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REVIEW

Biological therapies for the treatment of early stage pre-collapse osteonecrosis of the femoral head

Ioannis K. Triantafyllopoulos[1], Athanasios Papavasiliou[2]

[1]*Assistant Professor of Orthopaedics, MD, MSci, PhD, FEBOT, Head of the 5th Orthopaedic Department, HYGEIA Hospital*

[2]*BSc, MD, PhD, Orthopaedic Surgeon, Interbalkan European Medical Centre Thessaloniki, Greece*

ABSTRACT

The pathogenetic mechanism for non-traumatic osteonecrosis of the femoral head (ONFH) remains elusive. It is known, that an important part of the underlying pathology in ON is cell deficiency, hence, it is rational to consider the use of cell-based treatments to supplement more established surgical interventions. This chapter will focus surgically on Core Decompression (CD) and discuss a number of its technical advancements and variations. It will also focus on cell-based therapies that attempt to improve simple CD outcomes and argue their variability and safety.

KEY WORDS: osteonecrosis, femoral head, core decompression, cell therapy, stem cells

Introduction

Non-traumatic osteonecrosis of the femoral head (ONFH) typically affects relatively young, active patients and frequently results in considerable loss of function [1]. Osteonecrosis is derived by the Greek words osteo-bone and necrosis-death. The exact pathophysiology of non-traumatic ON is not thoroughly understood and various 'incriminating' factors such as vascular insult, fat emboli and increased intraosseous pressure have been proposed. If left untreated, the final outcome is the adjacent to the necrotic bone femoral head and articular cartilage to collapse resulting in arthritic changes approximately in 60-70% of the patients [2, 3].

Treatment is based on a number of parameters, such as lesion characteristics (size, the presence of collapse at the time of diagnosis, acetabular involvement), patient's age and comorbidities [2, 4]. The optimal treatment modality has not yet been identified. Several algorithms of medical and surgical treatments have been developed to delay its progression, with variable success [5]. Surgically, total hip replacement (THR) is the most frequent intervention for post-collapse treatment, and core decompression (CD) is the most common performed procedure for symptomatic, pre-collapse cases [6]. Historically, THR for osteonecrosis (ON) had poor results, attributed to the young and active character

CORRESPONDING AUTHOR, GUARANTOR

Ioannis K. Triantafyllopoulos,
MD,MSci,PhD,FEBOT
Assitant Professor of Orthopaedics , Head of the 5th Orthopaedic Dpt, HYGEIA Hospital, Athens, Greece, 210-6124007 (secr), sportdoc@otenet.gr

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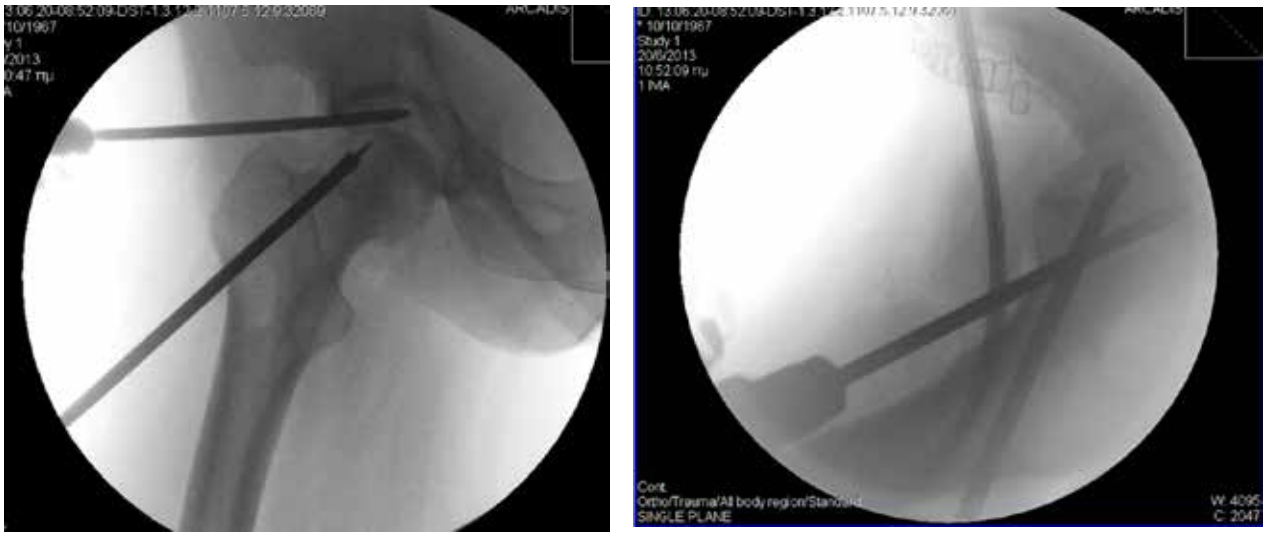

Figure 1: *Arthroscopic assisted Core Decompression retrograde drilling for ON. Intra-operative views on AP (a) and lateral (b)*

of the patients and possibly due to chronic abductor inefficiency secondary to the index disease. During the 1980s and early 1990s, studies reported high failure rates [7, 8]. More recent reports and systematic reviews show that the introduction of newer implants and better surgical technique, consistently deliver better clinical and implant survival results in comparison to the initial papers [9, 10]. The fact remains that we are dealing with mostly young patients the possibility of failure and revision of the THR constitutes a reality. As a result, there has been an increased focus on early interventions for ONFH aimed at preservation of the native articulation. During early stage disease, the most common joint preserving procedure performed is CD aiming to increase blood flow to the necrotic area by reducing the intraosseous pressure, alleviating pain and improving function [5, 6]. This chapter will focus on CD and discuss a number of its variations. It will also focus on adjunctive techniques introduced recently such as cell-based therapies that attempt to improve simple CD outcomes. This recent focus on biology is based on the hypothesis that the harvested cells injected or embedded into the necrotic zone of the femoral head will repopulate the lesion, restore the local cell population and enhance regeneration and remodeling [11, 12].

Core Decompression – (CD)

Core Decompression (CD) is the most common procedure performed for small or medium-sized lesions, especially at the pre-collapse stage [13, 14]. It is a generic term that is often accompanied with supplemental procedures (vascularized or non-vascularized grafts, injection of cells, grafting, electrical stimulation, etc.) [15]. Retrograde CD can be technically demanding, requiring biplanar imaging for proper placement of the core drill directly to the necrotic lesion [16].

During the last decade, the management of hip pathologies has progressed to less invasive techniques. Hence, hip arthroscopy has found its place in the management of ON. It can be of value, assessing the joint but also addressing mechanical pathology (chondral flap lesions, labral tears, loose bodies) commonly found in these hips. These lesions, are secondary to the periodic loss of the normal contour of the femoral head where the softened necrotic cancellous bone is unable to withstand physiologic forces.

Hip arthroscopy can also supplement fluoroscopic-assisted retrograde drilling, by guiding the accurate placement of the tip of the drill into the area of chondral softening or irregularity or the 'ballottable' segment of the femoral head, which corresponds to the underlying necrotic lesion [16]. Since

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Figure 2: *Core Decompression from the peripheral compartment to the necrotic lesion. Intra-operative AP Image Intensifier view*

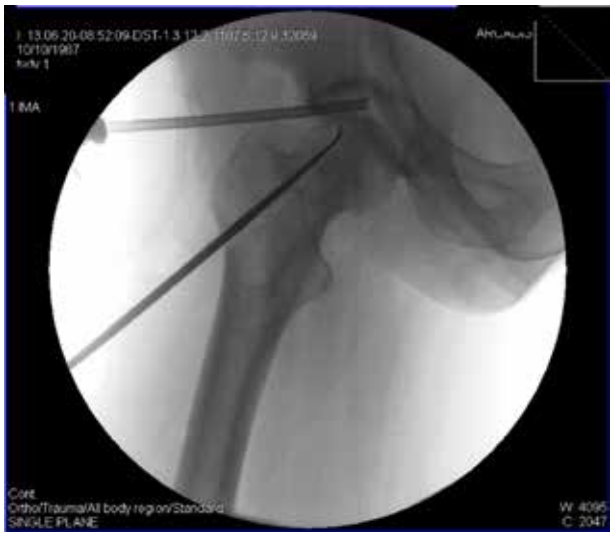

Figure 3: *Arthroscopic assisted curettage of the necrotic lesion prior to retrograde impaction of autologous graft.*

the drilling is done under direct vision it protects the femoral head from cartilage damage or penetration by the drill (**Fig. 1a, 1b**).

A modification to the retrograde drilling was proposed by Mont where the CD is performed through a window at the femoral head–neck junction (trapdoor technique) [17]. However, this procedure requires an extensive dissection, and it is also technically more difficult than a standard CD [15]. In a less invasive fashion, drilling can be guided arthroscopically under direct visualization by inserting the drill in the peripheral compartment thought the anterior or an auxiliary portal in the direction of the necrotic lesion. It is an area familiar to hip arthroscopists since it is the area that the cam lesion is located [18]. (**Fig. 2**)

Following the drilling, the necrotic lesion is cleared using a sharp curette. Fluoroscopic guidance is useful at this stage, helping to estimate the amount of necrotic lesion cleared. (**Fig. 3**)

At this stage, the preferred supplemental biological material can be placed in the lesion.

Conversely, joint effusion, secondary to ON related synovitis is seen up to 72% of cases regardless of articular collapse [19]. It is the author's opinion that an arthroscopic joint wash-out and synovectomy in selected cases can be of clinical benefit, since it reduces pain and joint effusion, improves range of motion and by reducing the capsular stress from the effusion possibly improving the blood flow to the femoral head [16].

Cell-based treatments of ONFH

The rational of cell-based treatments in ONFH

Most of the theories regarding the mechanism of spontaneous ONFH point toward alterations in intravascular blood flow, leading to decreased oxygenation, toxicity and cellular death. There are several recognized conditions and environmental insults that predispose patients to ONFH such as high-dose corticosteroid administration, alcohol abuse, hemoglobinopathy, Gaucher disease and coagulopathies [1, 13, 20].

A number of papers that have studied the exogenous insult of alcohol and corticosteroid administration suggest that they have a profound effect on bone marrow stromal cell differentiation, blood supply and oxygenation of the femoral head [21-

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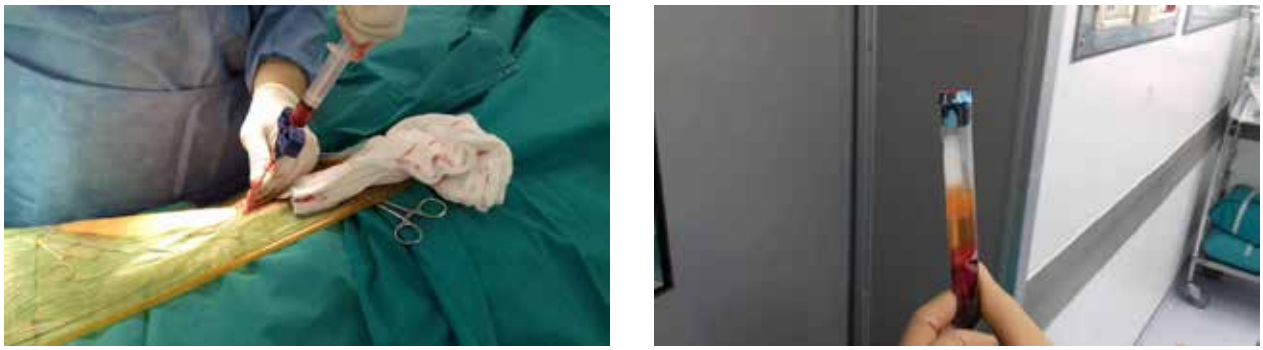

Figure 4: *Bone marrow aspiration from ASIS (a). The aspirate following centrifuge note the distinct cell separation (b).*

27]. Use of corticosteroids may deviate bone marrow stromal cells into the adipocytic pathway as opposed to the osteoblastic pathway [28–30]. A clinical study has also shown a decreased osteogenic differentiation in cells harvested from patients with corticosteroid or alcohol-associated ONFH [15]. Particular attention in this setting has been paid to the multipotent mesenchymal stem cells (MSCs), their ability to multiply and their capability to differentiate into various cellular types, such as osteoblasts, osteocytes, chondrocytes and adipocytes [12].

In ONFH, the decreased population and altered function of the MSCs may influence the two different events in the pathogenesis of ONFH; the actual occurrence of ONFH itself and the bone repair process that follows. Accepting the premise that an important part of the underlying pathology in ONFH is cell deficiency, the next rational step is to consider the use of cell-based treatments to enhance the regeneration of lost or damaged bone.

Although clinical experience has shown that dead bone may be replaced by living bone, the osteogenic potential for repair in ONFH is low. A decrease in osteogenic stem cells in the femoral head has been observed beneath the necrotic lesion up to the intertrochanteric region which might account for the insufficient creeping substitution in bone remodeling of the femoral head after ON. This can explain the fact that although reconstruction and repair has been observed after CD, it is usually slow and inadequate [29, 30].

Even though, MSCs act via not-completely understood multifaceted pathways, it seems that they perform two separate functions that can influence the natural history of ON: (i) secretion of a wide spectrum of factors with anti-inflammatory, antiapoptotic, proangiogenic, proliferative or chemo-attractive capacities, and (ii) initiating the differentiation process for functional tissue restoration [31]. In clinical practice, a common source for MSCs is bone marrow mononuclear cells (BMMCs) due to their ease of harvest (iliac crest or femoral condyles), their abundance and their marked osteogenic properties [31–34]. Tracking studies of BMMCs implanted directly into the necrotic area in ONFH showed 56% of installed cells remained in the implantation site 24hrs after implantation. Similar studies in animal models also demonstrated the survival and multiplications of these cells up to 12 weeks post-implantation [35–37].

The ideal number of transplanted cells

In 2002, Hernigou pioneered the technique of injecting MSCs combined with standard CD into the area of necrosis introducing the basic science of biology in ON [38]. In a study of 189 hips (116 patients), MSCs (in the form of concentrated iliac crest bone marrow) were injected through a CD tract into the area of necrosis. Patients with early (pre-collapse) disease had excellent results at 5–10 years of clinical follow-up, with only 9 of 145 hips requiring THR [39]. He also reported an association between the outcome of ONFH and the quantity of cells transplanted into the femoral head and recommended a specific minimum number of cell transplantation [11, 39, 40]. A total of 35.000 MSCs should be the

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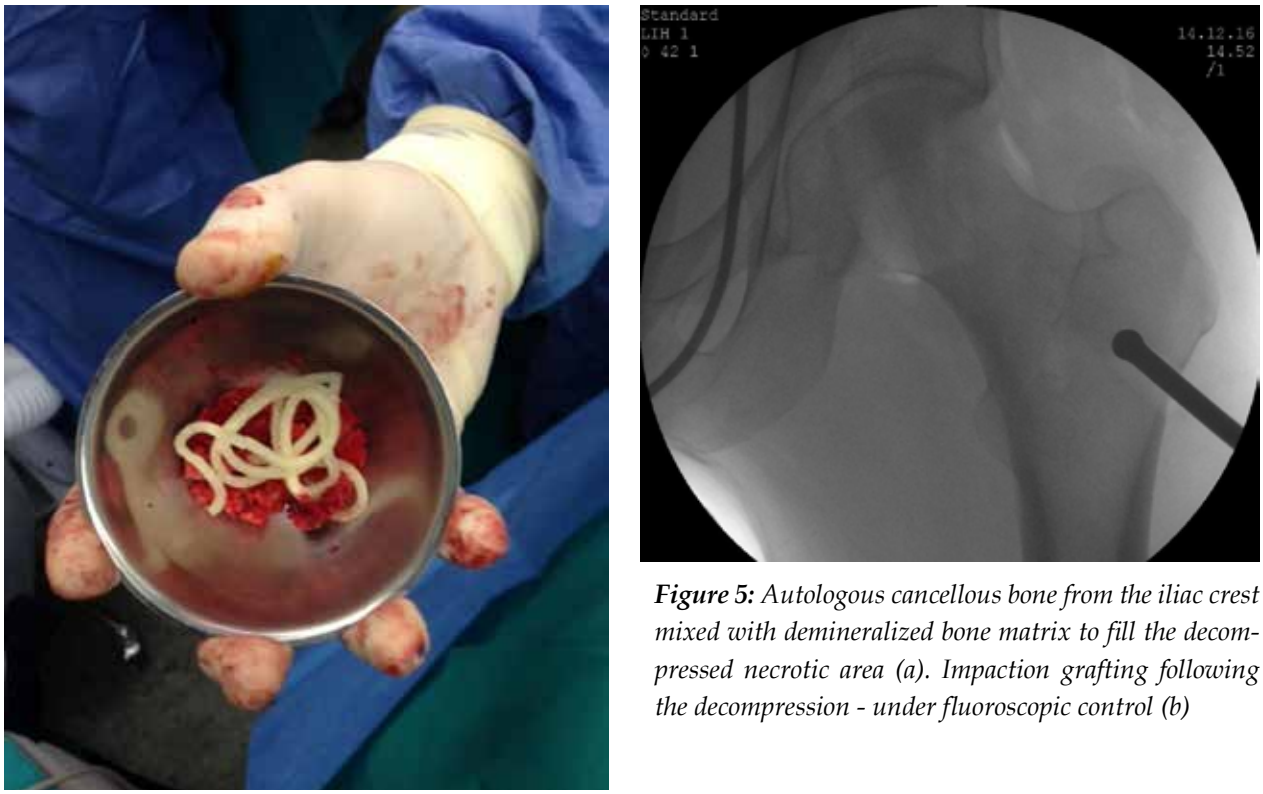

Figure 5: *Autologous cancellous bone from the iliac crest mixed with demineralized bone matrix to fill the decompressed necrotic area (a). Impaction grafting following the decompression - under fluoroscopic control (b)*

target number to load in an osteonecrotic femoral head in order to re-establish the same number of MSCs as in a normal femoral head [31]. However, the exact number of MSCs that is required to induce remodeling and repair of the osteonecrotic zone is still unknown. [12]

The harvesting technique of the cellular population

The most common site to collect bone marrow is either the anterior or posterior part of the iliac crest depending on the patient positioning and surgeon preference. (FIGURE 4a) Collection of bone marrow from the iliac crest can be accomplished by the use of a single beveled aspirating needle. A number of such systems are available commercially. The highest quality of bone marrow aspiration (number of stem/progenitor cells) is when the aspirate is in small volumes (1–2 ml) and from different locations since, when a greater volume is drawn from any single area the peripheral blood infiltrates and dilutes the aspirate [41]. Technically, in order to achieve this, the needle is turned during successive aspirations thereby affording access to the largest possible space. After one full turn, the needle is slowly moved toward the surface and the process is repeated. The pooled aspirates (the volume can range between 30 and 120 ml) is filtered to separate cellular aggregates and fat. (**Fig. 4b**) The aspirated material should be reduced in volume in order to increase the stem cell concentration. This is done with centrifugation, which separates the red blood cells (non-nucleated cells) and plasma in such a way as to retain only the nucleated cells: mononuclear stem cells, monocytes and lymphocytes. Removing the non-nucleated cells the aspirate is reduced to a concentrated myeloid suspension of stem cells which can be used for reinjection.

The intraosseous application of the cellular population

The procedure is performed at the time of CD. Following the drilling, the thin hip arthroscopy nitinol guidewire can be inserted in the femoral head following the CD track and then, over it, the cannulated arthroscopic needle. This ensures that the drill track is followed and the accurate placement of the injected MSCs in the necrotic lesion. Backflow of the injected medium is not observed since the fluid diffuses to surrounding cancellous bone of the femoral

head. During the injection time, the pressure in the femoral head can rise, but a normal pressure pattern is restored once the injection is finished [31]. Anecdotally, if excision of the cam deformity is done in conjunction with the CD drilling, overflow of the injected fluid can be observed from the exposed cancellous bone of the osteoplasty site after the injection of the first 10–15 ml, allowing the osteoplasty to act as a release 'valve' to the increased pressure [18].

Types of cell-based populations

a. Bone marrow mononuclear cells (BMMSCs)

In clinical practice, the most common source of cell therapies are BMMCs due to their ease of harvest (iliac crest) and their abundance [31–34]. Equally, the most common joint preserving procedure performed for ONFH is CD [5, 6]. Hence, the combination of the two is naturally the most researched and best published. There are a number of studies that use BMMC therapy [35, 40, 42–49]. These studies for the treatment group report variations in the source of cells, method of cell processing, cell characterization, quantitative and qualitative assessment of the cells used, surgical method of implantation, adjuvant therapies (i.e. use of structural graft), patient cohorts (age, etiology of ON), ONFH classification and the outcome measures used [3, 12, 37, 50]. The clinical effectiveness of a procedure is usually analyzed by the use of a patient-reported outcome (PRO), imaging and the endpoint which—in this case—is the conversion to a THR. A recent systematic review, including 11 studies with a level of evidence III or higher, concluded that the use of cell treatments for ON has been reported to be safe and suggest improved clinical outcomes with a lower rate of deterioration [3].

b. Peripheral blood stem cells (PBSCs)

A recent randomized clinical trial (55 patients and 89 hips) described the use of mechanical support treatment (porous tantalum rod implantation) in combination, for the treatment group, of intra-arterial delivery via medial circumflex femoral artery of PBSCs [51, 52]. At 36 months, compared with the control group, combination treatment significantly improved the functional scores, had better survival for conversion to THR and better radiological progression. The authors concluded that targeted intra-arterial infusion of PBSCs is capable of enhancing the efficacy of biomechanical support in the treatment of ONFH.

A. Non-cell-based biological treatment of ONFH

a. Bone morphogenetic proteins (BMPs)

In 2004, Lieberman et al. were the first to report a retrospective evaluation of 15 patients (17 hips) with symptomatic ONFH treated with CD combined with an allogeneic antigen-extracted, autolyzed fibular allograft and 50 mg of partially purified human BMP and non-collagenous protein [53]. The results were encouraging but there was no comparative group and therefore the exact therapeutic impact of BMP on the overall outcome cannot be verified. A large case series (39 hips) on the use of BMPs in ONFH was published by Seyler et al. [54]. They used the trap door technique to make a window at the head–neck junction to remove the necrotic bone and to pack the excavated area with autologous cancellous bone graft, marrow and OP-1(BMP 7).

The overall early clinical success rate was 67% after a mean follow-up period of 36 months. The size of the lesion and the staging of ONFH had a significant influence on the survival of the hips in their series. In 2014, Sun et al. evaluated clinical outcomes of impacted bone graft with or without human-recombinant BMP-2 for ONFH on 42 patients (72 hips) [55]. After a mean follow-up of 6.3 years, the survival rate of the FH was 64.1% in the group treated with the bone graft alone and 69.7% for those patients treated with bone graft and BMP-2. Therefore, no statistical difference was found.

The authors have used BMPs when the cleared necrotic lesion cannot be filled with just autologous graft (**Fig. 5a, 5b**).

b. Platelet-rich plasma (PRP)

A small study (3 patients) was published in the use of PRP and bone grafting for the ONFH treatment [56]. Arthroscopic CD was achieved by drilling through the base of the head and then 10 ml of 'liquid PRP' was delivered into the necrotic area. In

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cases with advanced stage ON, full debridement of the necrotic lesion was carried out by a window in the head and neck junction and autologous bone graft mixed with PRP was grafted into the necrotic area. Hemostasis and enhanced healing were obtained by placing autologous fibrin membranes over the cortical window opened in the base of the femoral head. All three patients reported a significant reduction in pain intensity by >60% on a VAS scale and a return to activities of daily living by 5months.

Postoperative evaluation and outcomes of biological treatment of ONFH

There are many variations of the MRI signal during the creeping regeneration in the absence of collapse; furthermore, when scaffolds are used, their presence remains visible in the femoral head for a long time, and act as an artifact limiting the ability of the MR to evaluate the exact repair. Therefore, traditionally, most clinical studies report as an imaging outcome measure the absence of collapse during the evolution of ON [31, 57, 58]. Cell-based therapies have structural modifying effect measured by both MRI and radiographs with decreased rate of ONFH progression or even in some cases, restoration of original MR signal of a living bone marrow [3]. In a recent review by Piuzzi, from 93 out of 380 hips (24.5%) that belonged to the treatment group and received cell therapy showed radiographic progression compared with 98 of 245 hips (40%) of the control group [3].

Improvements in one or more patient reported outcomes (PROs) were reported for cell therapy groups when compared with noncell therapy groups. It seems that cell therapy with CD showed improvement in mHHS, VAS and WOMAC scores when compared with CD alone [3].

In most studies, success or failure is determined mainly by the endpoint of patient undergoing a THR. THR conversion reported lower rates in the cell-therapies treatment groups [3]. These reports should be considered positively and even promising [35, 42, 44–46, 48, 50] despite the fact that the decision to offer THR (surgeon bias) and the decision to accept THR (patient bias) are subjective decisions that can be influenced by a number of factors.

Conclusions

Conclusively, a definitive pathogenetic mechanism for ONFH remains elusive. But, since an important part of the underlying pathology in ON is cell deficiency, it is rational to consider the use of cell-based treatments to potentially regenerate lost or damaged bone. Cell therapies, particularly when employed at early stages of ONFH, improve clinical results and the survivorship of the native hip, reducing the need for hip replacement. The debate remains on the ideal source, the lack of standardization and optimization of the harvested cells, their processing, method of transplantation and even method of surgical delivery. The abundance of different cell-based treatments and our ability to control the behavior of the cells after implantation naturally raises some concerns on their long-term safety. None of the studies reported any major adverse events but the quality of the evidence remains inadequate with long-term safety data still required [37].

It is the authors' belief that the use of cell-based therapies constitutes good clinical practice since it is safe, adds minimal surgical time and difficulty, very little morbidity, this of the donor site, and potentially can influence only positively the outcome of CD. We agree with other published literature that there is enough evidence that cell therapy should not be considered experimental but rather a developing technique [58, 59].

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Triantafyllopoulos IK, Papavasiliou A. Biological therapies for the treatment of early stage pre-collapse osteonecrosis of the femoral head. *Acta Orthop Trauma Hell* 2020; 71(1): 23-32.