Medical management of osteonecrosis of the hip: a review

Asim Rajpura, Andrew C. Wright, Timothy N. Board

The Centre for Hip Surgery, Wrightington Hospital, Wigan, Lancashire - UK

ABSTRACT: Osteonecrosis or avascular necrosis (AVN) of the hip is a progressive disease mainly affecting adults in their third, fourth or fifth decade of life. Studies into the natural history of the disease suggest that femoral head collapse occurs within 2-3yrs with associated degenerative changes and at that stage arthroplasty is the most reliable treatment option. Therefore prevention of femoral head collapse is highly desirable in this young patient group. In early stage disease, before femoral head collapse (Ficat and Arlet stage 1-3) core decompression of the femoral head is currently the most widely used procedure to try to relieve intraosseous pressure in the femoral head and restore blood supply. Greater understanding of the pathogenesis of osteonecrosis has led to research into non-surgical management of early stages of the disease, including pharmacological and biophysical treatments. There may be a reduction in symptoms and evidence of prevention of disease progression following some non-surgical treatments. Further studies are needed, including trials comparing medical management with surgical intervention.

KEY WORDS: Osteonecrosis, AVN, Femoral head, Non-operative, Avascular necrosis

Accepted: April 13, 2011

INTRODUCTION

Osteonecrosis or avascular necrosis (AVN) of the hip (Fig. 1) is a progressive, disabling condition often necessitating total hip arthroplasty (THA) at a young age. It is estimated that 5-12% of THA performed are due to this condition (1, 2). Treating the condition is particularly challenging as most patients are in their third, fourth or fifth decades of life and are therefore still highly active individuals (3).

Presentation typically occurs in the early stages of the disease with a painful hip. Changes may be visible on radiographs at this stage including sclerosis, cysts or subchondral fracture. However, it is not uncommon for radiographs to be normal and the diagnosis confirmed by MRI scan. The two most commonly used classifications are those described by Ficat and Arlet (4) (Tab. I), as well as that described by the Association Research Circulation Osseous (ARCO) (5) (Tab. II). There is a marked variation in the timescale of progression of osteonecrosis, dependent on the size of the involved area at presentation, with head collapse occurring over 2-3 years (6). Beyond 3 years further radiological deterioration is unlikely, but a degree of femoral head collapse may be inevitable in all cases in the long term (7).

Early stage osteonecrosis (Ficat and Arlet stage 1-3) has traditionally been treated surgically by ‘core decompression’ of the femoral head (8), but conclusive evidence in favour of this method is limited (9-11). Modern understanding of the disease has resulted in the
Medical management of osteonecrosis of the hip: a review

Fig. 1 - An AP radiograph showing early stage bilateral osteonecrosis of the hip.

TABLE I - CLASSIFICATION SYSTEM OF FICAT AND ARLET (4)

<table>
<thead>
<tr>
<th>Ficat and Arlet System</th>
<th>Radiological Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None (positive on MRI)</td>
</tr>
<tr>
<td>2</td>
<td>Diffuse sclerosis, cysts</td>
</tr>
<tr>
<td>3</td>
<td>Subchondral fracture Crescent sign</td>
</tr>
<tr>
<td>4</td>
<td>Femoral Head collapse, Acetabular involvement</td>
</tr>
</tbody>
</table>

TABLE II - CLASSIFICATION SYSTEM OF THE ASSOCIATION RESEARCH CIRCULATION OSSEOUS (5). IN STAGES 1-3 LESIONS ARE QUANTIFIED BY SIZE AS A, B OR C.

<table>
<thead>
<tr>
<th>ARCO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
</tbody>
</table>

development of non-surgical treatments for early stage osteonecrosis. Such non-invasive options may reduce discomfort and delay disease progression.

Pathophysiology and potential therapeutic targets

There are many recognized risk factors for developing femoral head osteonecrosis (Tab. III). Whilst each of these has a proven link, the exact pathophysiology and sequence of events has not yet been fully elucidated.

The terminal event in the cellular pathology of AVN is osteocyte cell death induced by either critical ischaemia or the direct action of potential toxins. Theories pertaining to cellular ischaemia involve either intra- or extraluminal obstruction of blood flow to the osteocytes (12). Figure 2 highlights potential mechanisms and associated treatments.

Intraluminal occlusion can occur as a result of thrombosis, emboli or sickle cell crises. Thrombophilic conditions have been associated with osteonecrosis. Mont et al found an 82% rate of coagulation defects in osteonecrosis patients compared with 30% in controls (13). Other research has also highlighted correlations with defects in specific genes or proteins causing a pro-thrombotic state in osteonecrosis patients (14-16). Hence, anticoagulants such as low molecular weight heparin and iloprost have been used in this condition (17).
Extraluminal obstruction can be caused by adipocyte hypertrophy. This is thought to occur most commonly secondary to corticosteroid intake. This leads to increased compartment pressure within the femoral head and consequent reduction in flow in the intraosseous blood vessels (18). Corticosteroids have also been shown to increase vascular sensitivity to vasopressors such as endothelin-1 and reduce the response to vasodilators such as bradykinin (19). Both of these effects can potentially lead to reduced blood flow and ischaemia. Vasodilators such as iloprost may therefore counteract the vasopressor effect of steroids and statins may reduce adipocyte hypertrophy. Impaired mesenchymal differentiation has also recently been implicated as a potential mechanism. Reduced ability of bone marrow stromal cells to differentiate down an osteogenic lineage has been noted in both idiopathic and ethanol-induced osteonecrosis (20, 21). Both ethanol and corticosteroids have also been shown to drive bone marrow stromal cells into an adipocytic lineage with an accompanying reduction in osteogenic potential (22, 23). This has led to interest in the use of pro-osteogenic substances to try and promote repair of the necrotic lesions.

**Evidence for medical management**

Whilst core decompression with or without bone grafting have traditionally formed the mainstay of treatment for early stage osteonecrosis, recent studies into the use of pharmacological and biophysical treatments have shown evidence that there may be alternative options for management of early stage disease where head concentricity is maintained.

**Pharmacological agents:**

**Bisphosphonates**

The largest numbers of studies in the literature have investigated the use of bisphosphonates. The proposed mode
of action is inhibition of osteoclast activity which reduces oedema and the rate of remodelling in the femoral head. This then increases bone mineral density and hence delays the progression of bone collapse. Evidence for bisphosphonate prevention of femoral head collapse in animal models is extensive (24-27). The bisphosphonate that has been most studied in human trials is alendronate.

Agarwala et al studied the effects of a total weekly dose of 70mg of alendronate in a cohort of 100 hips; 71 hips (41 patients) had data for one year, 42 hips (24 patients) for 2 years and 37 hips (21 patients) for more than 2 years (28). The Ficat stage of disease was stage I in 24, stage II in 42, stage III in 23 and stage IV in 11. Radiological deterioration (increase in stage of disease on serial radiographs) was seen in 10 of 71 cases in the one year data group, 12 of 42 in the 2 year group and 20 of 37 of the group followed for more than 2 years. During this period 10 hips required surgical intervention. All groups showed statistically significant improvement in the scores for clinical parameters examined (walking time, standing time, pain and disability) (28).

The same authors recently published work with longer follow up and larger patient numbers, again using a 70mg weekly dose of alendronate. They observed 395 hips and radiological progression was measured by an independent blinded radiologist (29). At a mean follow up of 4yrs deterioration was seen in 99 of 215 (46%) Ficat stage I hips, 70 of 129 (54%) stage II hips and 10 of 51 (20%) stage III hips. The overall collapse rate for stage I and II hips was 28.8% (99 of 344) at a mean follow up of 4yrs. This compares favorably with the known rate of progression of untreated hips.

Nishii et al added a control group for comparison of disease progression (30), using a total weekly dose of 35mg of alendronate. They observed 395 hips and radiological progression was measured by an independent blinded radiologist (29). At a mean follow up of 4yrs deterioration was seen in 99 of 215 (46%) Ficat stage I hips, 70 of 129 (54%) stage II hips and 10 of 51 (20%) stage III hips. The overall collapse rate for stage I and II hips was 28.8% (99 of 344) at a mean follow up of 4yrs. This compares favorably with the known rate of progression of untreated hips.

Iloprost

Iloprost is a vasoactive compound used in the treatment of vascular occlusion, vasculitis and pulmonary hypertension. It acts on the terminal vascular bed by inducing vasodilatation, reduction of capillary permeability and inhibits platelet aggregation (32). The use of the prostacyclin derivative iloprost (33) followed existing evidence relating to its use for bone marrow oedema in the acetabulum, foot and proximal femur (34, 35). 40 hips (33 patients) with ARCO stage I to III disease received an increasing five day schedule of intravenous iloprost. The doses given were patient specific and varied according to their weight. There was a significant increase in Harris Hip Score from 56.5 to 83.1 in stage I patients and 58.7 to 76.7 in stage II/III patients, and there was a statistically significant decrease in oedema seen on MRI scanning in all patients. No patients had experienced femoral head collapse or undergone surgery at 25 months follow up. However, side effects included severe headaches experienced by 13 of the 33 patients during the infusion, nausea by 7 and a temporary increase in hip pain by a further 7.17 patients had no adverse effects (33).

Jager et al expanded on this early work with a larger cohort of patients (36). Their study reviewed patients with osteonecrosis over a period of 6 months. These included 42 femoral heads with osteonecrosis; 20 at ARCO stage I, 12 at stage II, 9 at III and 1 classified as stage IV. At 6 months there was significant improvement in the femoral heads with early stage disease. 18 were now stage 0, 8 stage I and 6 stage II. There was no change in the numbers classified in stages III and IV. Significant improvement in the early pain scores and Harris Hip Scores were found in the first 3 months. The side effect rate was low with only 2 of their 50 patients experiencing severe headaches (36).

Enoxaparin

Glueck et al researched the use of enoxaparin for use in patients with osteonecrosis caused by thrombophilia or hypofibrinolysis (17). These conditions have been shown to produce venous thrombosis which causes a reduced
arterial flow through bone resulting in cell hypoxia. Their theory was that enoxaparin would slow or even reverse the resultant osteonecrosis by breakdown of venous thromboses. Patients self-administered 60mg of enoxaparin subcutaneously for 3 months (dose and length of time limited by the Federal Drug Administration guidelines) and then were followed up for 2 years. A historic control group of patients with osteonecrosis from other causes were used to provide a comparison of disease progression. All hips were either Ficat stage I or II initially. The group given enoxaparin contained 20 hips (13 patients), and at 2 yrs follow up only 1 hip had progressed to more severe osteonecrosis. The historic control group showed 12 of 15 hips (12 patients) progressed in Ficat stage over the same time period. This difference was statistically significant (17).

Statins

In vitro animal studies have shown statins to reduce bone marrow adipocyte size and therefore potentially reduce intraosseous pressure within the femoral head (37, 38). Statins have also been shown to have pro-osteoblastic and anti-adipogenic effects on bone marrow stromal cells by increasing BMP-2 expression, and reducing adipocyte-specific gene expression (39-43). These effects protect against corticosteroid-induced osteonecrosis. Clinical data however is limited and somewhat conflicting. Pritchett et al. retrospectively reviewed 284 patients who had received high dose steroids and were also taking statin therapy (44). They noted a 1% rate of osteonecrosis which is significantly lower than the generally reported 3-20% rate of osteonecrosis for patients receiving high dose steroids. Ajmal et al. however reviewed a renal transplant population taking steroids and found no significant difference in rates of osteonecrosis with or without statin intake (45). There have been no studies to date on the use of statins in patients with established osteonecrosis.

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy is thought to reverse cellular ischaemia by increasing the oxygen concentration of extracellular fluid and by reducing oedema by inducing vasoconstriction (46). Reis et al initially showed promising results in early femoral head osteonecrosis with reversal of lesions seen on MR imaging in 81% of treated individuals versus only 17% in the untreated group (47). A recently published randomized trial by Camporesi et al has also shown encouraging results (46). They randomized 19 patients with Ficat stage II disease to either a course of hyperbaric oxygen or hyperbaric air therapy for 6 weeks. Significant improvements in pain were seen in the oxygen group versus the air group. After 6 weeks all patients were given hyperbaric oxygen therapy and at 7 year follow up, 17 patients available for follow up all reported minimal pain with none requiring arthroplasty. 7 of 9 patients who had MR scans both before treatment and at 7 year follow up showed almost complete resolution of bony lesions. The numbers in the study were small but the results certainly suggest that further investigation is warranted.

Biophysical therapies:

Extra Corporeal Shockwave Therapy

Interest in the use of Extra Corporeal Shockwave Therapy (ESWT) for osteonecrosis stems from the incidental finding of increased pelvic bone density noted after using ESWT for renal calculi (48). Subsequent studies demonstrated increased expression of both vascular endothelial growth factor and type 2 bone morphogenetic protein in rabbit femoral heads, stimulating both angiogenesis and osteogenesis (49, 50).

Early data regarding the use of ESWT for femoral head osteonecrosis is favourable but limited (48). Wang et al compared treating hips with ESWT with core decompression and non-vascularised fibular grafting, and the results favoured ESWT (51). A recent study comparing ESWT and ESWT combined with alendronate showed the addition of the bisphosphonate to have little additional effect on the short-term outcome (52). Studies so far however have involved small numbers with short-term follow up. Further studies are necessary to assess this option further.

Pulsed electromagnetic field therapy

The use of pulsed electromagnetic fields has also been explored in both animal and human studies. The mechanism of action is thought to be similar to ESWT with stimulation of both angiogenesis and osteogenesis seen both in animals and ‘in vitro’ (53, 54). The best evidence comes from Massari et al who observed good relief of
pain and prevention of progression of osteonecrosis over a period of 28 months. Patients received 8 hrs of treatment per day for an average of 5 months (55). Once again the evidence is limited and further studies are necessary.

CONCLUSION

Femoral head collapse is the turning point in the treatment of osteonecrosis of the hip. The time period from diagnosis to femoral head collapse is generally 2-3 years (6). Before head collapse occurs the necrotic lesion can undergo repair and damage may be reversible. The research reviewed in this paper suggests that some non-invasive treatments can reduce symptoms and delay disease progression. Prospective randomised studies comparing core decompression directly with medical therapy are needed. The aetiology of osteonecrosis is multifactorial and varies between individuals. As the molecular pathways are increasingly understood, combinations of different treatments may evolve, tailored according to the specific factors relevant to each case (56, 57).

ACKNOWLEDGEMENTS

The authors would like to thank Dr Dan Berry of the Mayo Clinic, Rochester, USA for his help in preparing the manuscript.

Financial support: No financial support was received for the preparation of this article.

Conflict of interest: No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

Address for correspondence:
Mr Asim Rajpura
6 Manthorpe Ave
Worsley, M28 2AZ, UK
asimrajpura@gmail.com

REFERENCES


40. Hatano H, Maruo A, Bolander ME, Sarkar G. Statin stimulates bone morphogenetic protein-2, aggrecan, and type 2
Medical management of osteonecrosis of the hip: a review


