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OSTEONECROSIS OF THE FEMORAL HEAD: CURRENT STATE OF THERAPY AND OUTCOMES: STRATEGICAL STEP-BY-STEP APPROACH

Ziad El Rabih[1], Anton Doro[1], Yusuke Kubo[2], Thomas Pufe[2], Wolf Drescher[1,3]

[1]Department of Orthopedic Surgery of the Lower Limb and Arthroplasty, Rummelsberg Hospital, Schwarzenbruck, Germany
[2]Department of Anatomy and Cell Biology, RWTH Aachen University, Aachen, Germany
[3]Department of Orthopedic and Trauma Surgery, RWTH Aachen University, Aachen, Germany

Author for correspondence: Ziad El Rabih: ziad.elrabih@sana.de

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Abstract

Osteonecrosis of the femoral head (ONFH) is a challenging multifactorial condition that affects mainly young patients. The disease can lead to collapse of the femoral head and secondary degenerative osteoarthritis of the hip joint. Various therapies for different stages of ONFH have been well established. However, results are largely heterogeneous and there is still no universal consensus regarding the optimal approach. In this article, the current therapies of ONFH and their outcomes will be reviewed and categorized based on the ARCO classification.

Keywords: *Hip arthroplasty*; *Joint preserving surgery*; *Osteonecrosis of the femoral head*

BACKGROUND

Osteonecrosis of the femoral head (ONFH) remains a challenging condition that requires an individualized, strategical step-by-step approach. This multifactorial condition affects mainly young patients with the highest susceptibility seen between the ages of 30–50 years,[1] affecting both hips in an unsynchronized fashion in up to 90% of the cases.[2] ONFH associated with chemotherapy for hematological malignancies occurs in much younger patients with a mean age of 14.4 years.[3] If left untreated, ONFH causes collapse of the femoral head in up to 80% of cases and consequently leads to secondary degenerative osteoarthritis of the hip joint.[4,5] As joint preserving surgeries are indicated in early precollapse cases of ONFH, total hip arthroplasty (THA) remains the treatment of choice in late stages of ONFH accounting for up to 10% of all THA performed in the USA.[6] However, THA for secondary osteoarthritis of the hip joint due to ONFH has shown nonoptimal results when compared with THA for primary osteoarthritis, especially in patients under corticosteroids therapy, with sickle cell disease (SCD) and alcohol abuse.[7]

Approach Based on the Association Research Circulation Osseous-Classification (ARCO)

The ARCO classification describes the disease progression according to radiographic and magnetic resonance imaging (MRI) changes.[2] It is currently considered a reliable tool for choosing the optimal therapy for patients suffering from ONFH. Joint preserving surgeries such as core decompression (CD) with various combinations are mainly performed in early precollapse stages (ARCO 0–II b), where the necrotic lesion involves less than 30% of the femoral head. Whereas middle to advanced stages ONFH (ARCO II b to III c) with more than 30% involvement or > 2 mm depression of the femoral head usually requires the removal of the necrotic portion out of the weight-bearing region through femoral osteotomies. Terminal irreversible stages of the disease (ARCO IV) with secondary osteoarthritis of the hip joint necessitate a THA.

JOINT PRESERVING SURGERIES (ARCO 0 – III C)

Various joint preserving surgeries have been well established in the last decades. The success of joint preservation depends on the location (medial, central, or lateral), radiographic staging, extension of the necrotic lesion, underlying health conditions, surgical technique, and the age of the patient. Joint preserving procedures include CD augmented with mesenchymal-cell-transplantation (MSCT), platelet-rich plasma (PRP) or bone grafting, and femoral osteotomies.

Core-Decompression (ARCO stage I – II b)

Core decompression is the most widely studied and commonly performed procedure (Figure 1) for treatment of early precollapse stages of ONFH in an attempt to reduce hip pain and prevent disease progression.[8] Theoretically, core decompression decreases the intraosseous pressure and venous congestion and thereby improves blood flow to the femoral head. It was originally developed in the pre-MRI era by Ficat and Arlet in the 1960s when intraosseous pressure in the femoral head was measured, and a biopsy specimen from the femoral head was taken to confirm the diagnosis of ONFH in painful hips without radiological evidence.[9] The best prognostic outcomes are seen in early precollapse stages (ARCO I–II b) with medially located necrotic lesions of less than 30% of the femoral head or Kerboul angle of less than 200°.[2,10–13] Advanced stages (ARCO II c–III) with collapse of the articular surface show high failure rates and progression toward degenerative osteoarthritis.

Adjuvants to CD for ONFH

Mesenchymal stem cell transplantation (MSCT)

The pathogenesis of ONFH is considered to be associated with abnormal metabolism of stem cells and decline in their osteogenic differentiation

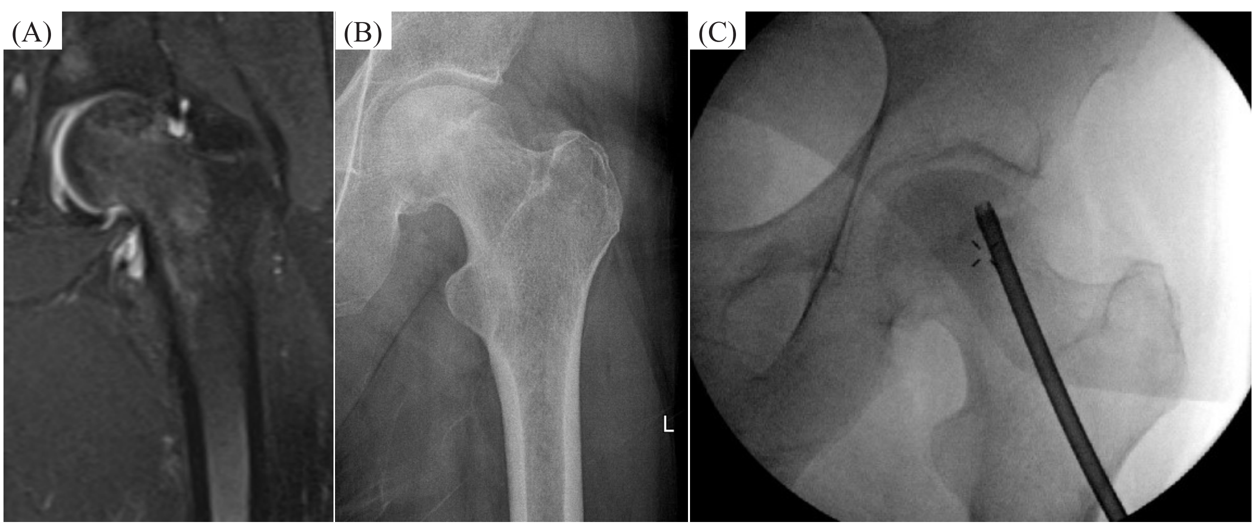

Figure 1. (A) Preoperative MRI of a laterally located ONFH (ARCO II-b) showing the extent of the necrotic lesion; (B) Preoperative X-ray showing mottled appearance of the femoral head and osteosclerosis; (C) Intraoperative X-ray after core decompression and autologous bone grafting.

potential.[14,15] In vitro studies have proven the ability of stem cells in stimulating neovascularisation and osteogenesis through transformation into endothelial cells and osteoblasts, respectively.[16,17] Stem cells can also stimulate blood supply to the necrotic regions through indirect paracrine signalling.[18]

Stem cells can be obtained from various tissues including bone marrow, peripheral blood, fat, or umbilical cord. Combination of core decompression and MSCT is the most described and widely performed method for implantation of stem cells.[19,20] Alternative combinations for MSCT include autologous bone marrow grafting and tantalum rods.[21]

The use of MSCT in combination with traditional core decompression was first described by Hernigou and Beaujean in 1993. Mesenchymal stem cells were harvested from iliac crest bone marrow and applied through the CD-tract in 189 hips. The study reported excellent results in precollapse stages of ONFH with 6.2 of patients requiring THA at 5–10 years follow-up.[15] A recent randomized control trial (RCT) with an average follow-up of 25 years comparing CD alone and bone marrow (BM) transplantation after CD for precollapse stages ONFH (ARCO I & II) showed a significant decrease in the volume of the necrotic region on MRI (45% of femoral head preoperatively vs 12% postoperatively) as well as decrease in THA required (24% in the CD/BM group vs 76% in the CD group).[22] Core decompression combined with MSCT has shown poor results in advanced stages of ONFH with existing articular collapse of the femoral head. In a double blinded RCT of 46 hips, Hauzeur et al. reported no clinical advantage of bone marrow autologous concentrate (BMAC) combined with core decompression in ARCO Stage III ONFH as 15 out of 23 hips (65%) progressed to THA at 24 months follow-up.[23]

Platelet-rich plasma (PRP)

Autologous platelet-rich plasma (PRP) contains numerous bioactive growth and differentiation factors that include platelet-derived growth factor (PDGF), transforming growth factor ß (TGF-ß), basic fibroblast growth factor (FGF), endothelial growth factor (EGF), and vascular endothelial growth factor (VEGF).[24] These factors have an important role in tissue repair through proliferation and differentiation of mesenchymal stem cells, as well as through regulation of various cellular processes including mitogenesis, chemotaxis, angiogenesis, and metabolism. Furthermore, PRP can inhibit inflammatory reactions occurring in necrotic regions by downregulating certain cytokines such as interleukin-1β, tumor necrosis factor-α, and interleukin-17A.[25] Studies on steroid-treated *in vitro* cell models and steroid-treated *in vivo* animal models have proven the significant role of PRP in the treatment of steroid-induced ONFH. PRP can prevent glucocorticoid-induced cell apoptosis through the activation of Act/Bad/Bcl-2 pathways and promote osteogenesis as well as angiogenesis by regulating the expression of numerous cytokines.[26–28]

Based on the above-mentioned rationale, PRP could be combined with core decompression and bone grafting to improve the treatment of early precollapse stages ONFH. Recent clinical results demonstrate a significant improvement after combining the two techniques. Aggarwal et al. compared CD alone and CD with PRP in a 4.5–6 years prospective randomized double blinded study on 53 hips with Ficat Stages I and II. Results showed a decrease in the modified Kerboul angle from 200.8 to 189.2° on postoperative MRI in the CD/PRP group versus increased modified Kerboul angle in the CD group. Progression to THA was seen in 78% in the CD/PRP group versus 92% in the CD group.[29] The combined application of MSCT with autologous PRP after core decompression represents "theoretically" an innovative intervention merging biotechnology that enhances osteogenesis and angiogenesis with surgical support through debridement of the necrotic region. In a recent study, Rocchi et al. combined core decompression and bone allografts with PRP and concentrated MSC. Best outcomes were seen in early precollapse stages with 16.7–20% progressing to THA in group ARCO Stage II a-b, whereas it was 75% in group ARCO Stage III b-IV after a minimum of 2 years follow-up.[30]

Vascularized Fibular Grafting

Since the 1970s, vascularized bone grafting has been applied as a joint preserving procedure in early precollapse stages ONFH (ARCO 0-II).[31] The transplanted bone provides a vital structural support and prevents the subchondral bone from collapsing. It also enhances osteogenesis and angiogenesis in the necrotic area due to the directly reconstructed vascularisation.[32] Vascularized bone grafts are most commonly harvested from the pelvic crest or from the fibula.[32,33] Alternative harvest sites include vascularized muscle-pedicle bone flaps from tensor fascia lata or Sartorius.[34,35] Following CD, the bone grafts are then introduced in the decompression tract in the femoral neck region and anastomosed to the lateral circumflex femoral artery microsurgically.[34]

In a study comparing vascularized and nonvascularized bone grafting in patients with early precollapse stages of ONFH (Pittsburgh I–II), Plakseychuk et al. reported an 84% 7-year survivorship in the vascularized group and only 30% in the nonvascularized group.[33] Urbaniak et al. described a 91% 5-year survivorship after vascularized fibula grafts in patients with Pittsburgh Stage II ONFH and 77% in patients with Stage III.[36] The success rate of this procedure is very limited in necrotic lesions extending more than 50% of the femoral head, articular surface collapse of > 2 mm, and in patients with comorbidities leading to graft failure such as smoking, alcohol abuse, and peripheral arterial disease.[37]

Femoral Osteotomies (ARCO II b - III c)

Several techniques of femoral osteotomies have been developed in an attempt to preserve the hip joint or delay the need for THA in young patients suffering from middle to advanced stages ONFH (ARCO IIb–IIIc). The principle behind this intervention is to move the affected necrotic area from the weight-bearing zone to a nonweight-bearing zone in order to prevent (further) collapse of the articular surface of the femoral head and promote healing of the necrotic lesion. Femoral osteotomies can be described as either angular or rotational. Through angular femoral osteotomies, the necrotic area is shifted medially or laterally thereby providing the weight-bearing area of the hip joint with a healthy nonnecrotic articular zone. Rotational osteotomies relocate the necrotic zone anteriorly or posteriorly around the femoral-neck axis.[38] The most well-known femoral osteotomies for the treatment of ONFH include the trans-trochanteric curved varus osteotomy (TCVO) and the trans-trochanteric rotational osteotomy (TRO).[39]

With TCVO, a curved osteotomy is performed between the greater and lesser trochanter, and the proximal fragment containing the necrotic area is shifted in a varus position. After confirmation of the targeted varus angle, the osteotomy is fixed with a plate and compression screws.[2,39] A success rate of 91.8%, defined as survival of the hip with no conversion to THA, has been reported after TCVO at 12.4 years follow-up.[40,41]

In TRO, the osteotomy is performed through the greater trochanter between the gluteus medius and piriformis posteriorly and between gluteus medius and vastus lateralis anteriorly. The proximal fragment is then rotated anteriorly or posteriorly depending on the location of the necrotic lesion. After confirmation of the final positioning, the osteotomy is fixed and the greater trochanter is reattached.[2,42] The results of TRO are highly controversial. Dean et al. reported nonsatisfactory results after performing Sugioka's trans-trochanteric anterior rotational osteotomy for ONFH on 18 hips. Success defined as no collapse of the femoral head was seen in only 17% of the cases at a mean follow-up of 5 years.[43] In Asian countries, however, several studies reported success rates ranging from 70 to 93%. [2,42]

In a retrospective study comparing TCVO (91 hips) and TRO (65 hips), Lee et al. reported shorter operation time and less blood loss in the TCVO group. Furthermore, higher collapse rates of the femoral head (28.6% in TRO group vs 10.8% in TCVO group) and subsequently higher rates of conversion to THA were observed in the TRO group (89.2%).[44]

ARCO IIIC – IV: HIP REPLACEMENT SURGERIES

Terminal nonsalvageable stages of ONFH (ARCO IIIc–IV) are characterized by an irreversible collapse of the articular surface and inevitable progression to degenerative osteoarthritis of the hip joint.

With regard to the reduction of pain and restoration of mobility, such patients do not benefit from joint preserving surgeries and often require hip replacement. Commonly performed joint replacement surgeries include joint resurfacing, total hip arthroplasty (THA), and short-stem THA.[45] Traditional THAs performed for postcollapse ONFH before the year 2000 have shown nonsatisfactory results due to failure rates as high as 53%.[46–48] Prospective analysis comparing THA for primary osteoarthritis (45,252 hips) and ONFH (2271 hips) from 2001 to 2012 has reported higher rates of surgical site infection, readmission, revisions, and mortality in patients with ONFH.[49]

Several underlying health conditions leading to ONFH are associated with increased failure rates after THA. Renal transplantation, corticosteroid therapy, SCD, smoking, and alcohol abuse are among the most widely reported contributors.[50–53] In the setting of alcohol-induced ONFH, Yuan et al. reported a high revision rate (29.2%) at a mean follow-up of 6.7 years.[50] More recent case series (62 hips) analyzing THA for ONFH due to alcohol abuse with mean follow-up of 8.6 years reported 8% early revision rate (< 2 years) for instability, periprosthetic acetabular fracture and component loosening, heterotopic ossification, superficial infection, and acute periprosthetic infection.[54] Higher failure rates in this young population can be attributed to the comorbidities associated with alcohol abuse including concomitant smoking history, alcohol withdrawal, noncompliance, and poor clinical follow-up.[50,54] Early retrospective studies (before 1990) on THA for patients with ONFH due to SCD have shown unfavorable results with very high revision rates (14/25 hips – 40%) especially in cemented THA at a mean follow-up of 8.6 years.[51] However, recent studies (after 1990) have confirmed excellent results with 98% 10-year survivorship when implanting cementless stems and cups in patients with SCD-induced terminal stage ONFH.[55]

Histological analysis of bone matrix composition in ONFH has revealed significant reduction in bone mass and trabecular quality in the trochanter major region (Figures 2–3). Moreover, histological studies confirmed extension of the necrosis below the trochanter minor region.[56–59] These histological changes in bone composition and metabolism can be seen as major contributors to aseptic stem loosening after THA in ONFH patients.

Mid-term results of short-stem THA (Figure 4) in patients with ONFH are very promising. At a mean follow-up of 7.9 years, Zeh et al. reported complete osseointegration of 26 short-stem THA implanted in 21 patients suffering from ONFH. When compared with a matched control group with implantation of short-stem THA for primary osteoarthritis, there

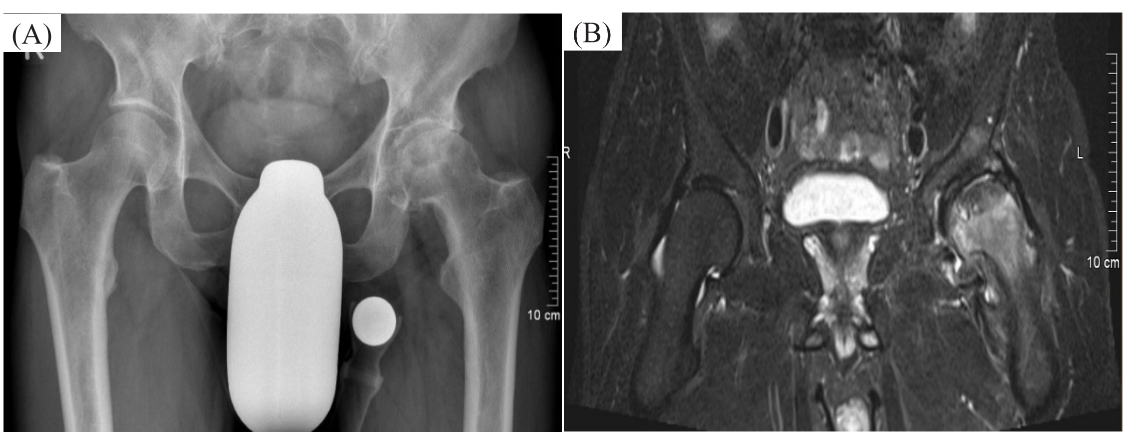

Figure 2. (A) Preoperative X-ray showing advanced secondary osteoarthritis with narrowing of the joint space, cyst formation and osteosclerosis; (B) MRI showing ONFH located centrally and laterally, involving > 30% of the femoral head.

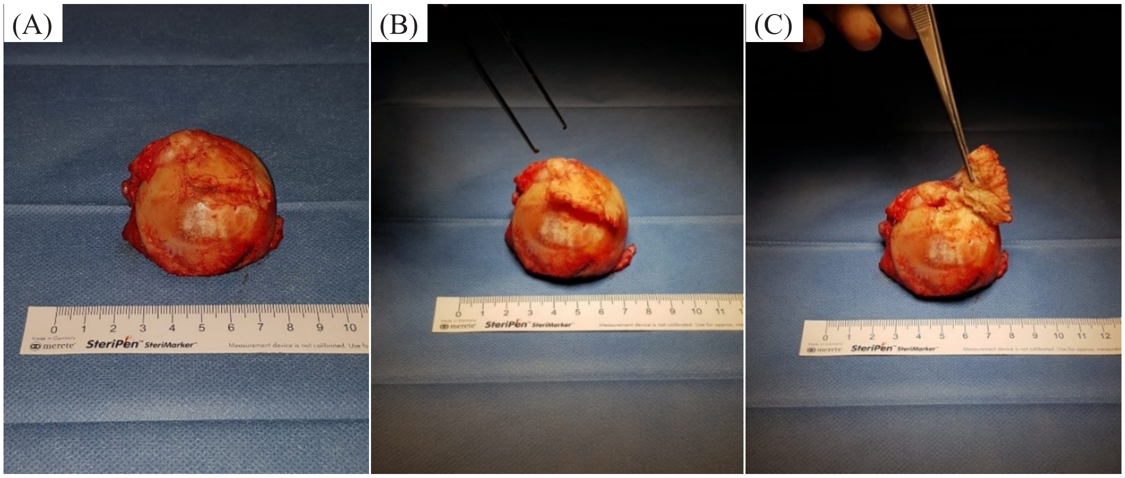

Figure 3. (A–C) Intraoperative finding showing loss of contour of the femoral head with subchondral fracture and collapse of the articular surface.

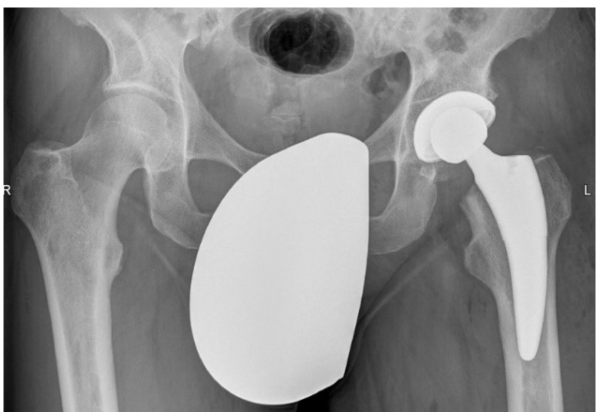

Figure 4. Postoperative X-ray after total hip arthroplasty with short-stem prosthesis.

was no significant increase in stem migration or tilting radiologically.[60] Capone et al. showed excellent clinical results and fixation pattern in 30 patients (37 hips) younger than 60 years who underwent short-stem THA for late stages ONFH (Steinberg IV–V).[50] In this case series, there was no reported revision for any reason at a mean follow-up of 5.6 years. Suksathien and Sueajui demonstrated 98.8% survivorship with the end point of stem revision for any reason and 100% survivorship for aseptic loosening at 7 years follow-up in 83 cases treated with short-stem THA for terminal stages ONFH (Stages III–IV after Ficat and Arlet).[61]

CONSERVATIVE THERAPIES (ARCO 0-I/ CONTRAINDICATION TO SURGERY)

Conservative treatment of ONFH has been proposed for early noncollapse stages (ARCO 0-I) with very small necrotic lesions or among patients where surgical intervention is contraindicated due to other comorbidities. Nonweight-bearing is usually recommended for reducing pain without long-term effect on the progression of the disease. Many pharmaceutical agents have been suggested and applied as conservative regimes to reduce pain and prevent further deterioration of ONFH. Statins have shown no significant outcomes in preventing or delaying the development of ONFH.[62] Iloprost, a prostaglandin analog that enhances blood flow and reduces coagulation, is commonly used for early precollapse stages of ONFH to reduce pain and bone marrow edema,[63] however with no evidence of long-term prognostic improvement for ONFH.[64] Bisphosphonates reduce bone turnover by increasing osteoclast apoptosis and reducing osteoblast apoptosis.[65] Regarding the rate of progression to THA, there were no differences shown between the alendronate and placebo groups.[66] Extracorporeal shock wave therapy, electromagnetic field stimulation, and hyperbaric oxygen therapy have been reported to be effective in alleviating pain and reducing bone marrow edema syndrome in patients with ONFH.[67] However, there is no clear evidence whether these therapies can prevent or delay the progression of ONFH.[68]

DISCUSSION

Despite extensive data on core decompression as a treatment option for early precollapse stages of ONFH, clinical outcomes are still controversial. This could be in part attributed to the numerous adjuvant methods applied with core decompression. On the other hand, the success of this procedure is highly dependent on the stage of the disease, the patients being selected, and the underlying conditions contributing to the development of ONFH.

Stem-cell therapy for ONFH is promising in regard to its effectiveness in treating early precollapse stages. However, many challenges such as clinical indication and safety profile are still faced in the clinical practice. Therefore, more RCTs are needed to standardize the surgical procedure, validate its safety, and investigate the future fate of the transplanted stem-cells in regard to tumorgenicity.

The utilization of PRP with CD is beginning to gain more focus in early stages of ONFH. However, various limitations still exist. There is no universal standard of procedure for PRP in treating ONFH, and the curative effects of PRP demonstrated in many articles are highly heterogeneous.

Femoral osteotomy is a valuable joint preserving treatment option in advanced stages ONFH (ARCO IIb–III). These surgical procedures demand high technical abilities and a standard routine. Specific complications of femoral osteotomies include iatrogenic lesion of the femoral circumflex arteries with further damage to the blood flow of the femoral head, delayed union or pseudarthrosis of the femoral osteotomy, intra-articular adhesions, heterotopic ossifications, excessive angular correction, impingement, leg length discrepancy, and high riding trochanter.[38] Appropriate patient selection for femoral osteotomies is essential. Best outcomes have been reported in patients not being treated with long-term corticosteroids, age < 40 years, with a body mass index (BMI) less than 24 kg/m^2, minimal osteoarthritic changes, a postoperative intact articular surface ratio of at least 33% and necrotic lesions with a Kerboul angle less than 200°.[2,69–72]

Short-stem THA offers a valuable alternative to conventional THA in this specific patient population due to their metaphyseal fixation and consequently reduced stress shielding on the proximal femur.[60,61] In addition, short-stem THA provides a potential advantage of bone stock preservation in cases of prosthesis revision in young patients. Although mid-term results are promising, further investigations are still needed to analyze the long-term durability of short-stem THA in ONFH. Moreover, further studies are required to determine optimal surface bearing of the implant as well as the factors contributing to implant failure.

CONCLUSION

ONFH remains a disease with unclear pathophysiology. The treatment necessitates a thorough understanding of the disease and the factors associated with its progression. In precollapse cases of ONFH early diagnosis and intervention are essential. The aim of joint preserving surgery is to prevent femoral head collapse and stop or delay the damage to the hip joint. Patients in this age group are highly active and therefore more physically demanding. So, encouraging prevention, seeking early diagnosis, emphasizing joint preserving procedures, and applying modern arthroplasty techniques should always be considered by the treating physician.

AUTHORS' CONTRIBUTIONS

The manuscript was written by Ziad El Rabih. All authors contributed to the complete review and rereview of the manuscript.

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Conflict of Interest

There is no conflict of interest regarding the content or authorship of this article.

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