6 to 10^9, with 10^8 being the most common.[28,29,35] In the current study, the median value of the final obtained stem cell count was 10.1×10^7 (IQR, 9.9–10.9 $\times 10^7$). It is considered that the number of MSCs used in our study was comparable to that of other studies and did not adversely affect the results. Furthermore, the quality and purity of osteoblasts were reliable because they were cultured by an accredited institution. However, we cannot conclude the optimal dose or which lineage of stem cell is appropriate. Therefore, more researches are needed. Nonetheless, our study can be considered valuable because we conducted a long-term follow-up in relatively young patients with pre-collapsed and early-collapsed stage ONFH.

This study has several limitations. First, there was no strictly controlled group and it had a retrospective cohort with the single-center design. Second, the sample size was relatively small. Third, we did not analyze the relationship between symptoms and femoral head collapse. Forth, new bone regeneration and calcification of the inserted CMP bead and load could not be clearly distinguished. This is because it is only possible through biopsy. Fifth, although mKCNA is a good tool for measuring the necrotic area and predicting the prognosis, we did not perfectly measure the necrotic area quantitatively in 3 dimensions. However, classification of the lesions is more important than the volume of the necrotic area for the prognosis of the disease. Therefore, 3-dimensional analysis is not considered necessary. Lastly, we cannot assure that our results are due to the pure effect of stem cells. We performed CD with extensive curettage of the necrotic lesions in our own method. It is not known whether curettage was perfectly matched to the exact margin of the necrotic lesion. Also, there may be a structural effect by using a mixture of CMP rod as a scaffold. Therefore, a mixed effect may have affected the good results. Despite these limitations, the strength of our work is that this is the unique study showing the reliable effect of a tissue engineering technique using osteoblasts expanded *ex vivo* from BMdMSCs and CMP in our own method for the treatment of ONFH. Large cohort with long-term follow-up studies are necessary to determine the feasibility of the stem cell therapy for the treatment of challenging ONFH.

In conclusion, the tissue engineering technique using osteoblasts expanded *ex vivo* from BMdMSCs and CMP showed promising outcomes for the treatment of pre-collapsed and early-collapsed stage ONFH with medium-to-large size, mainly located in weight-bearing areas.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

This research was supported by the Korean Fund for

Regenerative Medicine (KFRM) grant funded by the Korea Government (the Ministry of Science and ICT, the Ministry of Health & Welfare), No. 22D0801L1 and No. 22C0604L1.

The study was presented at the ARCO 2022 meeting in Seoul, and we were invited to submit this original article to *Clinics in Orthopedic Surgery*.

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