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Research article

Is core decompression and bone marrow concentrate with demineralized bone matrix and platelet-rich fibrin suitable for treating femoral head osteonecrosis?

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ABSTRACT

The aim of this article is to determine the safety and efficacy of core decompression (CD) combined with injection of autologous bone marrow concentrate (BMC), demineralized bone matrix (DBM), and platelet-rich fibrin (PRF) for treating femoral head osteonecrosis. Seventy-seven patients (53 males and 24 females) for a total of 87 hips were treated for hip osteonecrosis with CD combined with injection of autologous BMC, DBM, and PRF at Rizzoli Orthopedic Institute from September 2008 to December 2019. Patients were assessed at baseline, at 45 days, and at 3, 6, 12, 24, and 36 months postoperatively. The primary outcome was the survival rate of hips not converted to total hip arthroplasty (THA). The secondary outcomes were (I) radiographic positive evolution assessed by X-ray films and magnetic resonance imaging and (II) the clinical symptoms evaluated with the Harris Hip Score (HHS). Eighty-seven hips from 77 patients with femoral head osteonecrosis (FHON), 60 males and 27 females, with a median age of 34 years (range 15–55) were included. The cause of necrosis was steroid treatment in 30 patients (17 of these for hematological malignancies, 2 for lupus, 1 for Churg–Strauss syndrome, and the remaining for other causes), 1 was alcohol-related, 4 followed hip injury, while 15 patients had idiopathic causes. THA was carried out in 20 hips (40%). These patients had lesions classified as IIa on the Ficat stage in four cases, six were IIb, nine were III, and one was 4. No CD-related complications were found during THA surgery or at the last follow-up in these cohorts of patients. Radiographic progression of the FHON was found in 14 hips (28%), with a higher percentage on Ficat's stage IIb. There were procedure-related complications in two hips, including one femoral neck fracture and one deep infection. Nineteen hips with successful treatment had good to excellent functional results at a 3-year follow-up or more (HHS $\geq$ 80). The long-term outcomes of treatment with CD and injection with BMC combined with DBM and PRF are promising to prevent femoral head collapse in patients with FHON. Moreover, CD does not influence the outcome in cases of THA.

INTRODUCTION

Femoral head osteonecrosis (FHON) is a debilitating disease that mainly affects young adult patients aged between 20 and 40 years [1]. In most cases, the etiology is idiopathic, while known risk factors are trauma, corticosteroids, alcohol abuse, autoimmune diseases, and coagulopathies [2, 3]. The common pathologic pathway is characterized by the interruption or reduction of vascular supply to the femoral head and consequently the reduction of circulating progenitor cells, particularly osteoblasts precursors [4, 5]. If left untreated, this local condition can result in bone necrosis and a consequent progressive collapse of the femoral head in >90% of the cases [6]. The natural history of the disease leads to progressive joint and cartilage damage and secondary osteoarthritis, which requires a total hip arthroplasty (THA) in most cases [6]. Small osteonecrosis lesions may heal or remain stable without progression, causing significant joint damage only after a long time.

Several nonsurgical and surgical treatments have been described for painful FHON [7–9]. Most of these procedures have been reported with a broad range of results. Core decompression (CD) has been proven to be effective in a high number of cases (up to 60%). However, it is effective only in the early

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stages of osteonecrosis [10, 11]. It has been proven that CD or multiple drilling associated with biological supplements can relieve pain and partially restore the subchondral bone stock and quality [12–14].

The use of bone marrow stem cells in the treatment of avascular necrosis of the hip has been proposed for more than a decade. Many case studies and clinical trials performed with several surgical procedures, cellular processing methods, and different additional compounds have been published with impressive results [8, 15], but only a few studies with large populations and long-term follow-up have been reported in the literature.

Bone marrow injection has been associated with CD in an attempt to stimulate osteoblastic regeneration with promising results [8, 12, 14, 16]. The rationale for the use of bone inducers is to stimulate the intrinsic healing potential by ossification of FHON, providing sufficient factors such as stem cells and bone morphogenetic proteins, which improve the osteogenic potential in the necrotic area. The demineralized bone matrix (DBM) was mixed with bone marrow concentrate (BMC) as a scaffold and given to the preparation as a paste-like consistency that can be easily manipulated and injected as a bone graft substitute because of its osteoinductive properties [17]. Moreover, platelet-rich fibrin (PRF) provides high numbers of growth factors capable of stimulating and promoting repair.

In the present study, we present a long-term follow-up of patients with osteonecrosis of the femoral head who underwent CD followed by the injection of autologous BMC mixed with DBM and autologous PRF.

We therefore undertook a retrospective trial (I) to determine whether a single injection of BMC concentrate, DBM, and PRF associated with the CD is effective in treating FHON; (II) to assess the treatment failure rate in relation to the Ficat stage, etiology, gender, and age; and (III) to determinate if a single treatment is effective in improving the HHS index.

MATERIALS AND METHODS

In the present study, we reviewed all patients affected by FHON and treated with CD with the addition of BMCs between September 2008 and December 2020. The inclusion criteria were as follows: age between 16 and 65 years, chemotherapy interrupted at least 6 months prior, no evidence of active oncological disease, and radiographical diagnosis of unilateral or bilateral FHON. The exclusion criteria were as follows: FHNO associated with previous unsuccessful surgical treatments, previous CD without injection of biological components, active oncological disease, follow-up of <6 months, and Ficat stage of I. Patients who did not fit with the inclusion criteria were excluded from the study. The diagnosis and staging of FHON were made using magnetic resonance imaging (MRI) scans. We used the imaging-based classification of FHON proposed by Ficat [1], which recognizes five different stages of bone necrosis from Stage 0 to Stage 4 (Table 1). We collected data on 77 patients (53 males and 24 females) for a total of 87 hips.

The Ethics Committee of the Hospital approved the procedure and informed consent was obtained from all patients (Rizzoli Protocol Number 10747; date 27 April 2023).

Table 1. Ficat's classification of FHON.

Stage	Radiological features
0	Normal radiographs (silent hip)
I	Inconspicuous abnormality or minor osteopenia changes
II	Sclerotic or cystic lesions
	IIa: focal radiological changes
	IIb: crescent sign without flattening of the femoral head
III	Flattening of the femoral head or femoral head collapse and joint space normal
IV	Femoral head collapse and osteoarthritis of the hip (joint space collapse and acetabular changes)

Surgical procedure

The procedure was carried out in the operating theatre. First, 60 cc of bone marrow was harvested in small aliquots from the posterior iliac crest with the patient in the prone position under combined spinal and epidural anesthesia. Next, the bone marrow was centrifugated using Harvest® bone marrow aspirate concentrate system kit (Terumo BCT™, Lakewood, CO, USA) according to the manufacturer's operating instructions to obtain 5–6 ml of BMC. The mean surgical time was ∼15 min. The BMC was added to 10 cc of DBM from the local Musculoskeletal Tissue Bank (Rizzoli Orthopedic Institute) along with PRF (Vivostat A/S™, Borupvang, Denmark) to obtain a semi-solid mixture that avoids uncontrolled spread of the amalgam after injection.

Then, the patient was placed supine on a fracture table, the limb to be treated was in gentle traction, and both AP and axial views of the femoral neck were obtained by a radiological C arm intensifier. The skin was incised laterally to the great trochanter of the proximal femur, a guide wire was inserted from the subtrochanteric area into the necrotic area of the femoral head, and the CD was carried out with a 9-mm cannulated reamer. After the CD, the guide wire was removed, and the paste was easily injected into the femoral head using a 7-Gauce trocar. These procedures were performed under fluoroscopic AP and axial guidance. The total procedure lasted from 30 to 45 min.

The mean hospitalization was 2 days; patients were discharged the day after surgery. Restricted activity and walking without weight bearing were recommended for all patients for at least 6 weeks.

Follow-up

Patients were assessed in the outpatient clinic at baseline, at 45 days, at 3, 6, and 12 months, and then once per year. Plain radiographs of the treated hip (anteroposterior and lateral view) were obtained at each follow-up, while MRI (transversal and coronal view) was acquired every 6 months after surgery. Three of the authors (M.F., L.C., and B.S.) independently evaluated the MRI scans and plain radiographs. Patients' functional evaluation was performed using the total Harris Hip Score (HHS) [18] and Visual Analogue Scale (VAS) during the outpatient visit.

A patient was considered healed when no radiological progression of the necrotic area or subchondral femoral head collapse was observed on imaging, and the pain was below the threshold of 5 out of 10 on a VAS scale.

Table 2. Demographic and result of the treatment.

		No. of hips	%
Gender	M	60	69
	F	27	31
Age (years)	≤30	37	43
	>30	50	56
Etiology	Treatment in hematological malignancies	37	43
	Autoimmune	16	18
	Idiopathic	29	33
	Post-traumatic	5	6
Oncologic	No	50	57
	Yes	37	43
VAS baseline	≤4	61	70
	> 4	26	30
Ficat baseline	0 (others)	55	63
	1 (IIa)	32	37

The treatment was considered a failure if a radiographic progression of the FHON was observed on plain radiographs or MRI, pain was >5 out of 10 on a VAS scale, and a hip replacement was performed within 5 years of treatment due to persistent or recurrent pain, radiological progression, or limited functional performance.

Statistical analysis

Descriptive statistics were performed for all variables. The chi-squared test was used to test the association between categorical variables. Kaplan–Meier survival analysis [19] with 95% confidence intervals (CIs) was performed using the Mantel–Cox log-rank test to evaluate the influence of categorical variables on the outcomes. For abnormally distributed data, the Mann–Whitney test was used to analyze two independent populations. Next, multivariate Cox regression with the Wald backward method was performed to identify the most predictive model for healing. The odds ratio for each parameter with 95% CIs was used to express the Cox regression results. Statistical significance was set at *P*-value of ≤.05. All statistical analyses were performed with IBM SPSS Statistic 21.0 (IBM™ Corp, Armonk, NY, USA). The primary outcome was the long-term survival rate of hips that did not require a THA. Secondary outcomes included the evaluation of radiographic progression, the clinical symptoms evaluated with HHS and VAS, and the evaluation of risk factors affecting the efficacy of the procedure.

RESULTS

The median age at surgery was 35 years (range 13–68). The most represented etiology was prolonged and high-dose steroid therapy (53 patients) with 37 cases for onco-hematological diseases and 16 cases for autoimmune diseases. Post-traumatic etiology was found in five patients, and the remaining 29 patients were categorized as idiopathic (Table 2). According to the Ficat classification, there were 56 hips with a necrosis at Stage II (32 at IIa and 24 at IIb), 25 at Stage III, and 6 at Stage IV.

Treatment outcome

In 51 of 87 hips (59%), the treatment was successful. Total hip replacement was carried out in 36 hips (41%), 14 of these were idiopathic (39%), 17 steroid-induced (42%), 1 alcohol related (3%), and 3 post-traumatic (8%). The Ficat stage among failed hips were IIa for 8 cases, IIb for 12 cases, III for 13 cases, and IV for 3 cases. Twenty-one patients (24 hips) experienced progression in the Ficat stage, while 10 patients (12 hips) reported persistent pain without evidence of radiological progression at the Ficat stage. The mean time from the treatment to THA was 24 months (range 3–60). Three-year arthroplasty-free survival was 66% (95% CI 0.55–0.75) at the Kaplan–Meier survival analysis with THA as the end-point (Fig. 1).

Femoral head collapse was prevented in 63 hips (72%), while radiographic progression occurred in 24 of 87 patients (28%): 6 were pre-operative Ficat IIa stage, 10 IIb stage, and 8 III stage. No radiographic alterations were found in patients with Stage IV, as it is already an advanced stage of the disease. The radiological progression was statistically associated with the failure of the procedure ($P = .0047$). This correlation was not confirmed when considering the correlation between radiographic progression and etiology (Fig. 2).

Univariate and multivariate Cox regression (backward stepwise regression) analysis showed a significant difference in failure rate between Ficat IIa and other Ficat stages. Out of 32 hips, 24 (75%) with initial Ficat IIa stage avoided THA at the end of follow-up (Table 3). Stage IIa presented a higher healing rate compared to other stages during long-term follow-up [hazard ratio (HR) 3.1; 95% CI:1.35–7.50; $P = .008$).

One patient sustained a trochanteric fracture 2 days after the procedure. He underwent bone fixation with plate and screws. At the end of follow-up, the patient reported no pain, no radiographic progression of the FHNO, and the final HHS was 95. Even though the treatment was considered a failure, no evidence of FHON progression was observed.

Four patients developed deep infections that were treated with early surgical debridement followed by 6 weeks of antibiotic therapy with complete eradication of the infection in all cases. Due to persistent pain and clinical symptoms, one of these patients underwent THA 3 years after the procedure with the complete resolution of the infection.

Risk factors

Univariate and multivariate Cox regression analysis showed a significant difference in failure rate between idiopathic and steroid-related FHON. Hip replacement was avoided in 37 out of 57 hips (68.5%), with corticosteroid-related FHON, while only 14 out of 33 hips (42.4%) with other etiologies avoided THA (HR 2.3; 95% CI:1.14–4.75, $P = .018$).

Gender, age (cut-off of 30 years), and posthematological FHON had no influence on the outcome(Table 4).

Functional outcomes

The HHS values showed a universal increase trend after the procedure (mean value from 63 to 100), confirming the efficacy of the treatment with functional and symptomatic improvement.

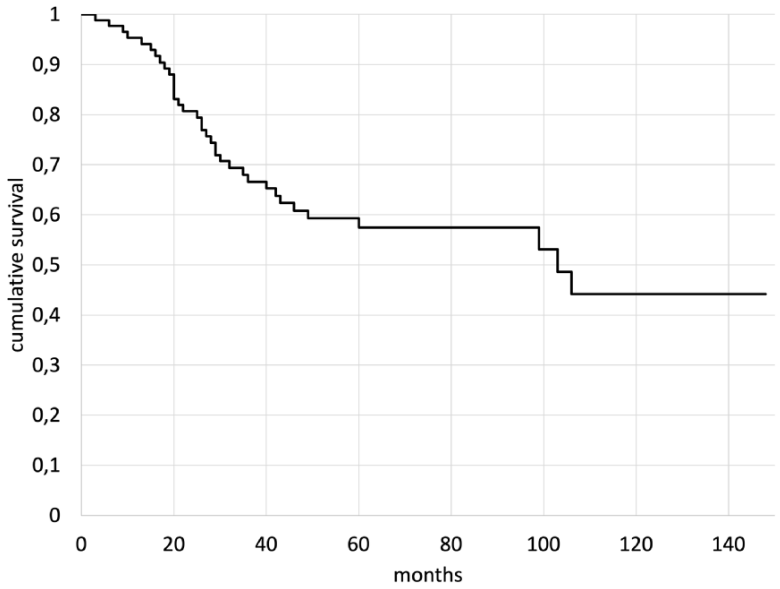

Figure 1. Lifetime table analysis of the treatment survival. THA was chosen as the end-point.

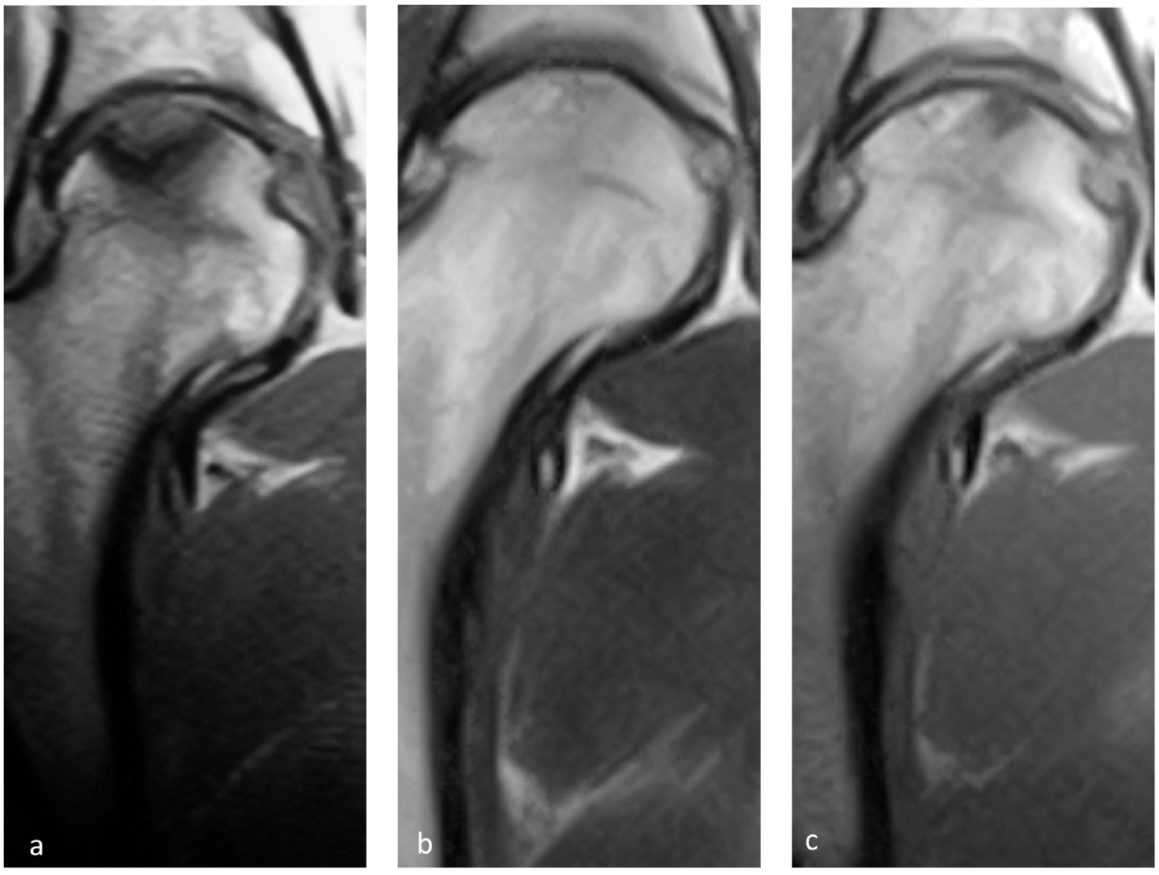

Figure 2. T2 MRI of a right femoral head, coronal section on the necrotic area: (a) preoperative; (b) 2 and (c) 5 years after CD and infiltration with DBM and PRF.

The correlation between HHS and the outcome (successful or unsuccessful procedure) resulted statistically significant at 12 and 18 months ($P < .001$ and $P = .045$, respectively).

The VAS values showed a gradual decrease after the treatment from baseline to 12 and 24 months (baseline VAS mean value 3.5, 95% CI: 3.19–3.89; 12-month VAS mean value 1.5, 95% CI: 1.21–1.78; 24-month VAS mean value 0.98, 95% CI:

Table 3. Correlation between the preoperative Ficat stage and the outcome.

Ficat stage	Femoral head preservation (*n*, %)	THA (*n*, %)	Total hips (*n*, %)
IIa	24 (47)	8 (23)	32 (36)
IIb	13 (25)	12 (33)	25 (29)
III	11 (22)	13 (36)	24 (28)
IV	3 (6)	3 (8)	6 (7)

0.648–1.31). No correlation was found between a VAS score of >4 out of 10 and a subsequent THA procedure.

DISCUSSION

Even though marked advancements in radiodiagnostic methods have improved and shortened the time to diagnosis, and despite of the evolution of surgical technique, the treatment for FHON has not advanced in recent years. Progress in prosthetic hip replacement over the last two decades in technique, tribology, and prosthesis design now allows for a primary total hip replacement with a lower rate of complications than before. This evolution reduces the risk of complication and failure rates even in fragile categories such as oncological or immunocompromised patients. The increase of durability of primary total hip replacement ensures a long-term clinical relief for patients and is now the mainstay of treatment for high-grade Ficat FHON. However, THA often cannot guarantee lifetime treatment due to the young age of patients, particularly in the onco-hematological population. In these young and active patients, it is important to avoid or at least delay a THA to reduce the risk of surgical revisions over time [20].

We therefore asked (I) whether a single injection of BMC, DBM, and PRF associated with CD is effective in treating FHON; (II) the treatment failure rate in relation to Ficat stage, etiology, gender, and age; and (3) if a single treatment is effective in improving the HHS index.

Limitations

The present study has several limitations. First, this cohort represents a heterogeneous population with numerous comorbidities and potential confounders, including ongoing or past onco-hematological therapies that may affect regenerative potential and the number of cells present in BMC. Additionally, the population has an intrinsic variability in FHON stage, with smaller populations for higher stages of disease. This may represent a confounder in various analyses: total overall survival, radiological progression, and functional outcome may be affected.

Lastly, this remains a retrospective work with all inherent limitations associated with such a design, including reliance on chart and clinic report abstraction and search algorithms to identify eligible patients.

Treatment outcomes

Our approach involved treating FHON patients with CD combined with the composite material (DBM, BMC, and PRF) in a

Table 4. Overall survival (OS) estimates from patient characteristics.

				Kaplan–Meier estimate			Cox multivariate estimate		
Factor	**Level**	***N***	**%**	**3 years of OS**	**95% CI**	***P*-value (log-rank test)**	**HR**	**95% CI**	***P*-value**
Gender	M	60	69	65	47-83	0.7260			
	F	27	31	69	44-82				
Age (years)	≤30	37	43	63	45-77	0.6843			
	>30	50	56	67	52-79				
Oncologic	No	50	57	65	49-76	0.7126			
	Yes	37	43	68	49-80				
VAS baseline	≤4	61	70	68	54-78	0.7793			
	>4	26	30	63	40-78				
Etiology	0 (no steroid)	33	38	54	35-69				
	1 (steroid)	54	62	74	60-84	0.030	0.40	0.21-0.79	.008
Ficat baseline	0 (others)	55	63	57	43-69				
	1 (IIa)	32	37	83	63-92	0.0108	0.32	0.14-0.71	0.005

one-step technique. The technique resulted in a simple and time-efficient surgery. The advantage of the 'one-step procedure' is the single admission into the hospital with a single anesthesia and a 2-day hospital stay.

The procedure prevented THA in 59% of the treated hips and arrested femoral head collapse in 72% of the cases.

The literature supports the use of biological products to improve healing potential and reports a range of 70%–90% prevention of femoral head collapse [21–24]. Although CD may be effective in decreasing pain shortly after surgery [25], it is not highly effective in preventing femoral head collapse or total hip replacement in most cases [26]. Key elements to improve bone and new vascular formation after CD are mesenchymal stem cells and bone inducers.

Based on the assumption that the greater the numbers of mesenchymal stem cells, the greater the healing potential, the debate is still open in the literature about how to improve the number of MSCs. Hernigou and Beaujean pioneered the cell-based strategies for the application of BMC in the treatment of avascular osteonecrosis, reporting 82% hip survival after CD and injection with BMC [12]. Recently, Barrena *et al.* [16] reported the use of CD and injection with expanded MSCs to treat FHON, preserving femoral head sphericity in 80% of the cases. However, the use of expanded MSCs is logistically demanding, with production and safety of culture conditions, leading to a costly therapeutic procedure. First, two separated surgeries are required, the first to harvest bone marrow and the second to carry out the CD and the injection of the expanded MSCs. The time to expand the culture is ~3 weeks, requiring the second surgery to be scheduled at the end of the expansion to reduce the risk of MSC apoptosis. The use of BMC offers a comparable final healing rate and the same capability to prevent THA as the expanded MSCs, with harvesting and injection of the biological product performed in the same operation. However, the comparative regenerative capacity of concentrated versus cultured cells remains unclear. Further studies are needed to define the real potential and limits of both procedures.

Key elements of bone regeneration involve the combination of biological and biomechanical therapies. To improve mechanical strength, several procedures can be associated with CD, such as bone grafting in various forms, including cortico-cancellous bone autograft, fibular or cortical allograft, and vascularized fibular transplant. All these methods have been shown to be effective but are associated with a higher morbidity rate [27–30]. We used DBM as bone graft substitute due to its high osteoinductive properties [17]. Moreover, the mixture of DBM and BMC can be easily injected directly into the femoral head after CD. According to data reported in the literature, we propose literature-based guidelines for treating FHON with BMC, DBM, and PRF (Fig. 3).

Risk factors

Stratification based on the Ficat stages demonstrated the failure of CD in later stage. These data are consistent with other studies where the early-stage FHON success rate of CD associated with BMC injection [8, 31–35] ranged from 70% to 100%, with the follow-up varying from 2 to 7 years and radiographic progressions from 3.7% to 33%. Hernigou and Beaujean confirmed the higher failure rate of late-stage FHON, showing a 63% THA conversion rate in 32 hips with Ficat Stage IV and significant progression to hip arthritis after CD [12].

The role of etiology is still unclear. Interestingly, the statistical analysis in the present study showed a better outcome in the corticosteroid-induced FHON population than in idiopathic one. Alcohol and steroid are common causes of FHON [36]; they cause lipid metabolism disorder [37, 38] leading to an increase in volume of fat cells and fat embolism, which plays an

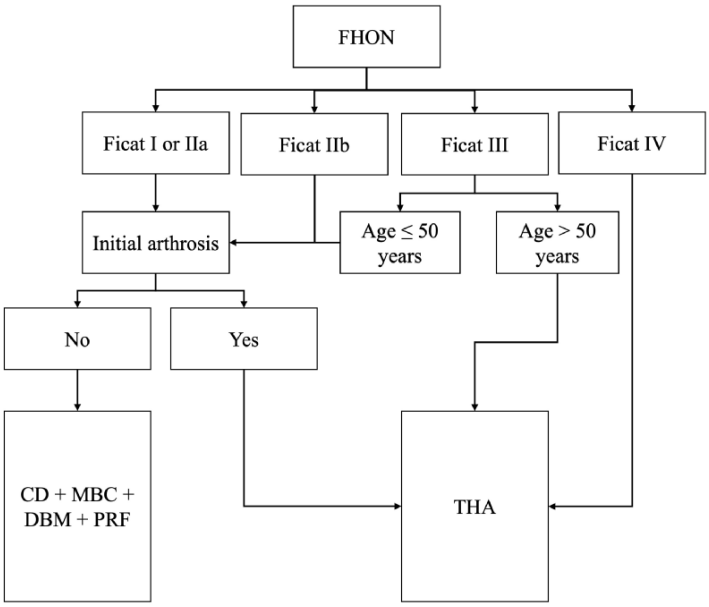

Figure 3. Literature-based flow-chart for treating FHON with BMC, DBM, and PRF. For patients older than 50 years, THAs should be the treatment of choice because the number and quality of mesenchymal stem cells decline with aging.

important role in the process of femoral head necrosis [39]. Further research studies are needed to confirm this trend and define a clinical correlation.

Functional outcomes

The HHS values showed a universal increasing trend after the procedure (mean value from 63 to 100), confirming the efficacy with functional and symptomatic improvement. HHS values at 12 and 18 months were compared between the successful and unsuccessful procedure population and a statistically significant difference was found, confirming that THR is considered when functional and clinical results are unsatisfying. In patients who did not require THA, good to excellent functional results were achieved.

CONCLUSION

This study further confirms that CD associated with the injection of autologous BMC, DBM, and PRF in the necrotic area plays a role in the treatment of patients with early stages of FHON. The success of procedure can guarantee pain relief and improved functional scores; a decrease in these two features and radiological progression are the main causes of failure and THA.

However, more studies with large population at long-term follow-up are needed to better explore the role of the different variables related to this cohort of patients.

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AUTHOR CONTRIBUTIONS

Drs L.C. and E.L.S. assisted with study conception and design.

Drs L.C., R.L., M.F., T.F., and B.S. assisted with acquisition of data.

Drs L.C., R.R., and M.F. assisted with analysis and interpretation of data.

Drs M.F., L.C., and B.D. assisted with drafting of manuscript.

Prof. D.M.D., Dr G.B., Dr E.L.S., Dr A.B., and A.M. assisted with critical revision.

CONFLICT OF INTEREST

None declared.

FUNDING

None declared.

DATA AVAILABILITY

Raw data were generated at the Rizzoli Orhopaedic Institute. Derived data supporting the findings of this study are available from the corresponding author upon request.

REFERENCES

1. Ficat RP. Idiopathic bone necrosis of the femoral head. Early diagnosis and treatment. *J Bone Joint Surg Br* 1985;**67**:3–9.
2. Lespasio MJ, Sodhi N, Mont MA. Osteonecrosis of the hip: a primer. *Perm J* 2019;**23**:18–100.
3. Aldridge JM, Urbaniak JR. Avascular necrosis of the femoral head: etiology, pathophysiology, classification, and current treatment guidelines. *Am J Orthop Belle Mead NJ* 2004;**33**:327–32.
4. Samara S, Dailiana Z, Chassanidis C *et al*. Expression profile of osteoprotegerin, RANK and RANKL genes in the femoral head of patients with avascular necrosis. *Exp Mol Pathol* 2014;**96**:9–14.
5. Weinstein RS. Glucocorticoid-induced osteonecrosis. *Endocrine* 2012;**41**:183–90.
6. Mont MA, Zywiel MG, Marker DR *et al*. The natural history of untreated asymptomatic osteonecrosis of the femoral head: a systematic literature review. *J Bone Joint Surg Am* 2010;**92**:2165–70.
7. Wang C-J, Cheng J-H, Huang C-C *et al*. Extracorporeal shockwave therapy for avascular necrosis of femoral head. *Int J Surg* 2015;**24**:184–87.
8. Gangji V, De Maertelaer V, Hauzeur J-P. Autologous bone marrow cell implantation in the treatment of non-traumatic osteonecrosis of the femoral head: five year follow-up of a prospective controlled study. *Bone* 2011;**49**:1005–09.
9. Zhang Y, Li L, Shi Z *et al*. Porous tantalum rod implant is an effective and safe choice for early-stage femoral head necrosis: a meta-analysis of clinical trials. *Eur J Orthop Surg Traumatol* 2013;**23**:211–17.
10. Pierce TP, Jauregui JJ, Elmallah RK *et al*. A current review of core decompression in the treatment of osteonecrosis of the femoral head. *Curr Rev Musculoskelet Med* 2015;**8**:228–32.
11. Zhao D, Zhang F, Wang B *et al*. Guidelines for clinical diagnosis and treatment of osteonecrosis of the femoral head in adults (2019 version). *J Orthop Translat* 2020;**21**:100–10.
12. Hernigou P, Beaujean F. Treatment of osteonecrosis with autologous bone marrow grafting. *Clin Orthop Relat Res* 2002;**405**:14–23.
13. Marker DR, Seyler TM, Ulrich SD *et al*. Do modern techniques improve core decompression outcomes for hip osteonecrosis? *Clin Orthop Relat Res* 2008;**466**:1093–103.
14. Song WS, Yoo JJ, Kim Y-M *et al*. Results of multiple drilling compared with those of conventional methods of core decompression. *Clin Orthop Relat Res* 2007;**454**:139–46.
15. Li X, Xu X, Wu W. Comparison of bone marrow mesenchymal stem cells and core decompression in treatment of osteonecrosis of the femoral head: a meta-analysis. *Int J Clin Exp Pathol* 2014;**7**:5024–30.
16. Gómez-Barrena E, Padilla-Eguiluz N, Rosset P *et al*. Osteonecrosis of the femoral head safely healed with autologous, expanded, bone marrow-derived mesenchymal stromal cells in a multicentric trial with minimum 5 years follow-up. *J Clin Med* 2021;**10**:508.
17. Urist MR, Dawson E. Intertransverse process fusion with the aid of chemosterilized autolyzed antigen-extracted allogeneic (AAA) bone. *Clin Orthop Relat Res* 1981;**154**:97–113.
18. Harris JD, Quatman CE, Manring MM *et al*. How to write a systematic review. *Am J Sports Med* 2014;**42**:2761–68.
19. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;**53**:457–81.
20. Walker RP, Gee M, Wong F *et al*. Functional outcomes of total hip arthroplasty in patients aged 30 years or less: a systematic review and meta-analysis. *Hip Int* 2016;**26**:424–31.
21. Calori GM, Mazza E, Colombo A *et al*. Core decompression and biotechnologies in the treatment of avascular necrosis of the femoral head. *EFORT Open Rev* 2017;**2**:41–50.
22. Andriolo L, Merli G, Tobar C *et al*. Regenerative therapies increase survivorship of avascular necrosis of the femoral head: a systematic review and meta-analysis. *Int Orthop* 2018;**42**:1689–704.
23. Hernigou P, Trousselier M, Roubineau F *et al*. Stem cell therapy for the treatment of hip osteonecrosis: a 30-year review of progress. *Clin Orthop Surg* 2016;**8**:1–8.
24. Xu W. Comparison of intramedullary nail versus conventional ilizarov method for lower limb lengthening: a systematic review and meta-analysis. *Orthop Surg* 2017;**9**:159–66.
25. Koo KH, Kim R, Ko GH *et al*. Preventing collapse in early osteonecrosis of the femoral head. A randomised clinical trial of core decompression. *J Bone Joint Surg Br Vol* 1995;**77-B**:870–74.
26. Cruz-Pardos A, Garcia-Rey E, Ortega-Chamarro JA *et al*. Mid-term comparative outcomes of autologous bone-marrow concentration to

treat osteonecrosis of the femoral head in standard practice. *HIP Int* 2016;**26**:432–37.
27. Feng Y, Wang S, Jin D *et al.* Free vascularised fibular grafting with OsteoSet®2 demineralised bone matrix versus autograft for large osteonecrotic lesions of the femoral head. *Int Orthop* 2011;**35**:475–81.
28. Yoo M-C, Kim K-I, Hahn C-S *et al.* Long-term followup of vascularized fibular grafting for femoral head necrosis. *Clin Orthop Relat Res* 2008;**466**:1133–40.
29. Asmus A, Vogel K, Vogel A *et al.* Pedicled vascularized iliac bone graft for treatment of osteonecrosis of the femoral head. *Oper Orthop Traumatol* 2020;**32**:127–38.
30. Yang F, Wei Q, Chen X *et al.* Vascularized pedicle iliac bone grafts as a hip-preserving surgery for femur head necrosis: a systematic review. *J Orthop Surg Res* 2019;**14**:270.
31. Hernigou P, Flouzat-Lachaniette C-H, Delambre J *et al.* Osteonecrosis repair with bone marrow cell therapies: state of the clinical art. *Bone* 2015;**70**:102–09.
32. Civinini R, De Biase P, Carulli C *et al.* The use of an injectable calcium sulphate/calcium phosphate bioceramic in the treatment of osteonecrosis of the femoral head. *Int Orthop* 2012;**36**:1583–88.
33. Rk S, Sk T, A S *et al.* Early results of core decompression and autologous bone marrow mononuclear cells instillation in femoral head osteonecrosis: a randomized control study. *J Arthroplasty* 2012;**27**:679–86.
34. Wang T, Wang W, Yin ZS. Treatment of osteonecrosis of the femoral head with thorough debridement, bone grafting and bone-marrow mononuclear cells implantation. *Eur J Orthop Surg Traumatol* 2014;**24**:197–202.
35. Zhao D, Cui D, Wang B *et al.* Treatment of early stage osteonecrosis of the femoral head with autologous implantation of bone marrow-derived and cultured mesenchymal stem cells. *Bone* 2012;**50**:325–30.
36. Zhang G, Qin L, Sheng H *et al.* A novel semisynthesized small molecule icaritin reduces incidence of steroid-associated osteonecrosis with inhibition of both thrombosis and lipid-deposition in a dose-dependent manner. *Bone* 2009;**44**:345–56.
37. Vande Berg BC, Gilon R, Malghem J *et al.* Correlation between baseline femoral neck marrow status and the development of femoral head osteonecrosis in corticosteroid-treated patients: a longitudinal study by MR imaging. *Eur J Radiol* 2006;**58**:444–49.
38. Qin L, Zhang G, Sheng H *et al.* Multiple bioimaging modalities in evaluation of an experimental osteonecrosis induced by a combination of lipopolysaccharide and methylprednisolone. *Bone* 2006;**39**:863–71.
39. Kitajima M, Shigematsu M, Ogawa K *et al.* Effects of glucocorticoid on adipocyte size in human bone marrow. *Med Mol Morphol* 2007;**40**:150–56.