Evidence for the use of cell-based therapy for the treatment of osteonecrosis of the femoral head: A Systematic Review of the literature

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ABSTRACT:

Background: Cell-therapy has been promoted among the therapeutic arsenal that can aid in bone formation and remodeling, in early stages of osteonecrosis of the femoral head (ONFH). The purpose of this systematic review was to assess the evidence supporting the: (1)clinical efficacy; (2)structural modifying effect; as evaluated radiographically (3) revision rates; and (4)safety of cell-therapy for the treatment of ONFH.

Methods: A systematic review was performed including studies with a Level of Evidence of III or higher. A total of 1,483 papers were screened. Eleven studies met the criteria for inclusion in this review (Level-of-evidence: 6 level-I, 1 level-II, and 4 level-III), including 683 cases of ONFH.

Results: All ten studies that reported patient reported outcomes showed improved outcomes in the cell therapy groups compared to control. Overall 24.5%(93/380 hips) that received cell-therapy showed radiographic progression compared to 40% (98/245 hips) in the control group. Nine of ten studies that reported failure rates showed a lower total hip arthroplasty conversion rate in the cell-therapy group 16%(62/380 hips) compared to the control group 21%(52/252 hips). There was a low complication rate (<3%) with no major adverse effects reported.

Conclusion: Cell-therapies for the treatment of ONFH have been reported to be safe and suggest improved clinical outcomes with lower disease progression rate. Cell-therapy may hold future promise as a stand-alone procedure or as an adjuvant therapy. Specific clinical indications and cell therapy standardization are required since studies varied widely with respect to cell sourcing, cell characterization, adjuvant therapies, and assessment of outcomes.

Level of Evidence: III, Systematic Review

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Conclusion: Cell-therapies for the treatment of ONFH have been reported to be safe and suggest improved clinical outcomes with lower disease progression rate. However there was substantial heterogeneity in the included studies, and in the cell-based therapies used. Cell-therapy may hold future promise as a therapy for ONFH. Specific clinical indications and cell therapy standardization are required since studies varied widely with respect to cell sourcing, cell characterization, adjuvant therapies, and assessment of outcomes.

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INTRODUCTION

Osteonecrosis of the femoral head (ONFH) accounts for approximately 8 to 12% of all total hip arthroplasties (THA) cases in the United States.[1] It is characterized by compromised subchondral microcirculation, necrosis of the bone, and microfracture accumulation without sustained remodeling.[2,3] Since ONFH most frequently occurs in young patients, and progression to symptoms or collapse occurs in approximate 60% of asymptomatic patients,[3,4] joint preserving techniques should be considered in early pre-collapse stages, to avoid or delay the cost and risk of THA, especially when patients are caught in early (pre-collapse) stages.[5]

Core decompression (CD) is a surgical technique for joint preservation in early ONFH, typically performed by drilling to remove a cylindrical core through the femoral neck deep into the osteonecrotic lesion.[1,6] This is believed to reduce the pressure in the femoral head and open an unobstructed path through which potential revascularization can occur with restoration of bone formation and remodeling. However, long-term results on this procedure can be unpredictable,[7] and its efficacy remains an area of controversy.[6]

Currently, there is no consensus regarding the treatment of early stages of ONFH.[2] Although a variety of treatments, ranging from non-operative (e.g. bisphosphonates) to operative (core decompression, bone grafting, vascularized fibular grafting, rotational osteotomy, etc.) have been proposed, none of these have been proven to be clearly superior so that widespread adoption has occurred. To date, THA is the most frequent intervention for post-collapse treatment, and core decompression is commonly performed for symptomatic, pre-collapse cases.[8] Adjunctive techniques have been described in an attempt to improve core decompression outcomes, and specifically cell-based therapies are being explored to restore the local cell population and to establish effective bone remodeling.[9,10] The purpose of the present study was to provide a systematic review of the current literature on the use of cell-based therapies for the treatment of ONFH. Our specific aims were to examine the evidence supporting their: (1) clinical efficacy, (2) structural modifying effect, as evaluated radiographically (3) revision rates, and (4) safety.

MATERIALS AND METHODS

Article identification and selection

This study was conducted in accordance with the 2009 Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement.[11] Reports were identified by using an electronic search of keyword terms and combinations. A systematic review of the literature regarding the cell-therapy treatment of ONFH in human patients was performed using the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, PubMed (1990-2016), and Medline (1990-2016). The queries were performed in October of 2016.

Four different searching criteria were utilized, using the search terms: cell-therapy, stem-cells, hip, osteonecrosis, and avascular necrosis:

Search 1: ("cell- and tissue-based therapy"[MeSH Terms] OR ("cell-"[All Fields] AND "tissue-based"[All Fields] AND "therapy"[All Fields]) OR "cell- and tissue-based therapy"[All Fields] OR ("cell"[All Fields] AND "therapy"[All Fields]) OR "cell therapy"[All Fields]) AND ("hip"[MeSH Terms] OR "hip"[All Fields])

Search 2: ("stem cells"[MeSH Terms] OR ("stem"[All Fields] AND "cells"[All Fields]) OR "stem cells"[All Fields] OR ("stem"[All Fields] AND "cell"[All Fields]) OR "stem cell"[All Fields]) AND ("hip"[MeSH Terms] OR "hip"[All Fields])

Search 3: (("osteonecrosis"[MeSH Terms] OR "osteonecrosis"[All Fields] OR ("avascular"[All Fields] AND "necrosis"[All Fields]) OR "avascular necrosis"[All Fields]) AND ("hip"[MeSH Terms] OR "hip"[All Fields])) AND ("cell- and tissue-based therapy"[MeSH Terms] OR ("cell-"[All Fields] AND "tissue-based"[All Fields] AND "therapy"[All Fields]) OR "cell- and tissue-based therapy"[All Fields] OR ("cell"[All Fields] AND "therapy"[All Fields]) OR "cell therapy"[All Fields])

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Studies were included in this systematic review if the reports contained clinical and/or radiological outcomes for cell-therapy in the treatment of ONFH with a minimum follow-up of 12 months, and had a level of evidence of I, II, or III. All included articles were presented in the English language, and were performed on human subjects. Exclusion criteria were as follows: cadaveric studies, animal studies, basic science articles, editorials, surveys, special topics, letters to the editor, and personal correspondence.

Two authors performed the initial search (NSP, JC), and three investigators (NSP, CPG, JC) independently reviewed the abstracts from all identified articles and inclusion and exclusion criteria were applied based on the information presented therein. If one or more authors selected a paper, it progressed to the following phase. Full-text articles were obtained to allow further assessment of inclusion and exclusion criteria, as needed. Additionally, all references from the included studies were reviewed and reconciled to verify that no relevant articles were missing from the systematic review.

Level-of-evidence was assigned using classifications specified by Wright et al.[12] Data was recorded into a custom information extraction table.[13]

Study Selection

Our initial systematic literature review yielded 1,483 individual studies, of which twelve met the inclusion criteria and were identified and included for analysis. (**Figure I)** One study was excluded after communication with the authors to avoid patient duplication.[14] After review of the eleven remaining reports according to the level of evidence, six were level I, one was level II, and four were level III.

Patient Demographics

The eleven studies included 528 ONFH patients as summarized in Table I. Of the 683 hips, 416 hips received a cell-therapy procedure for the treatment of ONFH and 155 were bilateral. Mean patient age was 37 years (range, 27 to 49 years). The classification systems utilized were: ARCO classification[15,16]: 47 (Grade I); 288 (Grade II); 50 (Grade III).[14,17–21] Ficat classification[22] 7 (Grade I); 134 (Grade II); and 67 (Grade III);[23,24] Japanese Orthopaedic Association Staging: 2 (Grade I), 25 (Grade II25), 3 Grade IIIA and Mitchell staging system: 13 (grade A); 13 (Grade B); 19 (Grade C) and 1 (Grade D) (5 patients were not classified according MRI Mitchell's classification because of hardware presence).[25] From this data, it can be calculated that 81% of the studied hips were Ficat stages 1 to 2. Mean follow-up was 37 months (range, 24 to 60 months).

Clinical efficacy - Patient Reported Outcomes Measures (PROs)

Ten of the eleven studies[17–21,23–28] analyzed the outcome of treatment in the cell-therapy and control treatment groups using Patient Reported Outcomes (PROs) (Table 2 & 3). Three studies reported pre-treatment and follow-up status using Western Ontario & McMaster Universities Arthritis Index score (WOMAC) [17,20,23]; and six studies reported pain using a visual analog scale (VAS). [14,17,20,23,26,27] Six studies reported Harris Hip Score (HHS) outcomes,[18,19,25–27] however, one study did not include standard deviations.[19] Two studies[17,23] reported baseline and follow-up status using a Lequesne index. One study reported clinical outcome with the System of Merle d´Aubigne and Postel.[28]

Structural modifying effect - Structural assessment with images

All eleven studies performed imaging structural assessments. Seven studies[17,19–21,25,27,28]did structural assessments with Magnetic Resonance Imaging (MRI) (Table 2 & 4) Four studies assessed disease progression through x-ray radiographic evaluation only.[18,23,24,26,29] Two hundred sixty-eight hips in 6 studies[19,20,23,25–27] were followed up for 24 months; 286 hips in 3 studies[17,21,24] were followed up for 60 months, 89 hips in one study[18] were followed for 36 months, 39 hips in one study were followed up for 18 months.[28]

Revision rates – Conversion to Total hip Arthroplasty (THA)

Ten of the eleven studies reported failure rates based on conversion to THA.[17–21,23,24,26–28]

Safety – Complications

Complications were reported in all eleven studies, although one of them did not provide details, and was excluded for the analysis.[24]

RESULTS

Overall cell-therapies showed improved clinical outcome, decreased radiographic progression and decreased revision rate. (**Table 2**)

Clinical efficacy - Patient Reported Outcomes Measures (PROs)

All ten studies that reported PROs showed improved outcomes in the cell therapy groups (278 hips) compared to control (254 hips). (**Table 3**) The five studies that reported pain according to VAS, demonstrated substantial improvement in cell therapies groups (91 hips) compared to control groups (90 hips). [21,25,28,31,32] Two of these five studies reported similar favorable findings with WOMAC score evaluations (39 hips treated with cell-therapy vs. 38 hips control),[25,28] even though one study[17] did not find differences between the cell-therapy (13 hips) and the control group (11 hips). Nonetheless, this later study included the Lequesne index and reported significant difference in favor of cell-therapy group (13 hips), compared to control group (11 hips).[17]

All six studies that provided a HHS score assessment showed improvement in both cell therapies (188 hips) and control groups (196 hips). Nevertheless the improvement was greater among the cell therapies groups among the six studies. [18,19,21,25–27]

Structural modifying effect - Structural assessment with images

Nine studies demonstrated a reduced progression, no progression or even regression of ONFH lesions with the use of cell-therapies (221 hips) compared to controls (252 hips).[17–21,23,25,27,28] In contrast, two studies [24,25] found no significant differences by MRI with the use of cell-therapy (154 cell therapy cases vs. 56 controls). Overall 24.5% (93/380 hips) that received cell therapy showed radiographic progression compared to 40% (98/245 hips) in the control group. (**Table 4**)

Revision rate – Conversion to Total hip Arthroplasty (THA)

Nine of ten studies that reported revision rates showed a lower THA conversion rate in the cell-therapy group 16% (62/380 hips) compared to the control group 21% (52/252 hips), however the difference was not significant in all studies: 0/10 to 3/30(10%)[19]; 3/48(6%) to 9/41(22%) ($p = 0.031$)[18]; 2/25(9%) to 4/24(22%)[23]; 0/53 to 5/51(11%) ($p<0.05$)[21]; 2/13(15%) to 3/11 (27%)($p=0.008$)[17]; 4/28(14%) to 5/27(19%)[26]; 1/30(3%) to 3/9(33%)[28]; 0/14 to 3/14(21%)[20] and 4/11(36%) to 6/14(43%) ($p>0.05$)[27] (See **Table 5**). Only one study had a higher THA conversion rate in the cell therapy group: 47/128(37%) to 11/31(35%)($p<0.8527$)[24], although this difference was not statically significant.

Safety – Complications

From the 10 included studies (524 hips) that provided data on complications, there were a total of 15/524 (2.8%) reported complications (**Table 5**). For these minor complications, six complications appeared in the control group (6 adverse events/246 hips: 2.4%), and eight complications in the cell-therapy group (8 adverse/ 278 hips: 2.9%). There were no major adverse effects reported. The most common complaint was pain in association with a hematoma at the site of the core decompression and pain at the bone marrow aspiration site. Two patients had an infection.[17,23] One of the patients presented with a positive bacteriological culture of the bone marrow (coagulase negative staphylococci) and was treated with antibiotics, but had no clinical symptoms of sepsis.[17] The other patient was in a control group and experienced a post-operative infection that was successfully treated with antibiotics.[18] We did not find significant different between cell-therapy groups and control

groups in term of complications and there were no reported events related to the cell therapy, no constitutional symptoms reported.

DISCUSSION

The most important findings of this study were that the utilization of cell therapies in patients with early stages of ONFH when compared to their control groups showed overall: (1) favorable results based on patient-reported outcomes, (2) a lower disease progression rate, (3) a lower failure rate, and (4) safety in the use of cell-based therapies with rare and minor complications.

Our systematic review had several limitations. First, there was a wide variation in the cell-based therapies used, specifically regarding the choice of cells, method of cell processing, cell characterization, quantitative and qualitative assessment of the cells used, surgical methods of cell delivery, the attributes of patient cohorts, and the outcome measures used. As a result, generalizable conclusions regarding the magnitude of treatment effect and the relative efficacy between the treatment strategies that have been evaluated must be made with caution. Second, the selection for success or failure was determined mainly by the endpoint of patient undergoing a THA, which may not be the most accurate measure. Third, although 81% of the studied hips were classified as Ficat stage I and stage II, we could not consistently analyze and correlate the size of lesion with progression, since it was infrequently reported. Fourth, the results presented in this study have a mean follow-up of 37 months (range 24 to 60 months), which could underestimate the progression and failure rate of these therapies. Despite these variations and limitations noted, these studies demonstrated generally beneficial effects of the cell-based therapies that warrant further investigation.

In each study, improvements in one or more PRO were reported for cell-therapy groups when compared to non-cell-therapy groups was found.[17–21,23–28] In our assessment, cell-therapy with core decompression treatment showed improvement in mHHS, VAS, and WOMAC scores when compared to core decompression alone. Our findings are supported by other pre-

clinical and clinical reviews on the use of cell-therapy for the treatment of ONFH.[29,30] After pain and function, conversion to THA can be considered to be the next most important outcome. Eight of nine studies[17–19,21,23,26–28] reporting on THA conversion reported lower rates in the cell-therapies treatment groups. These reports should be considered positively and may be promising. However, it must also be recognized that the decision to offer THA and the decision to accept THA are subjective decisions that are not immune from bias without double blind study design. Conversely structural modifying effect measured both by MRI and x-ray radiograph showed that cell-based therapies decreased the progression rate, with a more significant effect among earlier stages of ONFH.

The only study that did not encounter positive results in any aspect analyzed was Lim et al.[24] However looking at the data it appears that the cell group had a number of factors that could have introduced bias and predisposed to worse results: 1) Steroid was the cause of ONFH in 56% of cases in the cell therapy group while in the control group it was 29%. 2) Underlying disease in the cell therapy group comprised between leukemia, aplastic anemia and kidney transplantation a 47% while in the control group it was 19%. These differences might have introduced bias since these causes are known to have worst result not only in hip preservation procedures but in THA as well.[1,2,4,6,31,32]

Based on the current literature the use of cell therapies has been reported to be safe in multiple orthopaedic settings.[33–37] In this study, the rate of complications was low, and we did not find any difference between the cell therapy group and control group. All complications reported were related to donor site morbidity, from the harvest site and there were no reports of complications attributed to the delivery of cells or follow-up.

At early stages of ONFH, hip preservation techniques are often preferred, specifically in younger patients.[8,31,38–40] The rationale for the use of a cell-therapy approach is that regions of osteonecrosis can only be repaired by bone regeneration and remodeling through the action of bone forming osteogenic progenitors. As regenerative medicine and the application of cell therapies become available, a better understanding of these treatments will be required. Among the pool of “cell-based therapies” more diversity was present, and stem

and progenitor cell population varied among: i) sources; ii) patients; and iii) processing methods. Cell types available to be used may include: a) autologous or allogenic cells; b) adult, embryonic or IPSCs (induced pluripotential stem cells); c) native (tissue resident) stem and progenitor cells or cultured expanded cells (e.g.: Mesenchymal Stromal Cells - MSCs).[41–53] The analysis and description of these heterogeneous cell-therapy options are beyond the scope of this manuscript.

CONCLUSION

Cell-therapies in patients with early stages of ONFH suggest: (1) improved clinical outcomes; (2) decreased radiographic progression of disease; (3) decreased revision rate; and (4) a low complication rate. There was a high heterogeneity in cell-therapies used and the outcome measures selected. Cell-therapies offer a promising future; nevertheless its propagation and acceptance will demand the implementation of standardization to allow reproducibility. Additional blinded randomized control trials and clinical effectiveness trials with rigorous standards are needed to establish the efficacy of these therapies for the treatment of ONF

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Table 1. Demographic data of the inlcuded studies

Author	Country	Year	Journal	Ev	Study Design	Type	Treatment	Male	Female	Number cases (Hips)	Mean Age	Mean FU (months)	Etiogenic	Ficat classification	ARCO classification	Japanese Orthopaedic Association Staging	Mitchell Staging
Rastogi et al.	India	2013	Musculoskeletal Surg	III	RCT	Control	CD + unprocessed bone marrow	3/1 Ratio		30	33	24	Idiopathic (46%); Alcohol (7%); Smoking (13%); Steroid (33%)	N/A	IB (2), IC (5), IIB (3), IIC (8), IIIB (5)and IIIC (7).	N/A	N/A
						Study	CD + Cells	5/2 Ratio		30	34.67		Idiopathic (40%); Alcohol (20%); Smoking (13%); Steroid (27%)	N/A	IB (2), IC (5), IIB (3), IIC (8), IIIB (5)and IIIC (7).	N/A	N/A
Sen et al.	India	2012	The Journal of Arthroplasty	II	RCT	Control	CD	18	7	25	N/A	24	Traumatic 17 hips; Non-traumatic 34 hips, 8 chronic alcoholism, 2 idiopathic, 2 pregnancy induced , and 2 Cushing disease	N/A	N/A	N/A	A (7), B (4), C (8) and D (1)
						Study	CD + Cells	19	7	26				N/A	N/A	N/A	A (6), B (9), C (11)
Mao et al.	China	2015	Journal of Bone and Mineral Research	I	RCT	Control	Porous tantalum rod	13	12	41	36.12	36	Idiopathic (29%); Alcohol (34%); Steroid (36%)	N/A	I (10), II (23), IIIA	N/A	N/A
						Study	Porous tantalum rod + intraarterial cell infusion	17	13	48	34.6	36	Idiopathic (29%); Alcohol (37%); Steroid (33%)	N/A	I (8), II (29), IIIA (11)	N/A	N/A
Ma et al.	China	2014	Stem Cell Research & Therapy	I	RCT	Control	CD + autologous bone graft	13	5	24	34.78	24	Idiopathic (6); Alcohol (3); Steroid (13)	I (4), II (15), III (5)	N/A	N/A	N/A
						Study	CD + autologous bone graft + Cells	15	6	25	35.6	24	Idiopathic (6); Alcohol (4); Steroid (13)	I (3), II (17), III (5)	N/A	N/A	N/A
Zhao et al.	China	2012	Bone	I	RCT	Control	CD	26	24	51	33.8	60	Trauma (12); Idiopathic (13); Alcohol (7); Steroid (13); Caisson Disease (5)	N/A	IC (2), IIA (15), IIB (22), IIC (12)	N/A	N/A
						Study	CD + Cells	27	23	53	32.7	60	Trauma (8); Idiopathic (16); Alcohol (11); Steroid (10); Caisson Disease (5)	N/A	IC (4), IIA (15), IIB (23), IIC (11)	N/A	N/A
Tabatabaee et al.	Iran	2015	The Journal of Arthroplasty	I	RCT	Control	CD	10	4	14	26.8	24	Idiopathic (36%); Steroid (64%)	N/A	I (2), II (7), III (5)	N/A	N/A
						Study	CD + Cells	9	5	14	31	24	Idiopathic (29%); Steroid (71%)	N/A	I (3), II (9), III (2)	N/A	N/A
Gangji V et al. 2011	Belgium	2011	Bone	I	RCT	Contol	CD	9	10	11	45.7	60	Idiopathic (1); Alcohol (1); Steroid (9)	N/A	I (2), II (9)	N/A	N/A
						Study	CD + Cells			13	42.2	60	Idiopathic (1); Alcohol (1); Steroid (11)	N/A	I (2), II (11)	N/A	N/A
Lim et al.	Korea	2013	Experimental & Molecular Medicine	III	Retrospective Cohort Study	Control	CD + curettage + bone graft	16	5	31	34.4	60	Idiopathic (10); Steroid (6); Alcohol (4); other (1)	I (0), IIa (14), IIb (9), III (8)	N/A	N/A	N/A
						Study	Multiple drilling + cells	69	17	128	36.3	60	Idiopathic (15); Steroid (48); Alcohol (20); other (3)	I (0), IIa (42), IIb (37), III (49)	N/A	N/A	N/A
Liu et al.	China	2013	Arch Orthop Trauma Surg	III	Retrospective Cohort Study	Control	CD + hydroxyapatite bone filler	14	3	27	38.1	24.9	Idiopathic (4); Steroid (9); Alcohol (14)	N/A	IIB (12), IIC (15)	N/A	N/A
						Study	CD + hydroxyapatite bone filler +cells	13	4	28	38	26.7	Idiopathic (3); Steroid (10); Alcohol (15)	N/A	IIB (13), IIC (15)	N/A	N/A
Yamasaki T. Et al.	Japan	2010	The Journal of bone and joint. Br.	III	Retrospective Cohort Study	Control	CD + calcium hydroxyapatite bone filler	7	1	9	49	31	Idiopathic (3); Steroid (2); Alcohol (4)	N/A	N/A	II(8)	N/A
						Study	CD + calcium hydroxyapatite bone filler + cells	14	8	30	41	29	Idiopathic (2); Steroid (22); Alcohol (6)	N/A	N/A	I(2), II(25),IIIA(3)	N/A
Pepke W. Et al. 2016	Germany	2016	Orthopedic reviews	I	RCT	Control	CD	12	2	14	45	24	Idiopathic (9); chemotherapy (2); innmunosupression (3)	N/A	II(14)	N/A	N/A
						Study	CD + Cells	10	1	11	44.3	24	Idiopathic (10); chemotherapy (0); innmunosupression (1)	N/A	II(11)	N/A	N/A

Ev: Level of Evidence; **RCT**: Randomized Controlled Trial; **CD**: Core Decompression; N/A: Not Available

Table 2. Outcome analysis of the eleven studies included

Author	Group	Treatment	Number of ONFH	Clinical Outcome	Radiological outcome	Revision Rate - THA
Rastogi et al. 2013	Control	CD + unprocessed bone marrow	30			
	Study	CD + Cells	30	↑	↑★	↑★
Sen et al.2012	Control	CD	25		=	N/A
	Study	CD + Cells	26	↑★	=	N/A
Mao et al. 2015	Control	Porous tantalum rod	41			
	Study	Porous tantalum rod + intraarterial cell infusion	48	↑★	↑★	↑★
Ma et al. 2014	Control	CD + autologous bone graft	24			
	Study	CD + autologous bone graft + Cells	25	↑★	↑★	↑★
Zhao et al. 2012	Control	CD	51			
	Study	CD + Cells	53	↑★	↑★	↑★
Tabatabaee et al. 2015	Control	CD	14			
	Study	CD + Cells	14	↑★	↑★	↑★
Gangji V et al. 2011	Contol	CD	11			
	Study	CD + Cells	13	↑★	↑★	↑★
Lim et al. 2013	Control	CD + curettage + bone graft	31	=	=	=
	Study	CD + cells	128	=	=	=
Liu et al. 2013	Control	CD + hydroxyapatite bone filler	27			
	Study	CD + hydroxyapatite bone filler +cells	28	↑★	↑★	↑★
Yamasaki T. et al. 2010	Control	CD + calcium hydroxyapatite bone filler	9			
	Study	CD + calcium hydroxyapatite bone filler + cells	30	↑	↑★	↑★
Pepke W. Et al. 2016	Control	CD	14			
	Study	CD + Cells	11	↑	↑	↑

"N/A", Not available ″=″ No difference ↑ Better result ★ Significant difference ($p<0.05$)

Table 3. Clinical Outcome

Author	Group	Treatment	Number of ONFH	VAS baseline (mm)	VAS F/U (mm)	WOMAC baseline	WOMAC F/U	Lequesne index baseline	Lequesne index F/U	HHS baseline	HHS F/U	System of Merle d´Aubigne and Postel baseline	System of Merle d´Aubigne and Postel F/U
Rastogi et al. 2013	Control	CD + unprocessed bone marrow	30	N/A	N/A	N/A	N/A	N/A	N/A	47.08	66.8	N/A	N/A
	Study	CD + Cells	30	N/A	N/A	N/A	N/A	N/A	N/A	46.75	78.6	N/A	N/A
Sen et al.2012	Control	CD	25	N/A	N/A	N/A	N/A	N/A	N/A	65.7 ± 15.2	77.4 ± 17.0	N/A	N/A
	Study	CD + Cells	26	N/A	N/A	N/A	N/A	N/A	N/A	66.2 ± 13.0	82.4 ± 9.6	N/A	N/A
Mao et al. 2015	Control	Porous tantalum rod	41	N/A	N/A	N/A	N/A	N/A	N/A	64.6 +/- 8.6	78.5 +/- 8.7	N/A	N/A
	Study	Porous tantalum rod + intraarterial cell infusion	48	N/A	N/A	N/A	N/A	N/A	N/A	62.7 +/- 11.1	88.1 +/- 3.3	N/A	N/A
Ma et al. 2014	Control	CD + autologous bone graft	24	35.2 +/- 3.4	26.5 +/- 2.6	24*	22*	9.8	7*	N/A	N/A	N/A	N/A
	Study	CD + autologous bone graft + Cells	25	35.6 +/- 4.2	16.9 +/- 3.7	27.8 +/- 4.2	14.8 +/- 3.0	9.6 +/- 1	5.8 +/- 1	N/A	N/A	N/A	N/A
Zhao et al. 2012	Control	CD	51	N/A	N/A	N/A	N/A	N/A	N/A	CD + cells compared to CD alone contributed to greater improvement of HHS in hips of Stages IC (P<0.01), IIA (P=0.06), IIB (P<0.01), and IIC		N/A	N/A
	Study	CD + Cells	53	N/A	N/A	N/A	N/A	N/A	N/A			N/A	N/A
Tabatabaee et al. 2015	Control	CD	14	38.6 +/- 4.6	32.0 +/- 4.4	35.9 +/- 2.7	27.2 +/- 3.7	N/A	N/A	N/A	N/A	N/A	N/A
	Study	CD + Cells	14	35.9 +/- 4.5	16.0 +/- 2.5	32.0 +/- 3.8	9.7 +/- 1.8	N/A	N/A	N/A	N/A	N/A	N/A
Gangji V et al. 2011	Contol	CD	11	46.0 +/- 7.2	51*	30.5 +/- 5.5	CD + cells did not improve WOMAC score compared to the control group (p=0.091)	8.6 +/- 1.4	9*	N/A	N/A	N/A	N/A
	Study	CD + Cells	13	32.8 +/- 7.1	20.8 +/- 7.7	25.5 +/- 4.5		7.2 +/- 1.2	4.8 +/- 1.8	N/A	N/A	N/A	N/A
Lim et al. 2013	Control	CD + curettage + bone graft	31	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Study	Multiple drilling + cells	128	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Liu et al. 2013	Control	CD + hydroxyapatite bone filler	27	64.6 +-2.9	30*	N/A	N/A	N/A	N/A	64*	76*	N/A	N/A
	Study	CD + hydroxyapatite bone filler +cells	28	63.6 +-2.6	20*	N/A	N/A	N/A	N/A	64*	80*	N/A	N/A
Yamasaki T. et al. 2010	Control	CD + calcium hydroxyapatite bone filler	9	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	15.2 (14 to 17)	14.2 (12 to 15)
	Study	CD + calcium hydroxyapatite bone filler + cells	30	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	14.7 (13 to 16)	17 (15 to 18)
Pepke W. Et al. 2016	Control	CD	14	57*	26*	N/A	N/A	N/A	N/A	61*	75*	N/A	N/A
	Study	CD + Cells	11	48*	23*	N/A	N/A	N/A	N/A	61*	81*	N/A	N/A

CD: Core Decompression; **VAS**: Visual Analogue Scale; **F/U**: Follow up **WOMAC**: Western Ontario & McMaster Universities Arthritis Index score; **HHS**: Harris Hip Score; **THA**: Total Hip Arthroplasty; **N/A**: Not Available; *****data estimated from figures,

Table 4. Structural Assessment - Imaging

Author		Number cases	Baseline Assessment	Follow up Assessment	Time (months)	Lesion Size Baseline	Lesion Size Follow up
Rastogi et al. 2013	CD + unprocessed bone marrow	30	ARCO: IB (2), IC (5), IIB (3), IIC (8), IIIB (5)and IIIC (7).	MRI - Kerboul angle analysis: Mean increase of 1.08 degrees	24	N/A	N/A
	CD + Cells	30	ARCO: IB (2), IC (5), IIB (3), IIC (8), IIIB (5)and IIIC (7).	MRI - Mean decrease of 6.1 degrees (p = 0.03)		N/A	N/A
Sen et al. 2012	CD	25	. A-fat (7), B-blood (4), C-fluid (8) and D-fibrosis (1)	No significant difference in overall improvement of MRI features between the 2 groups	24	moderate (4) extensive (16)	N/A
	CD + Cells	26	A (6), B (9), C (11) and D (0)			moderate(14) extensive(12)	N/A
Mao et al. 2015	Porous tantalum rod	41	ARCO: I (10), II (23), IIIA (8)	Radiological progression: 13; Radiological collapse: 5 ARCO I (9), II (21), III (8), IV (3)	36	N/A	N/A
	Porous tantalum rod + intraarterial cell	48	ARCO: I (8), II (29), IIIA (11)	Radiological progression: 4; Radiological collapse: 3 ARCO I (9), II (24), III (11), IV (4)	36	N/A	N/A
Ma et al. 2014	CD + autologous bone graft	24	Ficat: I (4), II (15), III (5)	Radiological Progress rate: 33.3%; Progress rate for early-stage (I/II) hips: 33.3%	24	N/A	N/A
	CD + autologous bone graft + Cells	25	Ficat: I (3), II (17), III (5)	Radiological Progress rate: 8%; Progress rate for early-stage (I/II): 0%	24	N/A	N/A
Zhao et al. 2012	CD	51	ARCO: IC (2), IIA (15), IIB (22), IIC (12)	MRI - 20% (10 of 51) hips progressed to stage III or IV	60	N/A	N/A
	CD + Cells	53	ARCO: IC (3), IIA (15), IIB (23), IIC (10)	MRI- 4% (2 of 53) hips progrssed to stage III	60	N/A	N/A
Tabatabaee et al. 2015	CD	14	ARCO: I (2), II (7), III (5), MEAN MRI SCORE 2.2, MEAN MRI RANK 16	mean MRI score 2.8, mean MRI rank 18.6, progress rate 10/14hips (71%)	24	N/A	N/A
	CD + Cells	14	ARCO: I (3), II (9), III (2), MEAN MRI SCORE 1.93,	mean MRI score 1.7, mean MRI rank 8.5, progress rate 0%, 1 hip improved from III to II, 1 improved from II to I	24	N/A	N/A
Gangji V et al. 2011	CD	11	ARCO: I(2) II(9)	MRI - 73% (8 of 11) hips had deteriorated to stage III	60	volume of lesion/volume of femoral head (%) 19.2±3.9	lesion size decreased 22% at 60 months follow up.
	CD + Cells	13	ARCO: I(2) II(11)	MRI - 23% (3 of 13) hips had deteriorated to stage III	60	volume of lesion/volume of femoral head (%) 16.0±2.2	lesion size decreased 42% at 60 months follow up.
Lim et al. 2013	CD + curettage + bone graft	31	Ficat: I (0), IIa (14), IIb (9) III (8)	45% (14 of 31) considered unsuccessful	60	N/A	N/A
	Multiple drilling + cells	128	Ficat: I (0), IIa (42), IIb (37) III (49)	46% (59 of 128) hips considered unsuccessful	60	N/A	N/A
Liu et al. 2013	CD + hydroxyapatite	27	ARCO: IIB (12), IIC (15)	40.7% considered radiological success, 16/27 (59.3%) of hips exibithed collapse or aggravated collapse	25	N/A	N/A
	CD + hydroxyapatite bone filler +cells	28	ARCO: IIB (13), IIC (15)	78.6% considered radiological success, 6/28 (21.4%) of hips exibithed collapse or aggravated collapse	27	N/A	N/A
Yamasaki T. et al. 2010	CD + calcium hydroxyapatite bone filler	9	JOA II(8)	MRI - mild collpase 3 hips (33.%), Severe collapse >2mm in 6 hips (77%)	18	Method Steinberg, 22% (14% to 55%)	N/A
	CD + calcium hydroxyapatite bone filler + cells	30	JOA I(2), II(25),IIIA(3)	MRI - No progression 17 hips (57%), mild collpase 10 hips (33.%), Severe collapse >2mm in 3 hips (10%)	18	Method Steinberg, 21% (3% to 36%)	Method Steinberg, 8% (0.6% to 16%)
Pepke W. Et al. 2016	CD	14	ARCO: II(14)	MRI - head survival rate of 8/14 (57%)	24	N/A	N/A
	CD + Cells	11	ARCO: II(11)	MRI - head survival group 7/11 (64%)	24	N/A	N/A

Table 5. Complications and Failure rate

Author	Type	Treatment	Number cases (ONFH)	Complications	Revision Rate - Conversion to THA
Rastogi et al. 2013	Control	CD + unprocessed bone marrow	30	0	3 (10%)
	Study	CD + Cells	30	0	0
Sen et al. 2012	Control	CD	25	0	N/A
	Study	CD + Cells	26	0	N/A
Mao et al. 2015	Control	Porous tantalum rod	41	1 (infection)	9 (21.95%)
	Study	Porous tantalum rod + intraarterial cell infusion	48	1 displacement of the rod	3 (6.25 %)
Ma et al. 2014	Control	CD + autologous bone graft	24	0	4 (16.6%)
	Study	CD + autologous bone graft + Cells	25	0	2 (8%)
Zhao et al. 2012	Control	CD	51	0	5 (5%)
	Study	CD + Cells	53	0	0
Tabatabaee et al. 2015	Control	CD	14	0	3 (21%)
	Study	CD + Cells	14	0	0
Gangji V et al. 2011	Contol	CD	11	1 hematoma at side of the CD	3 (27.3%)
	Study	CD + Cells	13	3 Pain a the donor side/ 1 "infection"	2 (15.4%)
Lim et al. 2013	Control	CD + curettage + bone graft	31	N/A	11(35.5%)
	Study	Multiple drilling + cells	128	N/A	47 (36.7%)
Liu et al. 2013	Control	CD + hydroxyapatite bone filler	27	guidewire breakages (2), perforation of the subchondral bone (3)	5 (19%)
	Study	CD + hydroxyapatite bone filler +cells	28	guidewire breakages (2), perforation of the subchondral bone (1)	4 (14%)
Yamasaki T. et al. 2010	Control	CD + calcium hydroxyapatite bone filler	9	0	3 (33%)
	Study	CD + calcium hydroxyapatite bone filler + cells	30	0	1 (3%)
Pepke W. Et al. 2016	Control	CD	14	0	6 (43%)
	Study	CD + Cells	11	0	4 (36%)