



Cell-based Treatments of Femoral Head Osteonecrosis: A Literature Review

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ABSTRACT

The preferred desire of orthopedic surgeons is to preserve the femoral head in the early stages of femoral head osteonecrosis; however, hip arthroplasty is needed in most cases. The outcomes of traditional surgical treatments alone are not favorable. Thus, femoral head osteonecrosis frequently follows an unpredictable course resulting in significant hip arthritis. Through the years, it has been identified that decreased proliferation capacity and content of bone marrow stem cells (BMSCs) in the femoral head region play a key role in the pathogenesis of osteonecrosis of femoral head (ONFH). In the past two decades, researchers have focused on cell-based therapies for ONFH treatment. The regenerative potential of damaged cartilage and bone tissue with stem cells has become a new treatment approach in the field of orthopedics. Ongoing basic science and clinical studies are progressing toward efficient standard treatment options for this extremely challenging condition. In this article, we reviewed the recently developed methods of cell therapy for these types of musculoskeletal conditions.

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Introduction

The most common site of human osteonecrosis is the femoral head. The crude incidence rate of non-traumatic osteonecrosis of femoral head (ONFH) is 2.58 cases per 100,000 person-years, with a range of 1.5–3.7 per 100,000 people. In the United States, ONFH is the reason for about 10% of primary hip arthroplasties. With an annual rate of 330,000 primary hip replacements, it seems that more than 30,000 Americans annually undergo hip replacement with this diagnosis (1-4).

ONFH diagnosis is based on X-ray and magnetic resonance imaging (MRI). Popular classifications are Ficat and Association Research Circulation Osseous (ARCO) (5). With the necrosis of an area of the femoral head, the articular surface will no

longer be supported by the subchondral bone, and collapse of the femoral head would be inevitable. ONFH frequently follows an unrelenting course resulting in significant hip arthritis (6)

Despite attempts to use conservative treatments in the first stages of the disease, total hip arthroplasty is required in most cases. Core decompression (CD) is a favorable prophylactic surgery used in pre-collapse osteonecrosis, and structural allograft or autograft are usually combined with this technique. The outcomes CD alone generally worsen with more advanced lesions (7). In advanced stages, free vascularized fibular graft has been used as the treatment of choice and salvage surgery for decades. However, it is not indicated

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for all patients with ONFH and still remains technically challenging (8). Fibular allograft and other types of structural grafts were relatively effective, but there is no strong evidence supporting them (9-11).

Decreased proliferation capacity and number of BMSCs in the femoral head region is in association with ONFH (11). Hernigou et al. described the idea of cell therapy in ONFH for the first time. They added bone marrow concentrate (BMC) to CD in an invented method and performed it on sickle cell patients at the early stages of ONFH (12). Over the past 20 years, orthopedic surgeons have focused their work on cell-based therapies for ONFH. Ongoing basic science and clinical studies are progressing toward effective standard treatment options for this extremely challenging condition (12).

Table 1. Studies about unprocessed bone marrow injection.

Author Year Reference	Protocol	No. of patients/hips	Initial osteonecrosis of femoral head class	Follow-up (years)	Conclusion	Level of evidence
Rastogi et al. (2013) 14	CD+BMC vs unprocessed bone marrow	40/60	ARCO, I-III	2	Stem cells have better outcomes in early stages	III
Ma et al. (2014) 13	CD+BM buffy coat	53	Ficat I-III	2	Good pain relief and prevention of further progression	I

Ma et al. enrolled adult patients under 55 years of age with the confirmed diagnosis of ONFH in a randomized double-blind clinical trial. Control group underwent CD surgery only and Treated group received bone marrow buffy coat (BMBC) in addition to CD. At the end of follow-up, pain relief was significantly higher in the Treated group ($P < 0.05$). Furthermore, after two years, about one-third of the CD treated patients progressed to higher stages and four patients converted to total hip replacement, while this rate was 8% in BMBC; progression rate among Ficat stages I and II was 0% (13).

Bone marrow concentrates (BMC)

In this method, all aspirates must pool in an environment containing cell culture medium, citric acid, and dextrose. Fat and cellular aggregates should be removed. Conventional CD (creation of a tunnel with an 8-mm trephine) or multiple drilling (two or three small tracts) were performed through a proximal lateral femoral approach, and BMCs were injected via these tracts to the necrotic area. However, leakage of injected material through the track during and after the injection is a problem; therefore, bone plug or fibrin glue injection at the last step is an option. The modern drug delivery system like peptide hydrogels is also

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Unprocessed bone marrow

The simplest way to obtain stem cells is to inject a bone marrow aspiration after drilling or CD. Bone marrow is usually collected from the anterior (supine or lateral position) or posterior portion of the iliac crest (lateral or prone position). A direct puncture of the needle is possible most of the time, but overweight patients require a stab incision. Drawback of this technique is the low stem cell content of the injected material. Fat, clot debris, red blood cells, and polynucleate cells constitute a major portion of this fluid. Implantation of bone marrow has been shown to prevent further progression of the early stages, but it is less effective than BMC (Table 1) (13).

reported to maintain the injected material at the necrotic part (15-17).

Midterm results of a prospective study of 189 hips treated with BMC in a center showed more than 80% success, and total hip replacement was performed in only 34 hips (76% of them were Ficat stages III and IV before BMC implementation) (15).

Gangji et al. reported results of implantation of bone marrow cells in a prospective level II study at 5-year follow-up, less than one-fourth of patients who received BMCs combined with CD underwent hip replacement (versus over 70% in control group). Survival analysis showed a significant difference in time to failure (time needed to convert to hip replacement procedures) between the two groups at 60 months. Patients only showed minor side-effects after the treatment (16).

We found two studies with high levels of evidence regarding the effectiveness of BMCs. First, Tabatabaee et al. in a randomized clinical trial evaluated the advantages of BMCs in the early stages of ONFH. Two years' outcome showed considerable improvement of pain and hip function in BMCs group. Follow-up MRI at the end of this study showed significant deterioration in patients treated only with CD surgery without implementation of BMCs (18). Second, Sen et al. using the same method in a clinical trial on forty patients

reported an impressive improvement in patients treated with implementation of BMCs, even those who had clinical and imaging signs of poor outcome at enrollment such as effusion and edema in

the first MRI and low functional hip scores (21). We summarized the eligible reports that included BMCs in treatment options (Table 2).

Table 2. Bone marrow concentrates treatment for osteonecrosis of femoral head.

Author Year Reference	Protocol	No. of patients/hips	Initial osteonecrosis of femoral head class	Follow-up (years)	Conclusion	Level of evidence
Gangji et al. (2004) 16	CD + BMC	13/18	ARCO, I-III	2	Significant delay in collapse	III
Wang et al. (2010) 19	CD + BMC	45/59	ARCO, I-III	2	Good pain relief and prevention of further progression	II
Gangji et al. (2011) 20	CD vs BMC	19/24	ARCO, I-II	5	Significant pain relief -successful in earlier stages with BMC	II
Tabatabaee et al. (2015) 18	CD vs CD+B-MC	18/28	ARCO, I-III	2	Significantly better outcomes. MRI worsening was less in BMC group	I
Sen et al. (2012) 21	Multiple drilling +BMC vs CD	40/51	ARCO, I-II	<2	Better clinical outcomes, specifically in stage II with BMC	I
Lim et al. (2013) 22	Multiple drilling +BMC vs CD + bone graft	128/190	Ficat I-II	5	Almost the same success rate	III
Liu et al. (2013) 23	CD vs bone filler +BMC +CD	34/53	ARCO, I-III	2	Significantl higher results in BMC group	III

BMC: bone marrow concentrate, CD: core decompression, MRI: magnetic resonance imaging

Adipose tissue stem cell (ATSC)

Adipose tissue is an extra bone marrow appealing source of mesenchymal stem cells. Procurement of adipose stem cells is less invasive and much cheaper than BMSCs.

These stem cells can be extracted from isolated adipose tissue since it retains higher resource of stem cells than BMSCs (16). Zhu et al. reported that human lipoaspirate contains plentiful amounts of pluripotent cells and may represent an alternative stem cell source (17).

Liposuction is the first step, and the next step is digesting the lipoaspirates by collagenase to achieve mesenchymal stem cells. Finally, collagenase is washed out by centrifugation (16). In 2011, Pak reported that autologous ATSCs may have bone regeneration capability. He injected ADSCS percutaneously with platelet-rich plasma (PRP) and hydroxyapatite into hip joints of two patients and found clinical and MRI signs of regeneration (24,25). These patients experienced significant pain relief after one year, and MRIs showed posi-

tive T1 signal change consistent with the regeneration process (25).

Cultured mesenchymal stem cells

In a recently developed method, bone marrow stem cells were cultured ex-vitro for about two weeks, and then a considerable amount of stem cells was implemented into the necrotic part of the femoral head. In this technique, the primary cells can be directly obtained from subtrochanteric bone marrow during CD without any further iliac aspiration. The major advantage of this method is less morbidity of the incision site. Zhao et al. concluded that this method can prevent femoral head collapse. In a randomized clinical trial on 97 hips, they utilized ex-vivo expanded stem cells to treat the early stages of ONFH. They compared the volume of necrotic zone (based on T1 low signal intensity regions) before surgery and at final follow-up (5 years) between two groups. Cultured stem cell group (53 hips) had a significantly smaller necrotic zone in contrast to CD group (44 hips).

In the first group, only two hips progressed to higher stages of the disease and underwent vascularized graft surgery, whereas in the latter, about 25% of the hips converted to hip replacement surgery or vascularized graft (26).

Umbilical cord-derived stem cells

One of the potential sources of mesenchymal stem cells is the human umbilical cord (hUC). Umbilical cord stem cells have been used in the field of clinical hematology for several years. It is a relatively easier method of stem cell collection with no potential aspiration site morbidity in comparison to bone marrow; thus, it became an alternative source of stem cell in ONFH (27). Recently, Chen et al. reported in a case series that intraarterial injection of hUC could decrease the volume of necrotic area and improve hip function. They harvested stem cells from hUC, and then cultured stem cells were injected through an arterial access (femoral artery) to nine patients. After 24 months, MRI showed that the volume of necrotic area had decreased by about 20% (28).

All the above-mentioned treatment options showed significant improvement in patients' condition in early stages of the disease. Even though there is no consensus regarding the standard treatment for ONFH, the majority of reports showed that precollapsed stages and small necrotic lesion are correlated with better outcomes. The source of stem cells, technique of harvesting and concentration, methods of culture, culture media, and concomitant surgical procedures were completely different among these studies making it difficult to compare the findings.

Conclusion

There is not any standard treatment option for early stages of ONFH, but it seems that cell-based therapy has a great clinical potential to optimize the outcomes of these patients. Further clinical trials with larger sample sizes and clearer characterizations of treatment methods are needed.

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Conflict of Interest

The authors declare no conflict of interest.

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