

Non-traumatic Osteonecrosis of the Femoral Head – From Clinical to Bench

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Non-traumatic osteonecrosis of the femoral head commonly affects young adults between the third and fifth decade of life. It is the leading cause of hip joint replacements in many Asian countries including Taiwan. The ultimate goal is the preservation of the involved hip. However, this is often challenging since early diagnosis is difficult, the etiologies are miscellaneous, the pathogenesis is unclear, and successful treatment is undetermined. As a consequence, this disease remains well-known but not fully-understood. This review provides an update of the progress from clinical studies to basic bench work in terms of natural history, risk factors, genetic predilections, diagnosis, staging, and miscellaneous therapeutic modalities. (*Chang Gung Med J* 2010;33:351-60)



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Non-traumatic osteonecrosis of the femoral head (ONFH) is a debilitating disease that commonly affects young adults between the third and fifth decade of life. It is the leading cause of hip joint replacements in many Asian countries including Taiwan.⁽¹⁾ Since most of the patients are young when they are diagnosed, they inevitably need to be treated by a variety of modalities. The ultimate goal of treating ONFH is the preservation of the involved hip. However, this is often challenging since early diagnosis is difficult, the etiologies are miscellaneous, the pathogenesis is unclear, and the successful treatment is undetermined. As a consequence, this disease remains well-known but not fully-understood. This review provides an update of the progress of

clinical reports, biomechanical researches, and molecular genetic studies of ONFH.

Natural history

The prognosis of ONFH depends upon the stage, the size, the location, and the underlying risk factors. Steinberg et al. reported that 92% of 48 hips progressed to collapse when managed with non-operative treatment.⁽²⁾ Lee et al. studied the natural history of ONFH by following precollapse lesions in the contralateral hip of 100 patients in whom total hip arthroplasties were performed for the advanced collapse side. Follow-up ranged from 6 to 202 months (mean, 31 months).⁽³⁾ In the 100 hips, the overall collapse rate was 78% within 2 years. With

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different risk factors, it was 83% in alcohol-related, 78.6% in steroid-induced, 100% radiation-induced, and 68.8% idiopathic. Most studies suggest that ONFH does progress if left untreated.⁽⁴⁻⁹⁾ However, in some asymptomatic ONFH, slow progression of disease or even reduction of lesion size were reported by using magnetic resonance imaging studies.⁽¹⁰⁻¹³⁾

Nevertheless, it is generally agreed that the disease would involve bilateral hips in more than 50% of the cases at the time the diagnosis was established and 50% of them would progress to the advanced stage within 3 years and require major surgical procedures.^(14,15)

Risk factors

Clinical

Cases of ONFH have been related to various risk factors including venous outflow occlusion, steroid overuse, alcohol abuse, systemic lupus erythematosus, vasculitis, radiation therapy, arterial thrombosis or embolism, Gaucher disease, Caisson disease, and myeloproliferative disorders.^(9,14-24)

Corticosteroid was implicated in ONFH with the treatment of systemic lupus erythematosus, renal transplantation, septic shock, and severe acute respiratory syndrome (SARS).^(13-16,25,26) Alcohol abuse (more than 400 mL per week) was taken as another major risk factor attributed to bone marrow stem cells or lipid metabolism abnormalities.^(17,27,28) Many cases of ONFH, initially considered idiopathic, could be found with certain risk factors, such as thrombophilia and hypofibrinolysis.⁽²²⁾

It is important to identify risk factors before treating ONFH because they are highly related to the prognosis. By reducing the dosage of corticosteroid, some lesions would resolute or decrease in size.^(12,13) In Gaucher disease, despite unfavorable radiographic results, patients were asymptomatic for a long period of time.⁽²⁹⁾

Bench

The risk factors and pathogenesis of ONFH have been investigated by animal models. Corticosteroid-induced ONFH was investigated by using rabbits.^(30,31) It was suggested that both the cumulative doses and the added doses, given over a short period of time, were associated with the development of the disease. Dysbaric ONFH was studied using a sheep model and the vasculatures to the

femoral head could be obliterated by an air emboli.⁽³²⁾ Intravascular coagulation including thrombophilia and hypofibrinolysis was studied using a horse model.⁽³³⁾ However it was difficult to reproduce the clinical presentations and exact pathogenetic processes observed in human subjects. Until now, an ideal model to study ONFH is still lacking and the pathogenesis remains enigmatic.

Classification and staging

Clinical

The prognosis of ONFH is highly related to the extent and the location of the lesion involving the femoral head. Ohzono et al. reported that the lesions involving the lateral one third of the weight bearing area or diffuse femoral head involvement had more than a 90% chance of collapse.⁽³⁴⁾ The current 4-stage system, the Ficat and Arlet classification, the Association Research Circulation Osseous (ARCO) classification,^(14,35) the 6-stage system, the Steinberg system and the Marcus system,^(36,37) all integrate the concept of extent and location of necrotic lesions for staging. There are various methods for quantifying the extent of femoral head involvement, such as measuring the combined necrotic arc in two planes,⁽³⁸⁾ calculating the index of necrosis on coronal and sagittal images,^(39,40) and quantifying the necrotic volume with specialized methods.⁽⁴¹⁻⁴³⁾ Poor prognosis has been demonstrated with a combined necrotic arc greater than 200 degrees, an index of necrosis greater than 0.4, or a larger necrotic volume involving more than 30% of the femoral head. It is obvious that a meaningful and reproducible staging system for ONFH is needed to guide treatment plans and to allow comparison between series.

Bench

Plakseychuk et al. have demonstrated that the current classification and staging systems are associated with high interobserver and intraobserver errors.⁽⁴⁴⁾ With use of a simple stylus, pad, software and by multiplying the percentage seen in the antero-posterior view by that seen in the lateral view, Steinberg et al. concluded that the quantitative volumetric measurement was the most reliable method.^(36,43) However, this method has inherited errors that tend to underestimate the volume. For instance, when a lesion occupies 50% of the femoral head, depending on the projection of X-rays, the area

percentage on the anteroposterior and the lateral projection will range from 50% to 100%. By multiplying these two percentages, the estimated volume will be range from 25% to 50%. Unfortunately, the misleading concept is still used for estimating the extent of necrotic lesions in many reports. We currently suggest using the index of necrotic angles as a proxy for estimating the extent of necrosis.

Genetics

Clinical

Gaucher's disease, a lipid storage disease associated with hyper-viscosity, thrombocytopenia, and decreased levels of protein C, is a heritable disease with an increased risk of developing ONFH. Many previously classified idiopathic cases were found to be associated with heritable thrombophilia and hypofibrinolysis. Factor V Leiden mutation, polymorphism in the methylenetetrahydrofolate reductase gene, heritable 4G/5G single nucleotide insertion or deletion polymorphism in the plasminogen activator inhibitor-1 gene promoter region, and carriers of the 20210 A allele in the prothrombin gene have been associated with the development of osteonecrosis of the femur or the jaw in adults and Legg-Perthes disease in childhood.^(22,23,45-52)

Other than the coagulopathy, Chen et al. reported type II collagen (COL2A1) mutation in two Taiwanese pedigrees and suggested it was the candidate gene for the development of ONFH.⁽⁵³⁾ Mutation of the p-glycoprotein gene was found to be related with corticosteroid induced ONFH in renal transplant patients.⁽⁵⁴⁾ In addition, polymorphism of the endothelial nitric oxide gene was also found to be associated with multifocal osteonecrosis.⁽⁵⁵⁾

Bench

As yet, there is no genetically engineered animal model for the study of ONFH. It is accepted that subjects possessing more than one risk factor, especially with genetic susceptibility, may have substantially increased odds (double or triple jeopardy) of developing ONFH.

Non-operative treatment

Clinical

Non-operative treatments for ONFH are generally associated with less favorable results when compared with operative treatments.^(2,4,7) Non-operative

treatment, using bed rest and non-weight-bearing crutches resulted in 22.7% clinical success rate as compared with 53% for the core decompression group.⁽⁷⁾ According to the literatures, the elimination or avoidance of risk factors was effective for the prevention of disease progression only in steroid-related ONFH and renal transplant patients.^(12,13) However, recently new modalities of non-operative treatment for ONFH have been developed with some promising results. Hyperbaric oxygen therapy was used in 12 patients with stage-I ONFH. Daily therapy of 100% oxygen at 2 to 2.4 atmospheres absolute in a hyperbaric chamber for a total of 100 sessions had resulted in 81% success rate by using MRI as the evaluation tool.⁽⁵⁶⁾ By following 284 patients under high dose steroid therapy and concomitant use of statin for an average of 7.5 years, the lipid clearing agent seems to reduce the incidence of osteonecrosis to 1%.⁽⁵⁷⁾ The anti-osteoporotic agent, bisphosphonate, has also been reported to be effective in modifying the natural courses of both traumatic and non-traumatic ONFH.⁽⁵⁸⁻⁶⁰⁾ Theoretically, the disease could only be modified, or the time to collapse could only be delayed by bisphosphonates, because they only uncouple the bone remodeling process in the osteonecrotic femoral head. In contrast, a prostacyclin derivative iloprost was used in bone marrow edema or femoral osteonecrosis and resulted in significant improvements both clinically and radiographically by MRI analysis.⁽⁶¹⁾ Unfortunately, there is still not enough evidence to support the routine use of these pharmacologic agents for the treatment of ONFH in current practice. In addition, physical stimuli such as extracorporeal shock waves have also been reported as an effective treatment and inducing angiogenesis in the necrotic lesions.⁽⁶²⁻⁶⁴⁾

Bench

In vivo studies of the non-operative treatment for ONFH are limited in the literatures because an ideal animal model is still lacking. By using spontaneous hypertensive rats, hyperbaric oxygen therapy was found effective in the prevention of osteonecrosis and ossification disturbance.⁽⁶⁵⁾ In a chicken model using high dose steroids to induce osteonecrosis, a lipid-clearing agent, lovastatin, when combined with steroid, was effective in inhibiting the development of osteonecrosis.⁽⁶⁶⁾ Lovastatin can also counteract the inhibitory effects of steroids on osteoblastic

gene expression and the inductive effects of steroid on fat specific gene expression. Bisphosphonates are anti-osteoporotic agents that can inhibit osteoclast function and induce apoptosis in the osteoclasts. In vitro studies on osteoblasts or mesenchymal stem cells demonstrated that the function of osteoblasts would be enhanced when treated with bisphosphonates.^(67,68)

Operative treatment

Clinical

Operative treatments for ONFH are miscellaneous and can be divided into joint-preservation and replacement procedures.

Joint replacement

Joint replacement procedures can be categorized as partial replacements or total replacements. Partial replacements replace the femoral heads and leave the innate acetabular cartilage to couple with a metallic ball head for joint functions. Unipolar replacements were associated with unsatisfactory results in more than 75% of patients because of acetabular cartilage wear.⁽⁶⁹⁾ Hemi-resurfacing when performed on earlier stages of the disease had 61% good to excellent results in the intermediate term of follow-up.⁽⁷⁰⁾ To decrease the acetabular cartilage wear, bipolar prosthesis was designed to allow most of the joint motion between the inner polyethylene bearings.⁽⁷¹⁾ However, clinical results of bipolar hemiarthroplasty for the treatment of ONFH remain controversial and leave the total hip replacement as the ultimate treatment choice.^(72,73) Unfortunately, the results of total hip replacements in patients suffering from ONFH are inferior to those with other diagnoses.⁽⁷⁴⁾ Reasons responsible for the inferior results are not well elucidated but are usually attributed to the young and active life styles, the underlying risk factors, and abnormal bone quality affected by the disease. Recently, total resurfacing replacements have been reported for the treatment of ONFH in young active patients but the results are even more controversial.^(74,75) It is likely that total hip replacements can provide immediate pain-relief and good functional recovery of the patients. The negative impact on the implant durability may be minimized by the improvement of surgical techniques and choices of implants in the future.⁽⁷⁴⁾ However, it is too extensive a topic to be covered and is beyond the scope of this

review paper.

Core decompression

Joint-preservation procedures are miscellaneous. Among them, core decompression is the most common procedure for early-stage ONFH.⁽⁶⁻⁸⁾ In an extensive review of 1206 hips treated by core decompression, Mont et al. reported an overall 64% satisfactory results as compared with 23% in the non-operative treatment groups.^(7,76) Using the Ficat and Arlet classification, the result was good with 88% of stage I, 71% of stage II, and only 26% of stage III.⁽¹⁵⁾ Using small diameter trephine for multiple drilling, Lee et al. achieved an overall 56% success rate (with 67% of the pre-collapse stage and 40% of the post-collapse stage).⁽⁷⁷⁾ It was also shown that a large extent of the lesion (combined necrotic angle more than 200°), lateral location of the necrotic lesion, and higher intraosseous pressure in the intertrochanteric region were associated with unsatisfactory outcomes.^(76,77) Core decompression can also be supplemented with pulsing electromagnetic fields or electric stimulation, but they are not routinely used in clinical practice because of inconclusive outcomes.^(8,78)

Nonvascularized bone grafting

Nonvascularized bone grafting can be structural grafts or non-structural cancellous grafts. The advantages of this procedure include mechanical support to the femoral head, scaffolding for osteoconduction, and decompression of the necrotic lesion. Non-vascularized grafting techniques were often used as an adjunct to core decompression in the middle of the last century.^(79,80) The short-term results were good but they rapidly deteriorated after a mean of 14 years follow-up.^(15,81,82) To improve the results, many others reported new approaches such as the trapdoor technique,^(83,84) strut grafting,⁽⁸⁵⁾ and impaction bone grafting by the "light bulb procedure".^(86,87) In 13 of 15 hips (81%) treated by the "light bulb procedure", the hips were asymptomatic at a mean follow-up of 12 years.⁽⁸⁷⁾ We have developed a technique by combining local cancellous grafting and a wire coil implantation. With a mean follow-up of 61 months (range, 30 to 103 months), a clinical success rate of 73% was achieved.⁽⁸⁸⁾ This technique can decrease the amount of cancellous grafts and provide mechanical support to the subchondral bone of the osteonecrotic

femoral head.

Vascularized bone grafting

In addition to structural support and osteoconduction, vascularized grafting can provide viable cells for repair and a vascular channel to the ischemic femoral head. The reported three types of vascularized grafts are vascularized fibular, vascularized iliac, and muscle-pedicle grafts. Vascularized fibular grafting had an overall success rate of 50% to 80% when it was performed on both precollapse and early segmental collapse cases.⁽⁸⁹⁻⁹¹⁾ Vascularized iliac grafting was reported to have 80% successful clinical results and 70% successful radiologic results in precollapse cases at 2 to 12.5 years follow-up.⁽⁹²⁻⁹⁴⁾ Muscle pedicle grafting had 60% clinical success rate and 40% radiologic success rate in an average follow-up of 47 months.⁽⁹⁵⁾ For segmental collapse lesions, vascularized fibular grafting had 64.5% satisfactory results with a minimum follow-up of 5 years in a series of 224 hips.⁽⁹¹⁾ In contrast, only 24% clinical success rate was achieved in 33 segmental collapse osteonecrotic hips with a mean follow-up of 74 months.⁽⁹⁶⁾ Possible reasons for the better results of vascularized fibular grafting may be that (1) the vascular pedicle is bigger and not kinked after rerouting to the femoral head, (2) the structural support of the cortical fibular strut to the subchondral bone is stronger, (3) the position of the fibular graft can be more ideally placed under fluoroscopic guide, and (4) the reparative potential of the fibular graft is more reliable than that of the iliac crest which could possibly be affected by extensive osteonecrosis.⁽⁹⁶⁾

Alternative grafting

Alternatively, autologous bone marrow and bone morphogenetic protein could be used in combination with bone graft or demineralized bone matrix.⁽⁹⁷⁻⁹⁹⁾ Wire coils, metal cages, porous tantalum rods, and polymethylmethacrylate cement have also been used to provide mechanical support and decrease the amount of grafts needed to fill the voids after debridement.^(88,100-102) Although the early clinical results are promising, no long term follow-up is available to justify their routine clinical use.

Osteotomy

Femoral osteotomy has been devised as a salvage treatment in younger and more active patients.

The rationale of the procedure is to reduce the stresses on the necrotic zone and to prevent progressive collapse of the femoral head. Various types of osteotomies have been reported and two main types are intertrochanteric varus or valgus (combined with flexion or extension) osteotomies and transtrochanteric rotational osteotomies. The intertrochanteric varus or valgus osteotomies are less technically demanding but the capacities for correction are relatively smaller as compared with the rotational osteotomies. For instance, when the lesion extends to the lateral third of the femoral head leaving an intact arc of less than 20°, a varus osteotomy is inappropriate for moving the necrotic lesion away from the weight bearing area. In well-selected cases, treatments with varus osteotomy combined with flexion or extension, Mont et al. reported 76% good to excellent results at a mean of 11.5 years.⁽¹⁰³⁾ Similar results were achieved in 36 (80%) of 45 patients treated with valgus osteotomy and bone-grafting.⁽¹⁰⁴⁾

Transtrochanteric rotational osteotomy is more effective in repositioning the osteonecrotic lesion than varus or valgus osteotomies. The best results were reported by Sugioka et al. where a success rate of 78% was achieved in 229 of 295 hips followed for 3 to 16 years.⁽¹⁰⁵⁾ Similar results could not be reproduced by others and this procedure is considered to be highly technically demanding.^(106,107) Reasons for the high incidences of failure can be attributed to technical difficulty, improper patient selection, inadequate fixation devices, undue rotation angles, too early weight bearing, and possible ethnic differences.⁽¹⁰⁶⁻¹⁰⁹⁾

Conclusion

ONFH is the leading cause of total hip replacements in many countries including Taiwan. Although it is a well-known disease, its pathogenesis remains enigmatic. The ultimate goal of treatment is to preserve the joint by early diagnosis and proper intervention. With increasing knowledge about the genetic predilections and the cellular responses to physical or chemical stimuli, new pharmacologic and biomechanical strategies for the non-operative treatment of ONFH is emerging. Hopefully, more research efforts through are high-quality clinical studies and basic bench work can help us to improve our ability to treat ONFH patients in the future.

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股骨頭缺血性壞死的臨床與基礎研究進展

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股骨頭缺血性壞死常發生在年輕人，如果不治療通常都會演變成末期關節炎，在許多亞洲國家包括台灣，這個疾病是病人接受人工髖關節置換的主要原因。因此，如何早期診斷、早期治療以保留關節是最重要的關鍵。雖然股骨頭缺血性壞死是一個常見的疾病，但是造成的原因與致病機轉仍不明瞭。晚近以來，文獻報告關於新的臨床研究與生物力學或基因診斷的基礎研究，對於這個疾病有新的探討。這篇文章的目的是希望能彙整這些研究成果，以期有識者未來能更進一步將診斷與治療的層次提升。(長庚醫誌 2010;33:351-60)

關鍵詞：缺血性壞死，股骨頭，診斷，治療

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