



# Osteonecrosis of the Femoral Head: A Biological Approach for Precollapse Disease

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Multiple surgical and nonsurgical modalities and therapies exist to treat early stages of osteonecrosis of the femoral head. Recently, core decompression-type procedures combining biologic cellular therapies have gained interest and recognition with recent literature suggesting potentially enhanced clinical outcomes. Therefore, the purpose of this article was to discuss the indications and outline a specific technique of core decompression combined with cellular augmentation for treatment of early stages of osteonecrosis of the femoral head.

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## Introduction

There are approximately 10,000 to 20,000 new cases of nontraumatic osteonecrosis of the femoral head (ONFH) each year in the United States.<sup>1,2</sup> For precollapse (Steinberg or Ficat Stage 1) or advanced precollapse (Steinberg or Ficat stage 2) ONFH is often treated nonoperatively or with joint preservation techniques.<sup>3</sup> The aim of these joint preservation techniques is to treat pain, improve function, delay disease progression, and potentially reverse the disease process.<sup>4,5</sup> This may permit the patient to avoid more invasive procedures that would be needed for more advanced, postcollapse disease, such as hip arthroplasties.<sup>3-5</sup>

For precollapse lesions, core decompression is a common surgical technique that is widely utilized<sup>3</sup>. This technique is employed by creating a cylindrical core via drilling or tapping through the femoral neck and into the necrotic region.<sup>6,7</sup> This is thought to decrease the intraosseous pressure that is caused by necrosis and resultant cellular swelling.<sup>8,9</sup> In turn, the intraosseous blood flow resistance is decreased and

enhances the potential for revascularization, ultimately potentially allowing for healing and new bone formation.<sup>10</sup> Results of this procedure are promising, but they can be unpredictable and controversial especially for advanced precollapse disease.<sup>3</sup> For example, core decompression alone in patients who have early precollapse disease can have a 10-year hip survivorship of 96%<sup>11</sup>; whereas, those patients who have late precollapse disease treated with core decompression alone have reported failure rates up to 77%.<sup>12,13</sup>

With the above in mind, surgical adjuvants such as vascularized and nonvascularized bone grafting have been proposed, but have no clear benefit when compared to core decompression alone.<sup>3-5</sup> However, recent systematic reviews of the literature and comparative studies have demonstrated that core decompression in conjunction with biologic cellular therapies suggest improved clinical outcomes and lower disease progression rates compared to core decompression alone.<sup>6,7,14,15</sup> Generally, although biologic cellular therapies in musculoskeletal medicine are a source of great promise and opportunity, they are also the source of public controversy, confusion, and misinformation.<sup>16,17</sup>

Encouraged by the data presented to date, but cognizant of the limitations in the current literature, the authors of this report are performing core decompression with adjuvant cellular therapy for precollapse ONFH, with the intention of improving clinical outcomes. Ultimately, controlled prospective comparison to alternative therapies over extended

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follow-up will confirm the use or futility of this approach. However, a first step in advancing such a therapy approach is to rigorously define and standardize the methodology, so that it can be consistently repeated from 1 patient to the next and also reproduced (ie, performed the same way by another provider). To date, much of the current literature is confounded by heterogeneity in types of cellular therapy and we believe it is important to delineate the current state of knowledge.<sup>18</sup>

Therefore, the purpose of this article was to describe the surgical technique of core decompression plus biological and cellular augmentation with autologous platelet rich plasma (PRP) and bone marrow aspirate concentrate (BMAC), and to discuss the potential indications and value of adjuvant biologic and cellular therapy for precollapse ONFH.

## Indications

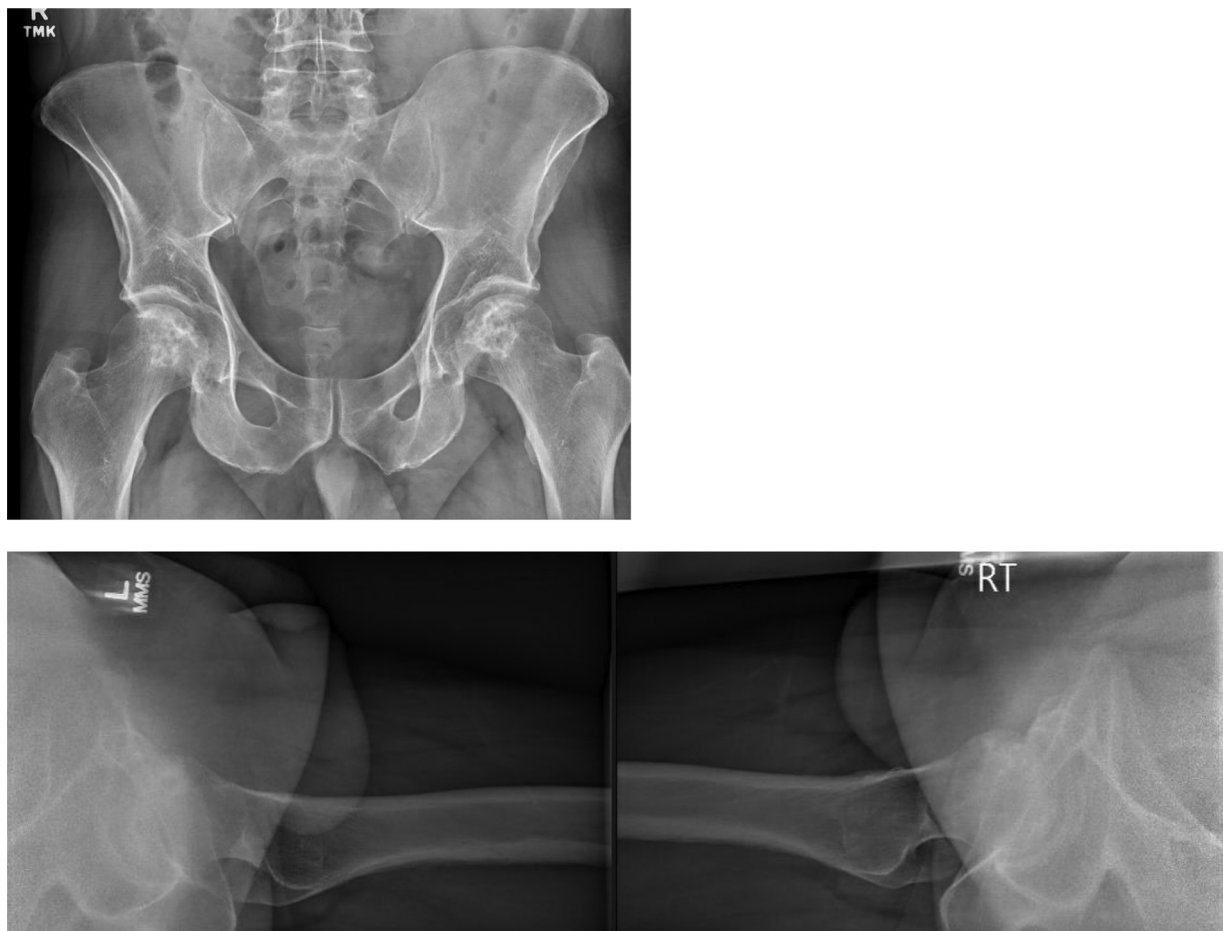
The indications proposed by the authors are generally patients who have symptomatic nontraumatic precollapse (Steinberg or Ficat Stage 1) or advanced precollapse (Steinberg or Ficat stage 2) ONFH. Radiographs of the pelvis and both hips are obtained. Lateral hip x-ray in addition to antero-posterior (AP) views. A “frog leg” lateral view can be

particularly important in silhouetting the anterior superior head, where early subchondral fracture is most likely to begin. MRI imaging is obtained to both determine the presence or absence of ONFH in the ipsilateral or contralateral side, and to determine the size and location of bone that is involved. Asymptomatic lesions involving less than 25% of the femoral head are less likely to collapse, while lesions involving 75% or more of the femoral head are at very high risk. This documentation will be necessary for future subset analysis to determine if lesion size or location may preclude a positive outcome and therefore become a contraindication in the future. The Kerboul or necrotic angles also represent variables known to be risk factors in collapse.<sup>3</sup>

Fig. 1 provides radiographic and MRI images from a 48-year-old male patient presenting with a history of alcohol abuse and 3 months of bilateral hip pain. Imaging revealed Stage II ONFH Bilateral core decompressions with adjuvant biologic cellular therapy was performed (Fig. 1).

## Surgical Technique

The patient was placed supine on a flat radiolucent table. After anesthesia, prepping, and draping, 30 milliliters (per hip) of autogenous blood was obtained from a peripheral site



**Figure 1** AP and lateral radiographs of the bilateral hips with evidence of ONFH (Steingberg or Ficat stage 2).

by the anesthesia team. This whole blood was processed using a commercially available centrifuge device according to the manufacturers standardized specifications to obtain PRP. While the PRP is prepared, bone marrow aspiration (BMA) is performed. The detailed BMA technique has been described in greater detail in a previous publication ONFH,<sup>19</sup> and the following are highlights. The iliac crest is the preferred aspiration site. Either the anterior or posterior iliac crest may be used. Either lateral or parallel technique may be used to place and reposition the aspiration needle.<sup>19</sup> The patient may be positioned in a lateral position to obtain samples and perform the core decompression on a single side. We prefer to position a patient supine in bilateral cases, allowing access to both hips and both anterior iliac crests. Aspiration is performed using a #11 blade to make a 2 mm stab incision approximately 4 to 5 centimeters posterior and lateral to the anterior superior iliac spine. Passage of an aspiration needle from this lateral site perpendicular to the iliac wing minimizes risks to the lateral femoral cutaneous nerve and the superior gluteal nerve. An 11-gauge aspiration needle with obturator is advanced to the lateral iliac crest outer table no more than 3-4 centimeters below the iliac crest, where the thickness of cancellous bone between the inner and outer tables becomes very thin. This improves cellular yield and reduces risk of inadvertent penetration through the inner table. The cannulated bone marrow aspiration needle can then be advanced, stabilizing the needle tip with one hand and using the other hand to apply controlled axial load and needle rotation. Once the lateral cortex is felt with the needle tip, a combination of gentle axial and rotational movements is used to advance the needle. At this point, an aspiration is performed and the sample is obtained. Once the sample is obtained (optimal is 1-2 mL from each site), the trocar or obturator is reintroduced and the needle is advanced 5 mm to engage a new site, to obtain further sample. Trying to obtain more than 1-2 mL's from each site will result in dilution of the marrow sample with peripheral blood, creating a suboptimal sample. It is recommended that the aspiration be performed using 10-mL syringes containing anticoagulant, to ensure immediate mixing of the aspirate sample to minimize clotting. Either sodium heparin or acid citrate dextrose are

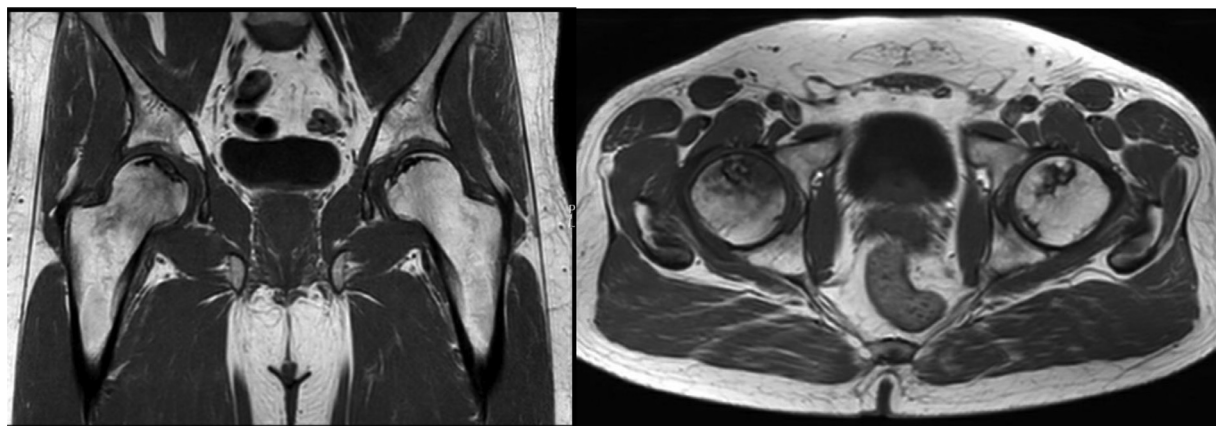
most commonly recommended in the protocols provided by manufacturers (Fig. 2).

An alternative approach to perform BMA is utilizing a "parallel technique", where needle entry is through the anterior superior iliac spine, and the needle is repositioned to depths up to 8 cm in a fan shaped area between the inner and outer tables.<sup>19</sup> A needle is always advanced in 5 mm increments, using the trocar to avoid impacting bone in the tip, aspirating not more than 2 cc at each of these sites (replacing the trocar for each advancement between aspirations) through the flat portion of the anterior or posterior iliac wings to a depth of 6-8 centimeters.

Overall BMA procedures represent minimal risk when performed with caution in a controlled surgery setting. Complications being extremely rare (less than 0.1%). The most frequently reported complication is bruising at the aspiration site. However, hematoma, infection, and chronic pain can occur.

Once sufficient bone marrow is obtained (60 milliliters per hip), it is placed in a centrifugation system to produce BMAC (approximately 6 milliliters). Finally, both the PRP (approximately 3 milliliters) and the BMAC are combined for injection into the lesion.

While the PRP and BMAC are being prepared, surgical access to the osteonecrotic sites in the femoral head are obtained. This was done using a small limited 2-3 cm lateral incision to allow for a cannulated trocar to enter the femoral neck through the lateral femoral cortex at an entry point just above the level of the lesser trochanter (Fig. 3). Fluoroscopic guidance is utilized while carefully referencing preoperative 3-dimensional advanced imaging studies to enter the lesion. Note that a mallet is used to advance the trocar to avoid heat necrosis, which could potentially occur with the use of drilling, and to ensure a tight apposition of bone and tissue around the needle to limit egress of fluid back along the core track. Once adequate placement is confirmed on AP and frog lateral views, the trocar is removed and the cannula remains. Sequential injection of the biological autologous preparation (BMAC + PRP) is done and the cannula is carefully removed with care to leave cancellous bone in the entry tract to avoid spillage of the biologic cellular therapy.



**Figure 2** Coronal and axial T1 magnetic resonance imaging with evidence of ONFH (Steingberg or Ficat stage 2).



**Figure 3** Intraoperative fluoroscopy demonstrating cannula with trocar removed to allow for insertion of biologic cellular therapy.

## Biologic and Cellular Therapy

Biologic therapy (eg, PRP, which does not contain nucleated cells) and cellular therapies (ie, containing nucleated cells) are potentially useful adjuvants in the treatment of osteonecrosis. However, if these are used and evaluated prospectively, it is important for providers and researchers to understand and standardize the characterization and reporting of both the methods used for aspiration and processing, as well as the composition of the bone marrow concentrate and platelet rich plasma with respect to the cell and platelet components. We emphasize that it is not uncommon for the term “Stem Cell” therapy to be utilized when describing PRP or BMAC therapies.<sup>18</sup> This is inappropriate and misleading to patients and clinicians. PRP does not contain “stem cells.” Moreover, while BMAC preparations may contain stem cell and progenitor cell populations (Hematopoietic stem cells, connective tissue progenitors [CTPs], and endothelial progenitors), these cell populations are the least common cells present in a BMAC preparation. Studies have shown that there can be as few as 1 viable CTP among 20,000-40,000 bone marrow nucleated cells, therefore stem cells are a rare population within BMAC.<sup>18</sup> Recognizing this, and choosing not to contribute to the false advertising that has confused both patients and the public in advertising and lay press, we use the term “cellular therapy” when describing BMAC and “biologic” therapy when describing PRP.

Density separation processing using a centrifuge does change the composition of blood and marrow aspirate. In the case of BMAC the concentration of nucleated cells (including the small fraction of stem and progenitor cells that are present) may be increased by 3-6 fold, while the concentration of erythrocytes is correspondingly decreased. Similarly, density separation of platelets from blood can increase the concentration of platelets by 2-6 fold, over that present in blood. This allows for an elevated number of platelets in the PRP, and nucleated cells in BMAC to be

delivered in a relatively small volume of plasma and contaminating erythrocytes.<sup>20</sup>

To date no specific mechanism of action has been established for BMAC or PRP, alone or in combination. One potential mechanism is the function of osteogenic bone marrow stem and progenitor cells which might proliferate and differentiate into bone. Other mechanisms involve the effect of soluble factors or even exosomes that may be secreted or released by the injected cells (progenitors or nonprogenitors). Local cell-cell interactions between local and injected cells or cells arriving from local bleeding or systemic circulation could also contribute. However, these mechanisms represent no more than speculation at this point.<sup>15</sup>

It is assumed that the composition of the BMA or PRP, and/or the biological potential of the cells that are transplanted will contribute to the success or failure of a given procedure. Hernigou et al, has reported an association between the success of core decompression and BMAC and the concentration of colony founding CTPs.<sup>21-24</sup> However, each patient is different. Each blood sample and each BMA sample provides a different concentration of cells, CTPs, and platelets as a starting material. Each processing kit and each run on each device has a different impact on concentration and prevalence of the cells, CTPs and platelets that are present. This often depends on the patient’s hematocrit, fluid viscosity, presence of clots (failure of aspiration technique or anticoagulation). As a result, neither BMAC nor PRP represent a truly standardized therapy at this point. The therapy provided to each patient may differ by 1-2 orders of magnitude with respect to cell, CTP and platelet concentration. For this reason, the authors are committing to a process of characterizing the composition of cells, CTPs and platelets that are used in the therapy of each patient. Future capabilities to archive samples of cells and serum for potential analysis of cytokine concentrations or exosome composition is also being developed. Workflows that would enable immediate assessment of cell and platelet count are also under examination. This would enable a clinician to set a minimum release criterion (quality standard) for cell and/or platelet concentration and then identify any patients in whom minimum criteria were not met, enabling more marrow or blood to be processed to achieve a minimum standard.

In addition to a general dearth of reporting on cellular composition (Cell, CTP and platelet concentration), the literature to date is severely limited by the lack of reporting, on the variation in cell sourcing methods, cell harvest technique, cell processing methods or systems, methods of cell delivery, use of adjuvant therapies, and assessment of outcomes.<sup>6,20,25</sup> Future studies must confront and address these limitations if we are to be effective in exploring and optimizing the use of autogenous biological and cellular therapies.

## Conclusion

Core decompression with adjuvant cellular therapy (BMAC + PRP) may be effective for precollapse ONFH. However, it is important to note that the methods that have been



reported in the literature are heterogeneous, nonstandardized, and are often vaguely described. Therefore, it is difficult to draw definitive conclusions on the best technique and formulation. In the present report, we have described a specific surgical technique and emphasize the importance of quantitatively documenting and standardizing cellular therapy preparation for the treatment of precollapse ONFH. Cellular therapies should be reported with attention to standardized nomenclature for cell source (tissue and location), cell harvest method, cell processing methods, and quantitative characterization of cell composition before and after processing. Further data collection on this technique and prospective comparison to alternative therapies or methods are needed to fully assess and optimize outcomes.

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