Hip Preservation With Autologous Osteoblast Cell-Based Treatment in Osteonecrosis of the Femoral Head

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abstract

Osteonecrosis of the femoral head is a progressive disease that leads to femoral head collapse and secondary osteoarthritis if left untreated. Head preservation surgeries are notable for their inefficiency in providing a pain-free hip joint in cases with extensive involvement of the femoral head. This single-center study evaluated the effectiveness of autologous cultured osteoblast cells implanted after core decompression and debridement in 15 patients diagnosed with early osteonecrosis of the femoral head from 2010 to 2012. Overall mean follow-up was 51 months; the longest follow-up was 7 years in 3 patients. At 9 months after implant, all of the patients had resumed their normal routine activities. Reduction in pain and dependency on walking support was remarkable, and none of the patients required revision. The femoral joints were preserved structurally, and the joint biomechanics, strength, and function were regained. The use of autologous osteoblast cell implant is recommended for patients with early osteonecrosis. [*Orthopedics*. 2021;44(2):e183-e189.]

Osteonecrosis of the femoral head (ONFH) is a refractory disease characterized by compromised subchondral microcirculation, bone necrosis, and microfracture accumulation without sustained compensatory remodeling.[1] Its complex etiology, variability in location (lateral, medial, or central), intra-bone edema, and inflammation add to the unpredictable prognosis. Although few patients regress spontaneously, the progressive nature and lack of curative treatment for ONFH thus far are the challenges faced in the management of ONFH.

Osteonecrosis of the femoral head typically affects relatively young, active individuals between 20 and 40 years old and follows an unrelenting course resulting in substantial loss of function.[2] The Indian Society of Hip and Knee Surgeons' Registry stated that 49% of total hip arthroplasty procedures in India are due to an irreversible stage of ONFH.[3] Osteonecrosis of the femoral head is idiopathic in most cases. Steroid and alcohol consumption are the second most common causes.[4] The term "silent hip" refers to an asymptomatic hip in patients with ONFH of the contralateral hip and is at risk of developing ONFH.[5]

Hip and groin pain and limp when patients walk are primary indicators. Radiography, magnetic resonance imaging (MRI), and computed tomography are tools for diagnosis, prognosis, and decision-making regarding treatment of ONHF. Crescent formation, collapse and anterolateral sequestration on radiographs, and a double line presentation on T2-weighted MRI provide confirmation of ONFH diagnosis.

The Ficat and Arlet staging of ONFH from I to IV indicates the progressive involvement and progression of the femoral head toward arthritis.[6] However, it does not allow prediction of the possibility of progression. Ficat and Arlet stage I with

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Table 1
Patient Characteristics

Characteristic	Value
Sex, No.	
Male	13
Female	2
Etiology, No.	
Idiopathic	8
Steroid	5
Alcohol+steroid	1
Traumatic	1
Laterality, No.	
Unilateral	6
Bilateral	9
Association Research Circulation Osseous stage (hips), No.	
II	15
III	9
Follow-up	
Minimum, mo	18
Maximum, y	7

extensive involvement of the femoral head will have a high chance of further progression to collapse. Steinberg grades of ONFH allow prediction of the possibility of progression to collapse in a precollapse hip.[7] The Association Research Circulation Osseous (ARCO) takes into consideration the location of the crescent, amount of cartilage depression, and the area and volume of the femoral head affected as reliable predictors of prognosis in early stage ONFH and is helpful for identifying a femoral head at risk of progression and collapse.[8]

The most common surgical intervention in early stage ONFH is core decompression.[9] However, core decompression is notable for its lack of effectivity in preventing collapse in cases where progression is most likely to happen (ie, in cases where there is extensive involvement [more than 30%] of the anterolateral region of the femoral head and crescent sign).[10] Among other surgical interventions, fibular graft (vascularized or nonvascularized) proximal femoral osteotomy has been described.[11]

Hernigou and Beaujean[12] reported abnormalities in the mesenchymal stem cell pool, which is known for its regenerative potential, following insult to the affected hip. Gangji et al[13] later reported qualitative and quantitative abnormalities of osteoblast cells within the proximal femur in ONFH patients. Thus, it is accepted that the regenerative and reparative capacity of bone in ONFH is severely compromised. However, more than two decades of experience using various orthobiologics has not been convincingly satisfying, and many groups have expressed limitations of these therapies.[14-16]

The pathology of ONFH involves ischemic imbalance of bone remodeling due to relatively enhanced osteoclastic action and poor regenerative potential of osteogenic cells in the proximal femur. The supply of differentiated osteogenic cells (osteoblasts) over time would result in arrest of ONFH progression. Core decompression would allow revascularization, and debridement of necrotic bone decreases the time needed for creeping substitution of new bone over dead bone. With this theoretical conviction, the author planned to use and assess the efficacy of autologous bone marrow–derived cultured osteoblasts following core decompression and debridement in the treatment of patients diagnosed with ARCO stages II and III ONFH.

Materials and Methods

Patient Demographics

The surgeries were conducted at various hospitals. Fifteen patients (13 male and 2 female), with a mean age of 32 years (range, 21-61 years), presented with typical ONFH symptoms. Patients were diagnosed with ARCO stage II or III ONFH (9 bilateral and 6 unilateral, for a total of 24 hips) on radiograph and MRI, and were considered for a predesigned treatment protocol that involved implantation of autologous cultured osteoblasts following core decompression and debridement.

Patient consent for inclusion in the study was obtained. The types of ONFH were idiopathic (8 patients), corticosteroid-induced (6 patients), and traumatic (1 patient) (**Table 1**). Efficacy of the treatment was assessed based on changes on radiograph and MRI and modified Harris Hip Score (mHHS), Oxford Hip Score (OHS), and visual analog scale (VAS) score after treatment. In a few patients, computed tomography also was performed.

Treatment

Treatment was performed in 2 steps.

Step 1. Percutaneous bone marrow aspiration from the iliac crest was performed and collected in transport media containing anticoagulant. This was transported under temperature-monitored conditions and processed at a good manufacturing practice–certified cell processing facility to obtain a predefined osteoblast culture (4 to 5 weeks).

The ex vivo culture of osteoblasts using bone marrow from the patient involved isolation of osteoprogenitor cells, osteogenic differentiation, and then expansion. Immunophenotypic characterization was performed to ensure the cultured cells tested positive for CD44+ and CD151+ markers. Alizarin red stain test ensured the presence of calcium deposits within the osteoblasts. Alkaline phosphatase test was used as an indicator of ability to form type I collagen.

Thus, ex vivo cultured live osteoblast cells, not less than 45 million, were filled and packed in sterile vials with appropriate transport/culture medium and were made available for individualized treatment. The cell viability was ensured during transport as well as after implant until the cells were integrated.

Step 2. The surgical implantation was planned as per the availability of cultured and expanded osteoblasts (4 to 5 weeks).

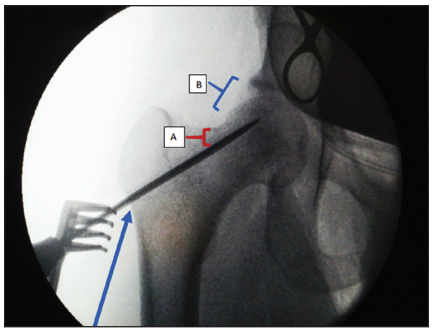

Figure 1: Surgical process details. The arrow indicates the high entry point of the guidewire at the vastus ridge targeting the area of osteonecrosis. A, 1-cm distance from the superior cortex to prevent fracture. B, varus appearance of the proximal femur due to mild flattening of the femoral head in the anterolateral femur in early osteonecrosis of the femoral head. This is the earliest sign observed radiographically and is indicative of stage IIB.

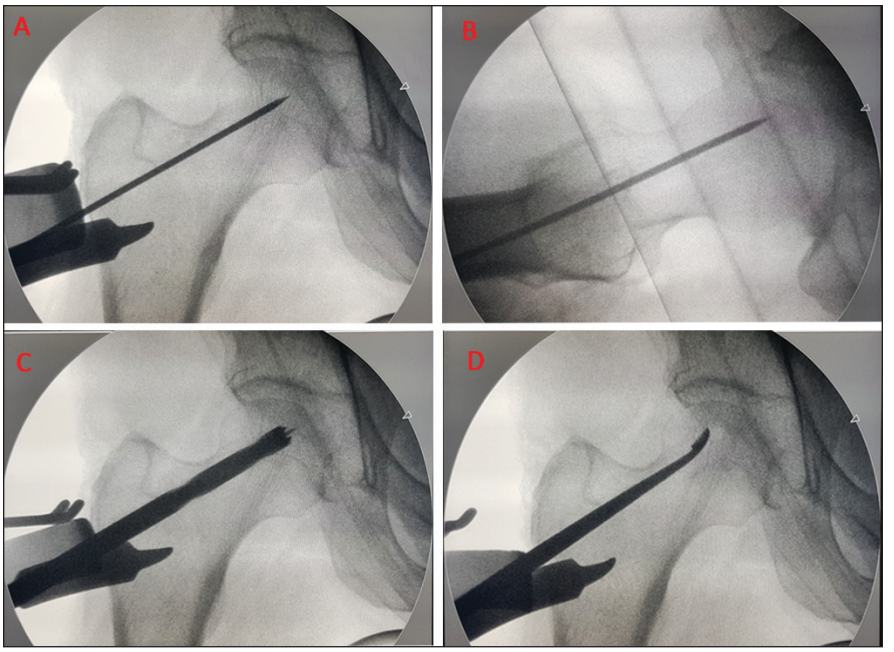

Figure 2: Surgical steps. Anteroposterior C-arm image of the hip with guidewire (A). Lateral C-arm image of the hip with guidewire (B). Drilling with 8-mm dynamic hip screw core drill bit (C). Anteroposterior C-arm image during curettage (D).

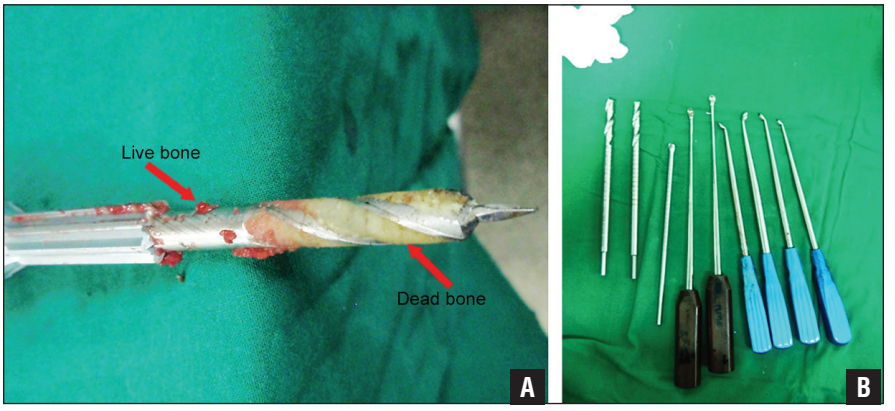

Figure 3: Drill bit with debrided live and dead bone (A). Instruments used during surgery (B).

In the first 3 patients, the osteoblast implant was performed soon after core decompression, whereas for the remaining 12 patients, core decompression was followed by debridement with implantation.

The location of the necrotic zone and its size was approximated on MRI. The patient was placed on a fracture table, and the C-arm was positioned as for routine core decompression. The entry point of the guidewire (2.5 mm) was chosen around the vastus ridge to allow faster healing in the cancellous bone (**Figure 1**).

The larger sagittal dimensions of the trochanteric area allowed for a posterior entry point to avoid a possible subtrochanteric fracture due to posterior cortical breaching during or after intervention. Special effort was made to avoid a subtrochanteric entry point. On no occasion was the posterior cortex of the femur violated. The guidewire was passed in the center of the lesion but at least 1 cm from the superior cortex. An 8-mm cannulated core drill (from the dynamic hip screw set) was used over the wire to make a tunnel until the necrotic zone. The steps of the surgical intervention are shown in **Figure 2**.

The tip of the drill, when removed, showed necrotic bone (**Figure 3A**), which was later sent for histopathology. Bone curettes of various sizes and angles then were used to curette the sequestrum under imaging guidance. The end point of curettage was the removal of hard sclerotic bone from the femoral head. If there was a bony ridge that was difficult to curette, a reamer was used. The author attempted to leave 1 cm of subchondral bone intact to allow faster revascularization of the femoral head by removing dead sclerotic bone. Curettes were kept at least 1 cm from the joint line.

After curettage was complete, the tunnel was plugged using an allograft of appropriate size. All of the instruments used during surgery are shown in **Figure 3B**. At this point, the patient was tilted to attain a gravity-dependent position of the operative hip to avoid any backflow of the implanted cells. A spinal needle was inserted through the small hole made in the allograft plug, and the osteoblast cell gel mixture was slowly injected in the space within the femoral head. Patients were held in the same position for ap-

Table 2

Pain and Function-Related Scores

Parameter	Mean±SD score	
	Baseline	18 months after treatment
HHS	64.3±6.13	86.0±8.62
VAS	8.41±0.73	2.40±1.40
OHS	31.5±3.48	48.0±6.04

Abbreviations: HHS, Harris Hip Score; OHS, Oxford Hip Score; VAS, visual analog scale.

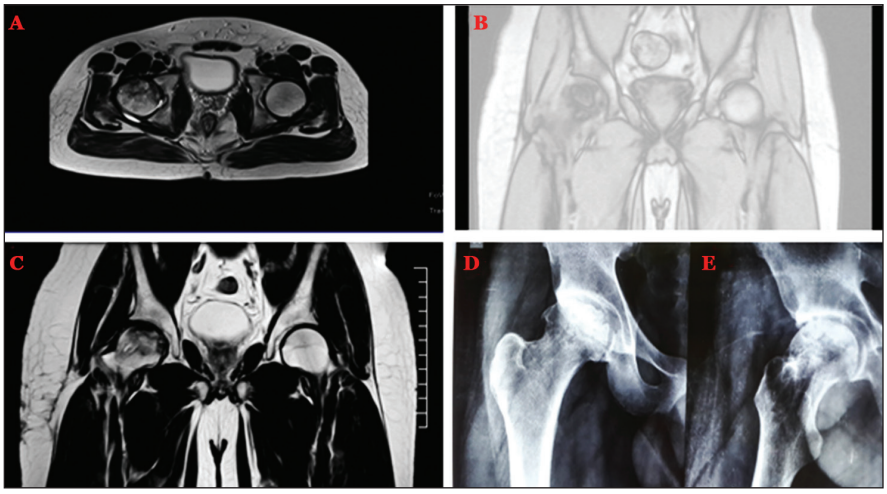

Figure 4: Patient M4. Preoperative magnetic resonance image of Association Research Circulation Osseous stage III of the right hip. Extensive involvement of the central and lateral regions (>50%), with the crescent having less than 2 mm of depression (A, B). Magnetic resonance image at 5 months after treatment (C). Preoperative anteroposterior radiograph (D). Anteroposterior radiograph at 6 years after treatment showing no further progression, with evident intramedullary changes. The joint space is preserved, which is consistent with good clinical function (E).

proximately 10 minutes to allow the cells to settle without spilling.

Postoperatively, patients were partial weight bearing for 4 weeks using a walker. They progressed to using a walking stick by week 6, and then full weight bearing was permitted by week 8. For patients treated for bilateral ONFH, use of a walker was encouraged until week 6. Physical exercises to regain muscle strength and all hip joint movements were encouraged as soon as possible.

All patients underwent regular follow-up during the rehabilitation period and thereafter at 6, 12, and 18 months, with all anteroposterior and lateral radiographs of the hip and magnetic resonance imaging completed at 18 months. Two patients were lost to follow-up thereafter, and 13 patients continued with regular follow-up visits; 3 patients had follow-up of 7 years.

Results

At 18 months after implant, no disease progression was observed on radiographs and MRIs for all patients. Postoperative mHHS, OHS, and VAS scores improved, and all of the patients had resumed normal routine activities and daily chores. Analysis of variance for HHS, OHS, and VAS scores showed a statistically significant difference (individual as well as mean values) from baseline to 18 months after implantation ($P<.5$; **Table 2**). Three patients who underwent follow-up for 7 years after implantation were assessed via telephone for HHS and VAS scores. For 1 of these patients, HHS improved from 90 to 95, and VAS score improved from 3 to 1 at 18 months. For another patient, HHS improved from 85 to 95, and VAS score improved from 2 to 1 at 18 months. One of the patients who underwent follow-up for 7 years walked daily for 3 to 4 km.

One male patient who was treated for bilateral ONFH with follow-up of 5 years showed good improvement in HHS (from 65 to 92.5) at the end of 18 months, and his VAS score improved from 9 at baseline to 3 in both hips at 18 months after treatment. At 5 years postoperatively, he reported pain only after sitting for several hours and was more comfortable using a cane when walking.

Another male patient was diagnosed with ARCO stage III of the right hip. He had extensive involvement of the central and lateral lesion (>50%) with crescent depression less than 2 mm. Although reports for direct comparison were not available at 6 years after treatment, radiographs showed no further progression, with intramedullary changes evident. The joint space was preserved, which is consistent with good clinical function (**Figure 4**).

One female patient had a history of tuberculosis treated with anti-Koch therapy–anti-tubercular therapy and corticosteroids for 9 months as the standard care. This patient presented with extensive bilateral femoral head involvement evident on radiograph and computed tomography scan. The crescent depression was 2 to 4 mm. She was diagnosed with ARCO stage II of the right hip and grade III of the left hip. Radiographs at 6 years postoperatively showed arrest of osteonecrosis progression with an otherwise high risk of collapse because the ONFH was steroid induced. Clinically, this patient was able to resume all of her routine activities, including a daily commute to work and reg-

ular yoga, floor exercises, and stationary cycling (**Figure 5**).

One male patient who was receiving long-term steroid treatment had relatively moderate improvement in HHS, from a baseline of 65 to 80 at 18 months after treatment. A female patient with bilateral ONFH had ARCO stage III in the right hip and a small, centrally located lesion (<30%) in the left hip. On radiograph and MRI, the right hip showed more than 90% involvement of the lateral, central, and medial regions but no crescent. The decision was made not to treat the left hip because it was deemed to have minimum possibility of progression. At 6 years after treatment, there was regression of necrosis. The patient has done well clinically and had a successful childbirth (**Figure 6**).

Overall, the short-term and long-term results of autologous cultured osteoblast treatment along with routine procedures have been satisfactory. None of the 8 patients who underwent follow-up for 5 to 7 years showed any signs of disease progression, and none of the patients required repeat treatment or total arthroplasty.

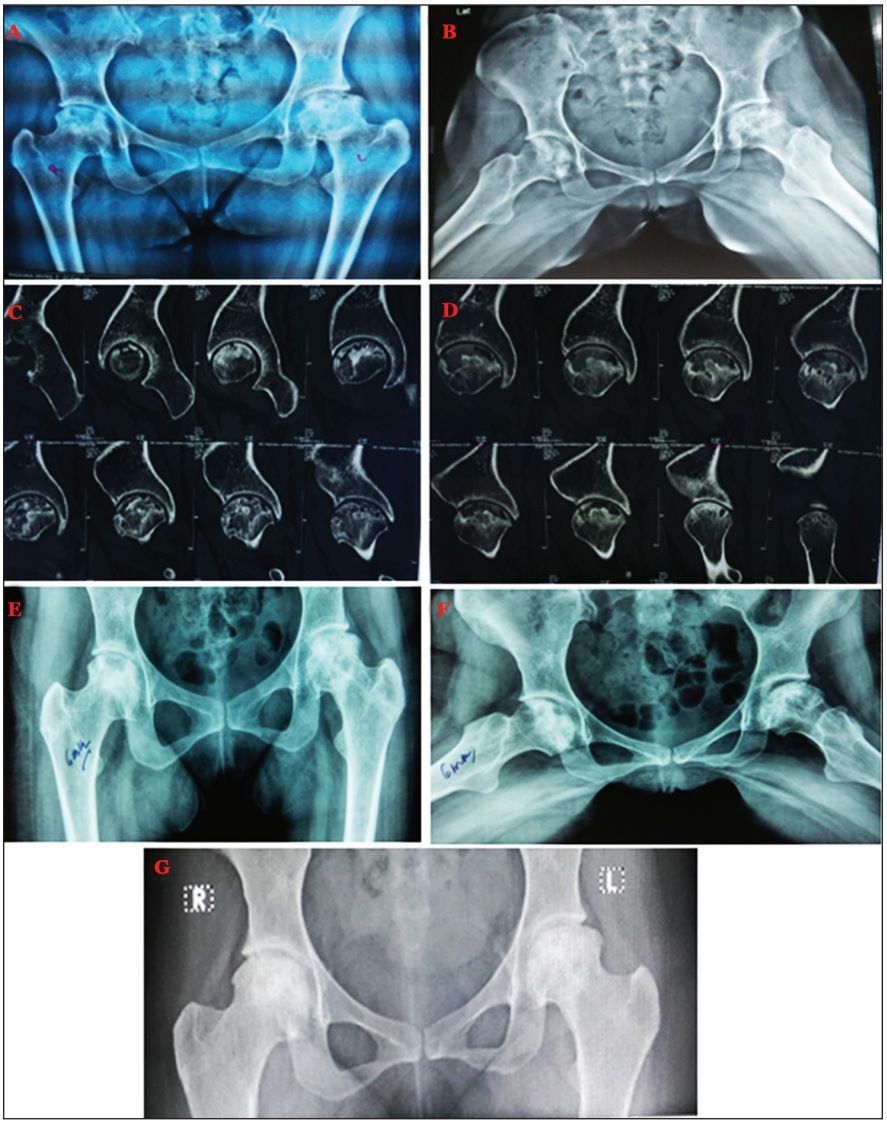

Figure 5: Patient F1. Preoperative anteroposterior radiographs (A, B). Preoperative computed tomography scans. There is extensive bilateral femoral head involvement (>30%), with 2 to 4 mm of depression of the crescent (C, D). Anteroposterior radiographs 6 months after treatment (E, F). Anteroposterior radiograph 6 years after treatment. Both femoral heads show arrest of osteonecrosis progression in a patient at high risk for collapse (G).

Discussion

Among invasive procedures, core decompression has been the standard of care for early stages of ONFH; however, varying degrees of improvement have been reported. Yoon et al[17] and Rajagopal et al[18] reported treatment of ONFH with core decompression was viable only in early stages, with the effect lasting for 2 to 3 years.

Among the biologics, platelet-rich plasma, growth factors, and bone marrow aspirate concentrate (BMAC) have been widely used along with conventional techniques such as core decompression or bone grafts.[19,20] Several contributions in terms of understanding the clinical application and efficacy of biologics for the treatment of ONFH have been published during the past two decades.[21-23] Inherent limitations such as the absence of controlled studies, uncertainty, and heterogenicity of the composition of biologics have resulted in inconsistent results, and no treatment option has passed the regulatory approval process.[24]

In a recent study, Hauzeur et al[25] reported obvious inefficacy of BMAC treatment in a randomized clinical trial comparing BMAC and core decompression vs core decompression alone. Their assessment criteria included clinical outcome, pain score, radiology, and the need for total hip arthroplasty.

Untreated bone marrow should be considered first-generation and processed bone marrow second-generation biological treatments for ONFH. The results using first- and second-generation biologics have been variable, and there are no long-term data and no formally approved products. Thus, curative treatment of ONFH,

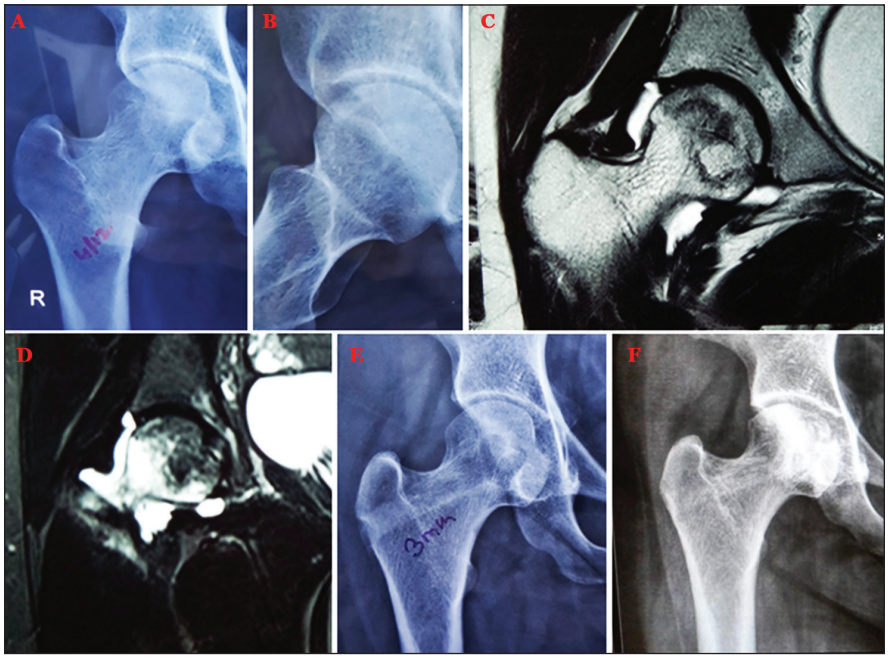

Figure 6: Patient F2. Preoperative anteroposterior radiographs of the right hip showing more than 90% involvement of the medial, central, and lateral regions. There is no crescent (A, B). Preoperative magnetic resonance images (C, D). Anteroposterior radiograph at 3 months after treatment (E). Anteroposterior radiograph at 6 years after treatment (F).

at least prior to the collapse stage, remains challenging.[26]

Kim et al[27] were the first to report the clinical use of cultured osteoblasts in a single patient with bilateral ONFH (Ficat Arlet grade II); they reported a good outcome at 5 years without progression of disease. Later, Gangji et al[28] compared the use of BMAC and autologous osteoblast cells in the treatment of avascular necrosis. They reported the group treated with osteoblast cells had twofold higher respondents at 36 months compared with the BMAC-treated group. These patients continued to have reduced pain until the end of the study period. Also, progression of disease from stage III to IV was more than 2 times higher in the BMAC-treated group compared with the osteoblast-treated group.[28]

The author proposes the evolution of biologics being used as first- and second-generation treatment, and the current modality of using autologous cultured osteoblasts as the latest and third-generation treatment. As such, the latter is the only modality that qualifies as cell-based therapy (**Table 3**).

Autologous cultured osteoblast implant is the most novel treatment modality for joint preservation. In the author's experience, 11 patients at 4 years, 6 patients at 5 years, and 3 patients at 7 years after transplant showed arrest of disease. Joint structure, biomechanics, strength, and function were regained in these patients, and they required no repeat treatment. Yet, unlike few other treatments, total arthroplasty still remains viable as a future option.

The assessment of ONFH progression on MRI after core decompression remains a sparsely studied subject. Therefore, radiographic and clinical examination during follow-up is crucial.

Conclusion

Autologous cultured osteoblast implantation is effective and safe for patients

Table 3

Proposed Generations of Orthobiologics

Orthobiologic	Generation	Cell component	Matrix/ECM	Osteogenic potential	Regulatory status
PRP	First	Nil	Platelets release multiple growth factors, cytokines in variable proportion	Not ascertained	No regulatory approval
BMAC/stromal vascular factor/ adipose-derived MSCs	Second	Heterogenous MSCs MNCs Others?	MSCs are assumed to differentiate into osteogenic progenitors	Ascertained in in vitro conditions	No regulatory approval
Autologous cultured osteoblasts for implantation	Third	Osteoblasts	Conducive for further maturation	Ascertained and assured	First approved bone-cell therapy product

Abbreviations: BMAC, bone marrow aspirate concentrate; ECM, extracellular matrix; MNC, mononuclear cells; MSC, mesenchymal stem cells; PRP, platelet-rich plasma.

with ARCO stages II and III ONFH. This third-generation biologic can be considered a joint-preserving treatment in correctly chosen patients.

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