Non-traumatic Osteonecrosis of the femoral head: an overview

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Abstract

Osteonecrosis of femoral head is a debilitating condition that frequently affects the young. Risk factors primarily include corticosteroid use, alcohol consumption, trauma, blood dyscrasias and coagulation abnormalities. Despite multiple theories, no single mechanism has been successful in fully explaining the pathophysiology, except for one common factor that impairment of circulation to the femoral head leading to subsequent development of necrotic patches. The natural history of the disease is eventual collapse of the hip joint and arthritis; therefore, early diagnosis and intervention are essential. Size and location of the lesion are prognostic factors of progression of the disease process and are best evaluated on magnetic resonance imaging. Management of non-traumatic osteonecrosis remains evolving with better knowledge of the disease process and advances in treatment options. In an early stage, joint-preservation is the primary objective, which offers options of core decompression alone or with adjunctive vascularized bone grafts, avascular grafts, bone morphogenetic proteins, stem cells, or combinations of the above or by transtrochanteric osteotomies. Once collapse has set in, total hip replacement has been the preferred treatment of choice. Nevertheless, careful patient selection and understanding the etiology plays a pivotal role in deciding course of management and choice of implants.

Keywords: Non-traumatic, Osteonecrosis, Avascular necrosis, Femoral head, Total hip arthroplasty

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Introduction

Osteonecrosis of the femoral head (OFH) with poorly understood etiology, is a debilitating condition that frequently affects young patients in 3rd to 5th decade of life [1]. Despite low incidence and prevalence compared with primary osteoarthritis, OFH has a significant economic impact because it largely affects the younger population. As the femoral head collapses, there is pain and loss of function. The natural history of the disease is progression to hip dysplasia, femoro-acetabular impingement to eventually total collapse of the hip joint and arthritis. When left untreated, it tends to lead to severe secondary joint destruction in the majority of patients [2]. Therefore, awareness of risk factors, early diagnosis and intervention are essential which can prevent complications.

Etiology and Pathogenesis Though the etiology of OFH is not yet absolutely clear, it is understood that a multi-factorial process is involved [3].

Long-term corticosteroid treatment is the most frequent risk factor of OFH, seen in 10 to 30% of cases [4]. Treatment for two to three months with a daily dose of 2 g prednisolone equivalent or more is regarded as critical. The patho-physiology of steroid-associated OFH is controversial, but proposed mechanisms include abnormalities of the lipid metabolism and bone marrow stem cell pool, hyperlipidemia, distribution of fat emboli in circulation, hypercoagulable state, vascular endothelial dysfunction and apoptosis of bone

tissues [4]. All these multiple factors influence each other, resulting in marrow ischaemia and eventually osteonecrosis.

Excessive alcohol consumption has also contributed to the incidence of non-traumatic OFH. Matsuo K et al showed that an intake of up to 320 g ethanol (equivalent to 5 bottles of wine) per week raised the risk of non-traumatic OFH by approximately a factor of 2.8 [5]. Alcohol has a significant effect in terms of increase in serum triglyceride/cholesterol levels, deposition of triglycerides in osteocytes leading to pyknosis, increased percentage of empty osteocyte lacunae, subchondral fat cell hypertrophy and proliferation and bone marrow fatty infiltration. Similar to corticosteroids, alcohol tends to increase adipogenesis at the cost of osteoblastic proliferation or function and hence leading to decreased osteogenesis, but through a different mechanism than steroid as alcohol-treated stromal cells did not show increase in PPAR-γ expression which was noted in steroid affected cells [6]. Although the mechanisms may differ between these two, the consequences of adipogenesis, hypercoagulability and diminished reparative capability all contribute to the final pathway of cell death.

Smoking has also been found as a risk factor, although no dose-effect relationship has been established. Heavy smokers (>20 cigarettes / day) demonstrated higher risks of OFH than light smokers (<20 cigarettes/day), who in turn showed higher risk when compared with nonsmokers [5,7].

OFH can be caused by hypercoagulability and thrombotic occlusion of the micro-circulation occurring from hereditary thrombophilia, impaired fibrinolysis, antiphospholipid antibodies or sickle cell disease and other hemoglobinopathies [8,9]. Additional causes include environmental or acquired / preexisting conditions, such as hyperlipidemia, hypersensitivity reactions, thromboplastin release during pregnancy, malignant tumors, and inflammatory bowel disease, all may contribute additional risk to individuals with an underlying genetic predisposition to form microvascular thrombi. Björkman A et al and Zalavras et al showed that mutations in the factor V Leiden or prothrombin 20210A gene and protein C and S deficiencies were significantly more common in patients with idiopathic OFH than in patients with steroid or alcohol-induced OFH, as well as in a population of healthy control subjects [10,11].

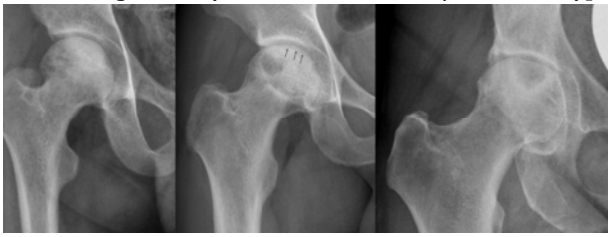
OFH has also been observed more frequently in HIV patients, with or without antiretroviral treatment. It is not known whether the association is due to protease inhibitors alone or whether there is a multi-factorial link in combination with other risk factors such as the HIV infection itself, a history of systemic corticosteroid use, or hyperlipidemia [12].

History, Clinical features and Diagnosis

The role of careful history is vital in screening for potential risk and/or prognostic factors, to determine if other joints are involved, to look for other conditions that might present with similar symptoms, and to chalk out management. The onset of disease is insidious and the symptoms and signs are usually minimal and nonspecific until the disease reaches an advanced stage. Therefore, a high index of suspicion and ordering early imaging may contribute to an early diagnosis, as diagnosis of OFH is primarily based upon imaging findings.`

Radio graphs are the most easily accessible, ready available, simple, low cost screening tool for diagnosis of OFH, which is seen as sclerosis surrounding an osteopenia area, cystic changes and crescent shaped lucent lesion in early stage and loss of sphericity, subchondral collapse and degenerative arthritis involving arthritic changes on the acetabular side as well in advanced stage (Figure 1).

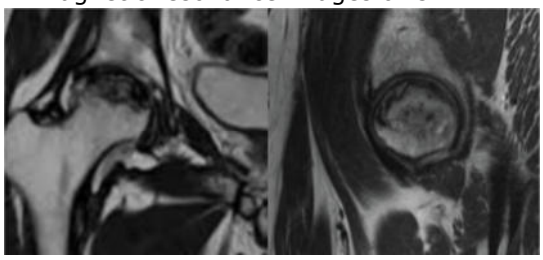
Fig 1. Radiographic images of different ARCO stages [A: stage II, B: stage IIIA (crescent sign) and C: stage IIIB (femoral head collapse >2mm)].



This is best visualized on the frog leg lateral view as it depicts the profile of the most common location for a subchondral fracture, i.e., the superior lateral portion of the femoral head's anterior segment. The disadvantage of radiographs is its insensitivity for detecting OFH in its early stages [13].

Magnetic resonance imaging (MRI) is useful screening tool for early diagnosis, quantitative evaluation of disease extent within the femoral head and staging of the disease and hence is the imaging method of choice with the highest sensitivity and specificity compared to plain radiographs, computed tomography, or scintigraphy [14] (Figure 2). A single-density thin "band-like" lesion with low signal intensity rim surrounding the necrosis on T1-weighted images and a "double-line" sign consisting of a low signal intensity outer rim and a high signal intensity inner rim on T2-weighted image are considered diagnostic of the disease [15,16].

Fig 2. Magnetic resonance images of OFH.



Computerized tomography (CT) While radiographs and MRI are useful, CT delineates the outline of the subchondral bone / necrotic zone / fracture most clearly in three dimensionally. CT also detects small areas of collapse which are not seen on plain radiographs or MRI [17]. In spite of these advantages, due to ionizing nature and since prognosis and decision making requires MRI, CT scan are not primarily advised.

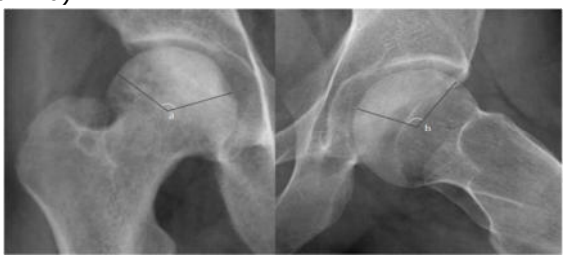
Technetium-99 isotope scan: Necrotic region of bone does not take up the radioactive isotope ("cold" on scan), whereas the surrounding rim of reactive bone remodeling takes up the isotope ("hot" on scan), hence in the early stage of disease, bone scan showing "cold within hot" area. After subchondral fracture, attempts of repair are seen as "hot lesion" that obscures the original cold area. Bone scan is limited by poor spatial resolution, low specificity to differentiate other disorders, and inability to quantify the lesion [16]. For these reasons, nuclear studies are inferior screening tools in the management of OFH.

Prognosis

Detecting prognostic factors (subchondral fracture, extent and location of the lesion) and understanding the treatment options based on the stage is essential part of the management.

Prognosis on radiological evaluation primarily depends on: (1) presence or absence of head collapse, (2) amount of head collapse, (3) size and site of the necrotic lesion, and (4) acetabular involvement. A change of more than 2 mm in the femoral head contour confers a worse prognosis. The combined necrotic angle of Kerboul measured on radiograph or MRI gives substantial detail on the size of the necrotic lesion, and are highly reliable and reproducible [15] (Figure 4). Regarding, location of the necrotic lesion, small medially located lesions may be treated by observation alone whereas acetabular involvement directs towards hip replacement and saving the femoral head is bound to fail [18,19].

Fig 3. Measuring combined kerboul's angle on AP and lateral radiographs (Combined angle of Kerboul = a + b)



There have been sixteen major classification systems to stage OFH and provide guidance on prognosis, decision making and outcome. The Ficat classification [20] (Table 1) is the most frequently used system (63%), followed by the University of Pennsylvania system (20%) [21] (Table 2), the Association Research Circulation Osseous (ARCO) system (12%) [22] and the Japanese Orthopaedic Association system (5%) [23]. The Association Research Circulation Osseous (ARCO) classification system was developed for clinical

trials, by merging the Ficat, Steinberg, and Japanese Orthopaedic Association systems. Recently in 2019, the ARCO classification was revised (Table 3) to provide uniform platform for clinical and research applications [24].

Table 1. Ficat and Arlet Classification [20]

Stage	Description	
I	Normal radiographs	
II	Sclerotic or cystic lesions	
	IIA	No sign of subchondral collapse
	IIB	Subchondral collapse (crescent sign on radiograph) without femoral head flattening
III	Femoral head flattening	
IV	Osteoarthritis with decreased joint space, articular collapse, or acetabular involvement	

Table 2. University of Pennsylvania Classification (Steinberg) [21].

Stage	Description	
0	Normal findings on radiographs and MRI	
I	Normal findings on radiographs and abnormal MRI findings	
	IA	<15% of head affected
	IB	15% to 30% of head affected
	IC	>30% of head affected
II	Sclerotic changes on radiographs	
	IIA	<15% of head affected
	IIB	15% to 30% of head affected
	IIC	>30% of head affected
III	Subchondral collapse and/or fracture	
	IIIA	<15% of head affected
	IIIB	15% to 30% of head affected
	IIIC	>30% of head affected
IV	Femoral head flattening	
	IVA	<15% of head affected and <2 mm of head depression
	IVB	15% to 30% of head affected or 2 to 4 mm of head depression
	IVC	>30% of head affected
V	Joint space narrowing with or without acetabular involvement	
VI	Advanced degenerative changes	

Table 3. The 2019 Revised ARCO Classification System for Osteonecrosis of the Femoral Head [24]

Stage	Description	
I	Normal radiograph; MRI shows band lesion (low intensity) around the necrotic area.	
II	Radiographic evidence of sclerosis, focal osteoporosis or cystic changes; no evidence of subchondral fracture or fracture in the necrotic portion.	
III	Subchondral fracture, fracture in the necrotic portion, and/or flattening of the femoral head on radiograph or CT scan.	
	IIIA	Femoral head depression of ≤2 mm
	IIIB	Femoral head depression of >2 mm
IV	Radiographic evidence of osteoarthritis, joint space narrowing, and degenerative acetabular changes.	

Treatment

Optimal treatment of OFH has been a subject of discussion and research for a long period of time, though no conclusive path has been framed till date. Treatment can broadly be divided into nonoperative and operative methods. The main aim of treatment is preservation of hip anatomy by preventing bone destruction and collapse of the femoral head. Non-operative treatment of pharmacological agents, physical therapy like hyperbaric oxygen and shock wave therapy, along with supportive treatment to offload the hip, have been tried with limited evidence of applicability [25,26].

Non-operative Treatment

Restricted weight-bearing to offload the affected hip have been suggested in patients awaiting surgery. Systematic review analysing the natural history of untreated asymptomatic OFH stated that 59% of such hips had disease progression at a mean of 7 years, with risk of collapse highest among sickle cell disease and least among systemic lupus eythematosus. Large lesions (involving>50%) had 84% chances of progression, while it was 32% in small- or medium-sized lesions [27].

Pharmacological agents

Various pharmacological agents used in preventing disease progression and preservation of unaffected areas are effective in the initial stages of the disease only. There is a paucity of multi-centre studies and research regarding comparison of various pharmacological agents and their benefit over surgical methods.

Bisphosphonates They acts by preventing osteoclastic resorption of the bone tissue, but their role in OFH have been a matter of debate with evidence, both promoting and discouraging, its use. Agrawala et al and Lai et al, found that alendronate significantly prevents the chances of collapse, preserves joint function and delays the chances of replacement surgeries when started in initial stages of the disease, but its benefit in later stages is limited [28,29]. In contrast to these studies mentioned above, there are multiple

studies stating that bisphosphonates have only a limited role, if any in preventing progression of the disease [30-32].

Lipid Lowering Agents (Statins) Statins by preventing adipogenesis can play an important role in preventing osteonecrotic collapse in steroid-induced OFH, but it may not be efficient in reversing the changes or induce healing in such cases [4,33]. Ajmal et al in 2881 renal transplant patients showed that on 15 (4.4%) patients out on 338 on statins and 180 of 2,543 (7%) patients who were not on statins, developed OFH [34].

Vasodilators Prostacyclin analogs like ilioprost has shown to lower intraosseous hypertension and increase blood flow to the ischemic area, seen as significant improvement in pain and functional scores as shown by Jager et al in 95 patients of OFH receiving ilioprost [35].

Anticoagulants Vitamin K inhibitors, low-molecular weight heparins and direct thrombin inhibitors have been used to prevent progression of OFH in patients without collapse due to coagulation disorders. Enoxaparin administered at a dose of 6000 IU or 60 mg daily or Warfarin given in 1-5 mg/kg/day dose for 12 weeks is found to be effective in preventing development of OFH or progression of disease [36].

Biophysical Methods

Various biophysical methods have been suggested for treatment in OFH.

Pulsed electromagnetic field therapy (PEFT) functions by stimulating osteogenesis and angiogenesis, but, its role in early-stage OFH treatment remains to be established [37].

Extra-corporeal shock wave therapy (ESWT) restores tissue oxygenation, reduces edema and induces angiogenesis and hence it offers a feasible and good substitute to invasive surgical modalities [38].

Hyperbaric oxygen (HBO) increases reactive oxygen and nitrogen species in tissues, induces modulation of endothelial progenitor cell proliferation, promotes neo-angiogenesis and neo-vascularization, increases extracellular oxygen concentration and reduces bone marrow pressure and improves oxygen delivery to ischemic cells, relieving compartment syndrome and preventing necrosis [39,40]. Moghamis et al showed no statistical significance between groups treated by hyperbaric oxygen and core decompression in terms of functional and radiological outcome, but hyperbaric oxygen was suggested as an effective noninvasive alternative to core decompression [41].

Non-operative modalities have generally been ineffective in halting the disease progression and are inappropriate options to prevent collapse. Majority of studies on non-operative treatment modalities are from single-centre, are of low evidence and have inconclusive results, these options are only suggested auxiliary to operative treatment [42].

Operative treatment

The choice of surgery depends upon the extent of involvement, and stage and location of the disease. Operative options are procedures that preserve the native hip joint and total hip replacement. Joint-preserving procedures, which aim to prevent or limit the disease progress are core decompression and its variants (i.e. adjunctive grafting, stem cell therapy), bone grafting and proximal femoral osteotomies. These procedures are preferably used in symptomatic young patients without femoral head collapse (precollapse) or in select patients with minimal collapse.

Core decompression is a surgical procedure wherein a core is drilled in the lesion to decompress the raised intraosseous pressure cause by cellular swelling and inflammatory cell infiltration, and facilitate a channel for new blood vessels [43]. Favorable outcomes of core decompression, in symptomatic precollapse small lesions to early collapse stages are seen when performed either using a single wide-bore trephine (10mm) or multiple small-diameter (3-8mm) drilling.

Studies have demonstrated an overall success rate of core decompression to 65% at an average follow-up of 54.3 months along with

failure rate of 14 to 25% in small lesions and that of 42 to 84% in larger lesions [44]. Song WS et al demonstrated 78% survivorship at five-year follow-up and 88% of small- to medium-sized lesions did not require surgery at a mean follow-up period of 7.2 years. He found standard core decompression and multiple drilling both equally effective with no difference in the odds of improvement [45]. Arthroscopy-assisted core decompression provides added advantages of articular cartilage visualization, evaluation of degree of collapse, guide the reamer and avoid the risk of joint penetration [46].

Core Decompression with adjunctive therapy Incorporating cell-based components like bone marrow stem cells, platelet-rich plasma or tantalum rods into the tract created by drilling is performed adjuvant to core decompression with varying success rates.

Bone marrow aspirate concentrate augmentation of core decompression in comparison to core decompression alone, improves hip function, decreases stage progression, delays the collapse of femoral head and decreases the THA conversion rate better, especially in pre-collapse disease, but not in advanced lesions [47,48].

To sum-up, results of cell-based therapies with core decompression are promising. However, the lack of standardization of harvesting, processing and transplant methods, lack of knowledge on amount of cells needed for definitive success, and doubtful potency of mesenchymal stem cells of patients with osteonecrosis are setbacks to their incorporation into regular practice.

Non-vascularized bone grafting is used in symptomatic precollapse and early postcollapse lesions when the overlying articular cartilage is relatively undamaged, as bone grafting provides structural support and scaffold for bone remodelling, in addition to reduction in intraosseous hypertension, and removal of necrotic bone. Three approaches for placing bone graft are described (1) Phemister technique - cortical graft is placed through a core tract in the femoral neck and head; (2) trapdoor technique - graft is placed through a trapdoor created through the articular cartilage of the femoral head; and (3) light-bulb technique - graft is placed through a window created in the femoral neck at the base of the head [18]. Non-vascularized fibula can be placed as a cortical strut graft, either single or double in the tract drilled following core decompression. Wu CT et al reported 88.5% and 76.9% of 5-year and 12-year survival rate after double-fibular allograft strut grafts in hips with collapse <2mm respectively [49]. Studies suggest that bone grafting procedures are reserved for small to medium sized lesions in young adults only [50].

Vascularized bone grafting provides added benefit of restoration of vascular supply to the necrotic lesion and is primarily advocated in precollapse lesions. Free vascularized fibular graft and vascularized iliac crest bone graft are most commonly practiced vascularised bone grafting types. Ünal MB et al reported post-operative HHS>80 in 15 of 16 hips of grade II disease and in 6 of 7 hips of grade III in mean follow up of 7.6 years after vascularized fibular graft [51]. Vascularized grafts are limited by setbacks of dedicated team, availability of operating microscope, technical difficulty, long-operating hours, concerns over patency of anastamosis, and potential harvest-site morbidity.

Muscle-pedicled bone grafts utilize locally available bone while maintaining its vascular pedicle, in turn acting as vascularized bone graft. Various such grafts like Meyer's quadratus femoris muscle-pedicle bone graft, Baksi's sartorius-pedicle or tensor fascia lata muscle-pedicle iliac bone grafts, and other's lateral femoral circumflex vessel pedicled iliac graft and gluteus medius-pedicle greater trochanter flaps have been performed successfully with reduction in stage progression and conversion to arthroplasty, equally as shown by Zhang L et al and Zhao D et al [52,53].

Femoral osteotomy The goal of proximal femoral osteotomies is to shift the necrosed segment away from the weight-bearing region. Success rates of femoral osteotomies vary from 70 to 93%, with two types of osteotomies (1) angular intertrochanteric (2)

transtrochanteric rotational osteotomies. Since, rotational osteotomies allow a greater degree of translation of the necrotic area, it shows better outcome in terms of preventing stage progression, preventing collapse and conversion to THR, compared to intertrochanteric curved varus osteotomy, but rotational osteotomies are difficult to perform and are associated with higher risk of non-union [18]. These procedures can produce good results in the earlier stages of necrosis but when collapse has set in, these osteotomies bound to fail. Femoral osteotomies have varied acceptance owing to limitations in patient selection, indications of osteotomies regarding lesions, difficulty in performing the procedure, uncertain outcome, prolonged immobilisation, and difficulty in subsequent conversion into THA [54].

Head sacrificing procedures

Joint-preserving procedures are inadequate and hip arthroplasty is indicated in large precollapse and postcollapse lesions, advanced stage when the femoral head has collapsed >2mm, arthritic changes at the hip joint or for salvage, when other modalities have failed. Head sacrificing procedures include: (1) hemiresurfacing (2) hemiarthroplasty (3) total hip arthroplasty (cemented or cementless).

Hemiresurfacing was introduced as time-buying procedure after failure of joint-preserving surgeries, as THA was an unfavourable in the young patient and they preserved bone stock and had lower dislocation rates. Amstutz HC et al demonstrated survivorship of 80%, 63% and 36% at 5, 10 and 13 years after hemiresurfacing respectively [55]. Due to complications of resurfacing like metal-on-metal interface complications, decreased survivorship, and increased risk of periprosthetic fractures, these procedures are seldom done these days [25].

Hemiarthroplasty can be considered when the acetabular cartilage does not show any arthritic changes. Chan et al showed no significant differences in rate of additional procedures at mean of 6.4 years after hemiarthroplasty or THA [56]. Femoral loosening, acetabular protrusion, osteolysis, polyethylene wear and high failure rates in long term lead to fallout of hemiarthroplasty as a treatment option in OFH.

Total hip arthroplasty Cemented and cementless total hip arthroplasty (THA) have been extensively used and analysed for OFH.

Cemented THA done for OFH have shown survivorship of 99% and 64% at 10 and 20 year follow-ups respectively. Early studies attributed, failure of interdigitation of cement to defective cancellous bone in patients with osteonecrosis, as the cause of aseptic loosening in cemented THA [111]. Improvements in implant surfaces, highly cross-linked polyethylene and improved sterilization and storage of polyethylene have led to lower wear rates and increased survivorship of >90%.

Cementless THA have survivorship of 94% in at an average follow-up of 16 years. Kim YH et al reported 99% survivorship of the femoral component and 99.4% of the acetabular component, after a mean follow-up of 14.7 years, after ultra-short proximal loading uncemented femoral component for Ficat and Arlet stage III or IV osteonecrosis [57]. Selection of the femoral prosthesis should be according to the overall quality of bone and age of patient. As patients of non-traumatic OFH are usually of the younger age group, short-stem with diaphyseal anchorage components are preferred to preserve the metaphyseal bone stock and prevent aseptic loosening. Recent studies, have demonstrated excellent long-term clinical outcomes after THA with median HHS of 93 points and 15 year revision rate was 6.6%. Owing to improvements in prosthesis design and surgical techniques, the outcomes of THA have drastically improved.

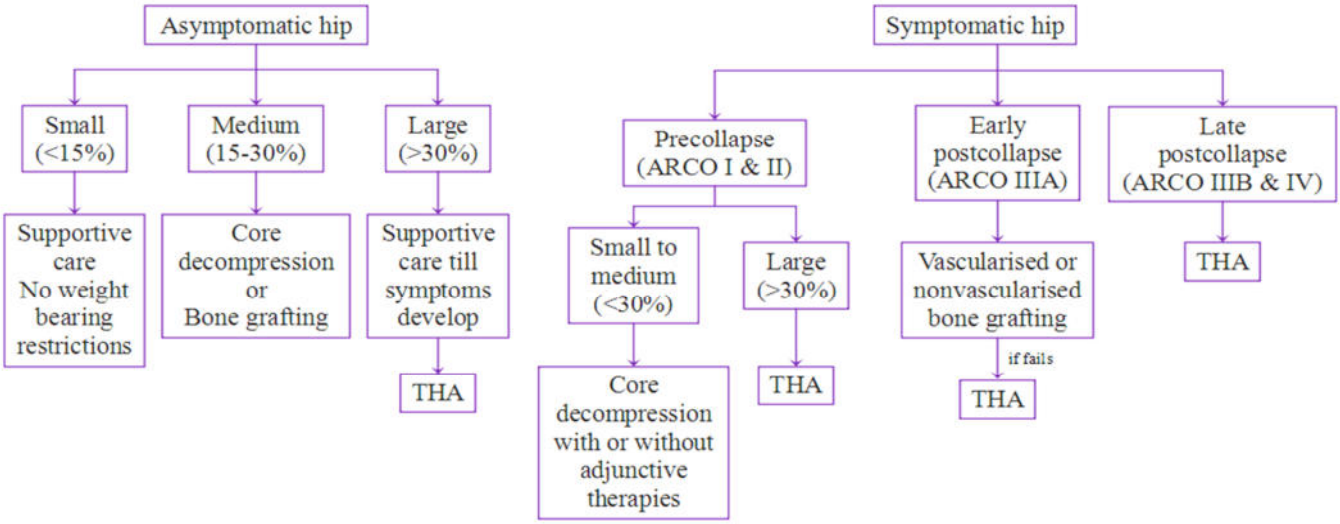
Approach to management

The choice of treatment plan for OFH depend on multiple comprehensive factors including manifestations of blood supply changes in the necrotic femoral head, staging and classification of OFH, necrosis volume, joint function, age and occupation of the patient,

and his/her compliance to rehabilitation following joint-preservation procedures.

Following comprehensive analysis on classification, prognosis and clinical outcomes, Mont MA et al staged OFH according to collapse; precollapse, early precollapse (head depression ≤2 mm), and late collapse (depression >2 mm or acetabular changes) [25]. Depending on this stage of collapse and the size of lesion, the authors suggest the algorithm for guiding the treatment (Figure 4).

Fig 4. Treatment algorithm for non-traumatic osteonecrosis of the femoral head (Adapted from Mont MA et al [25])



Conclusion

Osteonecrosis of the femoral head is a progressive disease which can be a major source of disability for young patients. It requires a proper understanding of the underlying disease being dealt with. Being a progressive condition, it needs to be tackled at the foremost instance. MRI is both a sensitive and specific screening tool to identify the disease at its earliest stages. Recent evidence states that nonoperative modalities are neither effective in halting the progression of the disease nor in preventing collapse. In precollapse and early stages, the primary objective is preservation of the native joint. Core decompression, vascularized or non-vascularized bone grafting, and femoral osteotomies have been described. Biological augmentation of core decompression has shown to have promising results in early stages of the disease. Patients with lesions more than 2 mm femoral head collapse or acetabular changes require total hip arthroplasty.

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