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Tuberculosis of hip
A current concept review

Shyam Kumar Saraf[1], Surendra Mohan Tuli[1,2]

Abstract

Tuberculosis (TB) of the hip is second to spine only hence a good number of cases are visiting the medical facilities every year. Many present in the advanced stage of the disease due to delayed diagnosis. In early stages of TB of hip, there is a diagnostic dilemma when plain X-rays are negative. In the present time, diagnostic modalities have improved from the days when diagnosis was based essentially on clinicoradiological presentation alone. By the time definite radiological changes appear on plain X-ray, the disease has moderately advanced. The modern diagnostic facilities like ultrasonography (USG) or magnetic resonance imaging of the hip joint, USG guided aspiration of synovial fluid and obtaining the material for polymerase chain reaction and tissue diagnosis must be utilized. In the treatment, current emphasis is more on mobility with stability at hip. Joint debridement, skeletal traction, and mobilization exercises may give more satisfying results as compared to the immobilization by hip spica. Adults with advanced arthritis and healed infection should be informed and discussed the various treatment modalities including the joint replacement. More and more surgeons are taking up the challenge of putting the total hip replacement in the active stage of the disease. Until the long term results in active disease are well established, we recommend it for the healed disease only in selected cases.

Key words: Tubercular arthritis, hip, children, total hip replacement
MeSH terms: Tubercular osteoarticular, hip, hip prosthesis, arthroplasty

Introduction

Tuberculosis (TB) of the musculoskeletal system, though accounts for only 1-3% of total TB cases,[1] however, as one fourth of all TB cases are in India,[2] the absolute number of cases with musculoskeletal TB become large. TB of hip constitutes 15-20% of the musculoskeletal system.[1] The majority of cases of hip TB are presenting as painful, restricted movements of the hip and there comes, the dilemma of accurate diagnosis as several pathologies may mimic this presentation. For example in children, Perthes disease, juvenile rheumatoid arthritis, transient synovitis, bleeding disorders, pyogenic arthritis etc., has to be differentiated. Similarly in adult's avascular necrosis (AVN), degenerative and inflammatory conditions may pose a problem in the diagnosis. Though the diagnosis of TB hip conventionally is still largely based on clinicoradiological findings, however, it is desirable to make a early diagnosis for good results. How helpful are the modern diagnostic imaging modalities like ultrasonography (USG), magnetic resonance imaging (MRI), bone scan or immunological and molecular diagnostic tests like polymerase chain reaction (PCR) to diagnose TB hip at an early stage? Is it mandatory to subject every patient for tissue diagnosis particularly in the endemic zones for TB, before we start the antitubercular treatment? Even after the diagnosis is made in early stages, what should be our treatment protocol? When presenting late, there are permanent changes in the joint with varying disability and there is a dilemma of dealing with this morbid anatomical and pathological changes in the joint. Literature has described various treatment options both nonoperative[3] and operative.[4-7] The surgical options vary from excision arthroplasty to hip replacement. Total hip replacement (THR) in the active stage of the disease is yet another area of controversy. We have discussed some of these issues on the basis of available knowledge on the subject. We suggest that treatment options offered to the patients should depend on the stage of involvement and must be discussed thoroughly with the patient, despite the stage of involvement before decision is taken.

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Materials and Methods

A PubMed search was done with the key word "TB of hip joint, tubercular arthritis of the hip, THR in tubercular arthritis of the hip, TB hip in children and epidemiology of TB." We could trace about 250 papers on the subject. In addition, our good source of information was a book from co-author Tuli[1] We also looked into in details the various articles published in the symposium on "musculoskeletal TB".[8-11] The data from all these sources were pooled and the relevant information for this review was included.

Pathogenesis and pathology

Osteoarticular TB is secondary to primary pathology in lungs, lymph nodes or any of the viscera. Through the hematogenous route, the bacteria reach either to synovium or bone. When it lodges first in synovium, the synovial membrane becomes swollen and congested. The granulation tissue from the synovium extends over the bone resulting in necrosis of sub chondral bone, sequetra and may be kissing lesion on either side of joint.[8] The bacteria may also lodge first in the epiphyseal or metaphyseal region of the adjoining bones like head or neck of femur, greater trochanter or acetabulum to start the destructive process [Figure 1]. It may start as extra articular or juxta articular lesion. When the disease starts as intraarticular, it progresses fast to involve the whole joint. An extra articular lesion can also progress further to involve the joint. Cold abscess that usually forms within the joint may perforate the capsule to present around the hip joint in the femoral triangle, medial, lateral or posterior aspects of thigh, ischio rectal fossa.[1]

Clinical presentations

Disease usually starts during first three decades but no age is immune. Pain in the hip, limp, restriction of movements is present in almost all the cases. Depending upon the extent of involvement there can be deformity, shortening of the limb, swelling, pathological dislocations, and sinuses. In the stage of synovitis, there is effusion in the joint and the affected limb is flexed, abducted, and externally rotated with an apparent lengthening of the extremity. There is a restriction essentially of terminal range of movements. In the stage of early arthritis, with progressive destruction of the joint, the limb goes into flexion, adduction, and internal rotation, with an apparent limb shortening. In the active stage, there is muscle spasm, every attempted movement of the hip can be painful, and child walks with an antalgic gait. The joint space is still maintained in this stage. In the stage of advanced arthritis the destruction leads to irregular and hazy joint margins with diminished joint space [Figure 2]. The hip movements are painful and grossly restricted with shortening of the limb. Pathological dislocation/subluxation occurs in the stage of advanced arthritis as a result of gross destruction of the femoral head or the superior acetabular margin (wandering acetabulum), it adds to further shortening and deformity. The attitude of the limb and deformity does not always correspond with the stage of arthritis. The hip is subluxated posteriorly and superiorly with true shortening of the involved limb.[12] Sometimes head of the femur, instead of displacing posteriorly may protrude medially through weakly destroyed acetabulum. Babhulkar and Pande[9] introduced a classification, based on above clinicoradiological presentations into stage of synovitis, early arthritis, stage of arthritis and stage of advanced arthritis. The presence of apparent shortening or true shortening separated early arthritis and arthritis [Table 1]. Tuli[1] suggested modification in this classification [Table 2]. He classified it as synovitis, early arthritis, advanced arthritis and advanced arthritis with subluxation/dislocation.

Investigations

It is suggested that in the endemic regions for TB, a clinical diagnosis supported by radiographs is adequate

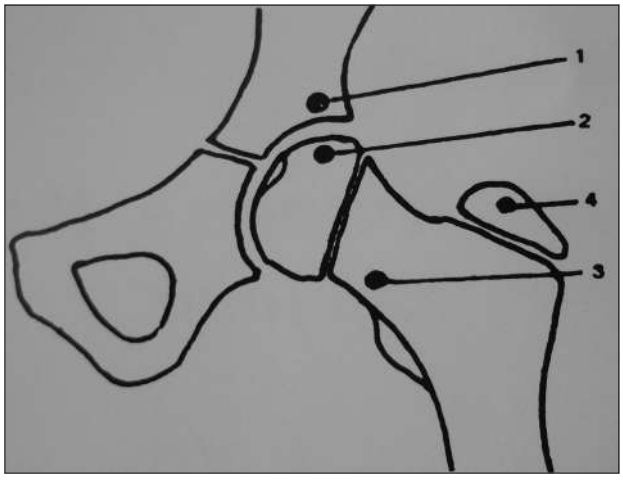

Figure 1: Diagrammatic representation of the location of osseous origin of tuberculosis of left hip joint; (1) acetabulum (2) femoral head/epiphysis (3) femoral neck/metaphysic (4) greater trochanter (reprinted with permission from Tuli[1])

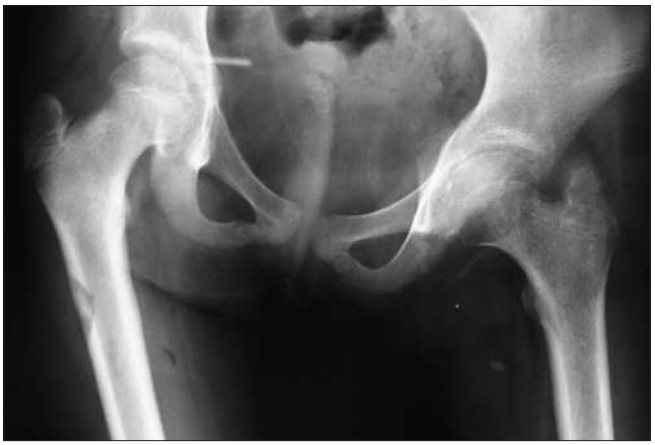

Figure 2: Plain X-ray showing "stage of arthritis;" pathology involving articular surface. Irregular and hazy joint margins with diminished joint space on left side

Table 1: Clinicoradiological classification of tuberculosis of the hip

Staging	Clinical findings	Radiologic features
I Stage of synovitis	Flexion, abduction, external rotation, apparent lengthening	Haziness, rarefaction
II Stage of early arthritis	Flexion, adduction, internal rotation, apparent shortening	Rarefaction, osteopenia, bony lesion in femoral head, acetabulum or both. No reduction in joint space
III Stage of arthritis	Flexion, adduction, internal rotation, shortening	All of the above and destruction of articular surface, reduction in joint space
IV Stage of advanced arthritis	Flexion, adduction, internal rotation with gross shortening	Complete destruction, no joint space, wandering acetabulum

Source: Babhulkar and Pande, Clin Ortho Rel Res 2002

Table 2: Clinicoradiological classification of tuberculosis of the hip

Stages	Clinical findings	Radiologic features
Synovitis	Flexion, abduction, external rotation, apparent lengthening	Haziness of articular margins and rarefaction
Early arthritis	Flexion, adduction, internal rotation, apparent shortening	Rarefaction, osteopenia, bony erosions in femoral head, acetabulum or both. No reduction in joint space
Advanced arthritis	Flexion, adduction, internal rotation, shortening	All of the above and destruction of articular surface, reduction in joint space
Advanced arthritis with subluxation/ dislocation	Flexion, adduction, internal rotation with gross shortening	Gross destruction and reduction of joint space, wandering acetabulum

Source: Tuli, Tuberculosis of Skeletal System, 4th ed., 2010. p. 72

for starting the treatment.[8,13,14] The patient presenting with clinical features of pain, limp, painful restriction of joint movements and deformity at hip supported by radiological features of para articular osteoporosis, soft tissue swelling, diminishion of joint space and irregular and fuzzy joint margins is suggestive of tubercular disease of hip joint. In the stage of synovitis, there may not be changes in the joint and many a time's diagnosis is missed; hence confirmation of diagnosis by demonstration of tubercular bacilli or histological features in biopsy is recommended. In advance stages of arthritis, radiological changes are typical and tissue diagnosis may not be required. Some other hip conditions presenting with pain and limp are transient synovitis of the hip, Legg–Calve–Perthes disease, osteomyelitis of the upper end of the femur, injury hip, acute infective arthritis of infancy and childhood, osteoid osteoma of the neck of the femur with synovial involvement, villonodular synovitis, rheumatoid arthritis, AVN of the head of the femur, giant cell variants of upper femur, etc., Tissue biopsy can help in reaching a conclusive diagnosis. In the stage of synovitis in TB of hip, plain X-rays do not show any findings or at the most only soft tissue swelling is visible. With further progression of the disease, periarticular osteoporosis, hazy, and irregular joint margins with reduction in the joint space is seen. In advanced arthritis, the picture is of travelling/wandering acetabulum [Figure 3], dislocated hip, Perthes type [Figure 4], protusio acetabuli, atrophic type, mortar, and pestle as described in Shanmugasundaram's classification are observed.[15] He proposed this classification in 1983 on plain x-rays. Campbell and Hoffman[16] suggested that there is a relationship between various radiological types and the functional outcome. In the present time MRI has helped us to detect the early morbid pathology in the joint as it shows the predestructive lesion like edema and inflammation. It is a sensitive test to detect soft tissue abnormalities in and around the joint. MRI is not specific for TB of hip.[17] MRI in early stages may show synovial effusion and varying degree of bone edema, minimal areas of bone destruction. The tissue diagnosis may be indicated in such instances.[18] Most of the literature on the subject agrees that the diagnosis in endemic regions can be made on the basis of clinical features supported by plain X-ray findings alone, however, in the countries where disease is rare, additional investigations in the form of ultrasound or MRI of the hip, and/or biopsy may be necessary. The tissue obtained from the diseased site must be subjected to histology, AFB staining PCR and also for culture and sensitivity. Singhal *et al*.[17-19] opined that arthroscopic synovial biopsy gives definitive diagnosis of various joint ailments. It is an important useful investigative adjunct to correlate and confirm the diagnosis after clinical and synovial fluid evaluation. Synovial biopsy may give conclusive diagnosis where clinical diagnosis is equivocal.

Management

Early diagnosis and effective chemotherapy are vital to save the joint.[20] In view of the nonspecific findings early in the course of the disease, failure to consider TB can lead to devastating outcomes.[21] We recommend the standard chemotherapy as accepted universally with four anti tubercular drugs to start with in all the stages of presentation. In addition to medical treatment, traction preferably skeletal is recommended to all patients. In the case of the abduction deformity, traction on the other limb is also applied to stabilize the pelvis. Traction relieves the muscle spasm, prevents or corrects deformity and subluxation, maintains the joint space, minimizes the chances of development of migration of acetabulum and permits close observation of the hip region. Another advantage with traction is that it keeps the joint surfaces apart; hence with an early start of mobilization exercises of the hip, functional range of movements can be achieved. With late presentation, the deformities may become permanent. The TB heals with fibrosis, hence may not respond to traction. Unlike pyogenic infections, proteolytic enzymes are not produced in tubercular infection; articular cartilage survives for a

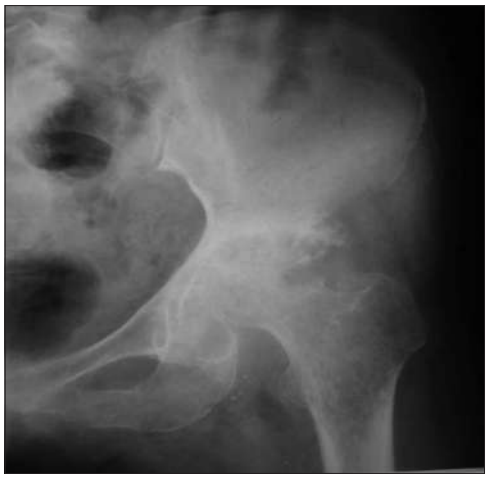

Figure 3: X-ray left hip joint anteroposterior view showing the "wandering acetabulum"

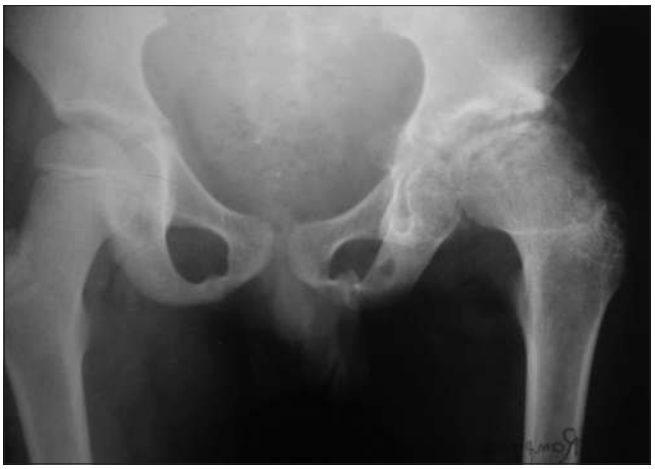

Figure 4: X-ray pelvis with both hip joints showing the "Perthes type" of appearance on left side

long time thus preserving mobility in many patients. Tuli[8] earlier was recommending partial weight-bearing only after 4-6 months of treatment, and full weight-bearing only at 18 months. However, in the present day scenario, we recommend weight-bearing earlier, whenever patient can tolerate the pain. Moon *et al*. Recommends early rehabilitation regimen for ambulation as it boosted the patients' confidence and activity level.[22] In addition to ATT, nutritional supplementation and traction, the specific treatment depends upon the stage of involvement at the time of diagnosis.

Synovitis stage

To establish the diagnosis the patient should be subjected to USG examination; synovial effusion can be aspirated and subjected for cytology, AFB smear and PCR examination. If necessary, biopsy can be taken from diseased tissue to establish the diagnosis. The prognosis after chemotherapy, traction, rest and mobilization exercises is very good in this stage and the surgical interventions usually are not required.

Early arthritis

As clinical features of pain, spasm, limp, painful movements are more pronounced, supported by radiological features of para articular osteoporosis, localized erosions in the head/acetabulum, a high suspicion index of early arthritis is kept. MRI may show synovial effusion, osseous edema and areas of bone destruction. In addition to traction and chemotherapy, analgesics supplementation is necessary till spasm of the muscles is relieved. Nonweight bearing range of motion exercises are started whenever patient is able to co-operate. A vigorous passive exercise may produce further pain and spasm and should be avoided. Failure to respond in the form of improvement in constitutional features, reduction of pain around hip, increase in the range of movements to nonoperative treatment may call for confirmation of diagnosis. Synovectomy and joint debridement are done with an aim to reduce the disease tissue load and ascertain diagnosis. Vora[23] cautioned that during synovectomy, utmost attention should be given to safeguard the feeding vessels to the head, located beneath the hypertrophied synovium. He also suggested that femoral head should not be dislocated to facilitate the synovectomy procedure. Moon *et al*. [22] however, observed that the response to chemotherapy in the hips appearing normal on X-rays is same in different therapeutic groups (nonsynovectomy and synovectomy). The prognosis in general is good. Deformities are correctable, shortening is minimal and range of movements can be more than functional depending upon how seriously exercises regimen is followed.

Advanced arthritis

The clinicoradiological presentation is typical of tubercular arthritis in this stage. Irregular and hazy joint margins, destruction of bone on either side of joint, erosions and reduced joint space are classical plain X-ray findings. There is gross destruction of capsule, synovium, bones and articular cartilage. Shortening of limb and deformity further complicates the condition. In addition to the treatment as advocated above, arthrolysis of joint with joint debridement can be very helpful. The end result after the procedure is usually a healed disease with shortening of limb and moderate to gross restriction of movements. Arthrolysis aims to achieve the useful range of movements in the cases with gross limitation of movements not responding to traction and exercises.[8,9] The arthrolysis helps in the cases where limitation of movement is because of fibrous ankylosis and not to mechanical restriction as a result of mainly alteration in the anatomy of the joint. For example, it may not help in wandering acetabulum type or pathological dislocation or even in pestle and mortal appearance. All pathological and fibrous tissues are excised carefully without compromising with vascularity of remaining part of the upper end of the femur. It is wise to

leave the posterior capsule undisturbed because it carries vital blood supply to the femoral head. Posterior capsule is generally not shortened as most of the patients have flexion deformity. Before the completion of the operative procedure, ensure that adequate range has been achieved by passive movements (while under anesthesia). After surgery, skeletal traction is applied, and movements of the hip are allowed under supervision as soon as patient is able to do.

Advanced arthritis with subluxation/dislocation

As expected, gross destructive changes in the joint will not allow for even functional range of movements. Gross deformities and shortening are another problems to tackle. The different lines of management of this complex problem could be as follows.

Conservative traction regimen

Sandhu *et al*.[3] reported healing of disease in 98% of cases by advocating ATT and traction. Of his 41 patients of the advance arthritis, 40 had appreciable range of movements. Patients presenting with sound ankylosis, short fibrous or bony in a bad position required upper femoral corrective osteotomy. This operation is a simple extra capsular procedure and can be done at any age. The ideal site for corrective osteotomy is as near the deformed joint as possible.[1]

Excision arthroplasty

In the Indian subcontinent and in many Asian countries, people do not accept a stiff hip joint as squatting, sitting cross-legged, and kneeling are essential socioeconomic actives in their day to day life. Girdlestone's excision arthroplasty can be safely carried out in healed or active disease after the completion of growth potential of bones of the hip joint [Figure 5a and b]. This procedure provides a mobile, painless hip joint with control of infection and correction of deformity. However, some degree of shortening and instability is unavoidable. Application of postoperative traction for 3 months minimizes shortening and gross instability.[4] With the employment of effective antitubercular drugs the chances of recrudescence reduces significantly in such patients than in those who obtained sound ankylosis. About 90% of patients are able to squat and kneel and able to sit cross-legged. With the help of the stick, all are able to stand on the operated extremity and able to climb up the stairs. We would safely recommend excision arthroplasty for active or healed tuberculous arthritis in adults without any apprehension of increased incidence of reactivation of the infection. The shortcomings of excision arthroplasty like shortening of the limb and instability of hip joint can be minimized to some extent by prolonged skeletal traction upto 3 months with on traction exercises in bed. The patient should bear weight with support by holding stick in opposite hand. For further improvement

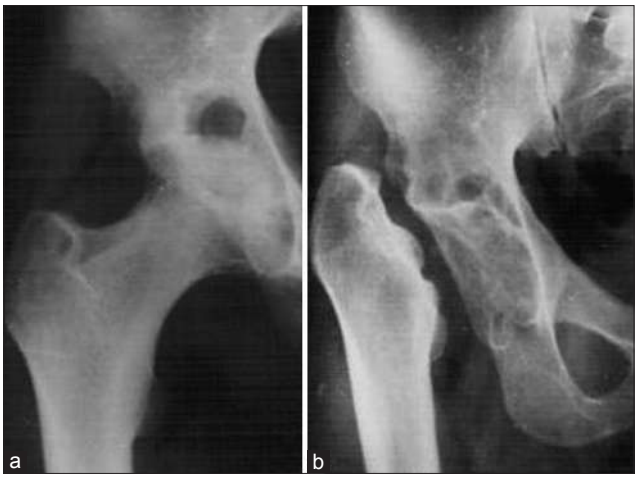

Figure 5: X-ray of right hip joint anteroposterior view showing (a) active tubercular arthritis of right hip. (b) After Girdlestone excision arthroplasty

in instability, one can do Tactoplasty as advocated by Saito *et al*.[24] The pelvic support osteotomy as advocated by Milch[25] can be another procedure to reduce the instability. If warranted, limb lengthening can be done to take care of limb shortening.

Arthrodesis

Arthrodesis of the hip, though relieves the pain, and corrects the deformity. However it is at the cost of loss of movements. Its acceptance in Indian subcontinent is very low due to socio cultural reasons. Young adult with sound bony ankylosis in functioning position has to learn to adopt himself for the active life. One has however to resort to chair and commode toilet system for whole life.

Hip replacement

In tubercular arthritis, as acetabulum is involved, there is no role of hemi replacement. Total hip arthroplasty (THA) in the hip with active tuberculous infection is a controversial issue due to the potential risk of reactivation of TB.[26] The acceptability of the THA is gradually increasing globally [Figure 6a and b] with reports that metal can be safely used in tuberculous lesions.[5,10] THA in a patient with healed TB of the hip is now an accepted procedure[27-29] Majority perform it in the stage of the advance arthritis or in sequalae of advance arthritis when the joint is unsalvageable. Babhulkar and Pande[9] recommended it to be performed after 10 years or more between active infection and replacement surgery. Its role in active TB is debatable. Wang *et al*.[5] recommend a combination of antituberculous drugs for at least 2 weeks prior to the operation and subsequently for at least 12 months after operation. Neogi *et al*.[30] recommends routine preoperative computed tomography-guided biopsy, with specimens subjected to culture and sensitivity testing, in view of the emergence of drug resistant Tubercular bacilli.

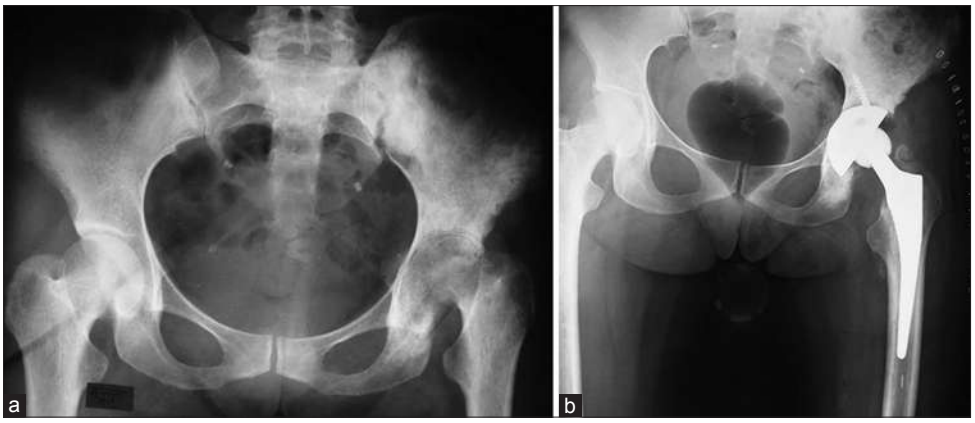

Figure 6: X-ray pelvis with both hip joints anteroposterior view showing (a) tubercular arthritis of left hip. (b) After uncemented total hip arthroplasty (with permission from A K Rai, BHU)

Sidhu *et al*.[6] performed cemented THR in 23 patients with active tuberculous arthritis of the hip. His patients had received at least 3 months of antitubercular therapy before surgery and treatment were continued for a total of 18 months. With a mean followup of 4.7 years, no activation of the infection or implant-loosening was recorded. They concluded that hip replacement in the presence of active tuberculous arthritis of the hip may be a safe procedure when peri operative chemotherapy was used. Kim *et al*.[27] had reported good results with THR. The interval between active disease and THA in his cases ranged from 3 months to 45 years. The mean Harris hip score at averaged 4 years was 85. Wang *et al*.[5] opined that in advanced active TB of the hip, THR is a safe procedure providing symptomatic relief and functional improvement. Thorough debridement of infected tissues and postoperative antituberculous chemotherapy are the keys to lowering the potential risk of reactivation of TB. Neogi *et al*.[30] reported similar opinion and results. The adequate surgical debridement and ATT was the key for a successful outcome.[27,31] Kim *et al*. [26] evaluated the outcome of THR in patients with active TB of the hip in referenced articles published between 1950 and 2012. A total of 65 patients of histologically confirmed TB were reviewed with a mean followup was 53.2 months (24-108). Antitubercular treatment continued postoperatively between 6 and 15 months. Their analysis concluded that THR in patients with active TB of the hip is a safe procedure. If undertaken in association with extensive debridement and appropriate anti-TB treatment, it provides symptomatic relief and functional improvement It is reasonable to believe that THA placed in an active disease with structurally weak bone would fail biomechanically more often, however, the follow of THR in such cases hardly show recurrence of disease or loosening of implant. Oztürkmen *et al*[32] did not observed any reactivation of disease in his 9 cases. At an followup of average 5.6 years, all the femoral stems and acetabular cups were radiologically stable and demonstrated signs of bone ingrowth. Similarly in Wang *et al*.[5] series, after mean followup of 49 months, there was no case of hip dislocation, loosening of implant or recrudescence.Similar observations were made by Yoon *et al*.,[31] Neogi *et al*.[30] or in Kim's multidata analysis[26] of 65 cases in mean followup ranging between 41 to 56 months.

However, Kim *et al*.[33] warned on the difficulty with exposure related to contracted scar tissue and the difficulty with wound healing. Kim *et al*. observed no difference in the reactivation or healing with cemented or cementless implants.[27] Till long term followup results are established, we may not agree with the statement of Wang *et al*.[5] that THA in advanced active TB of the hip is a safe procedure providing symptomatic relief and functional improvement. Yoon *et al*.[27,31] reported advanced active tuberculous arthritis of the hip patients treated with cementless THA. Postoperatively antituberculous medications were continued for 1-year. With average followup of 4.8 years, reactivation of the infection was not detected. They concluded that THA in the tuberculous hip is a safe procedure and produces superior functional results compared with resection arthroplasty or arthrodesis.

Thorough debridement of infected tissues and postoperative antituberculous therapy are the keys to lowering the potential risk of reactivation of TB.[5] Babhulkar and Pande[9] insisted that the joint replacement in patients with the active stage of the disease is contraindicated because of a probable high reactivation rate. The senior author (SMT) has observed a few patients with persistent sinuses and continued activity of infection after THA. The implants were removed in four patients. The disease healed and the excision arthroplasty like clinical presentation was accepted by the patient and family. In healed TB with subluxation/dislocation of long duration, where replacement surgery is not advisable, the stability can be provided by tectoplasty[24] an acetabuloplasty, which aims to provide an extra-articular weight-bearing surface in cases of dysplastic acetabulum, hip subluxation or dislocation with a false acetabulum [Figure 7a and b] (Reproduced

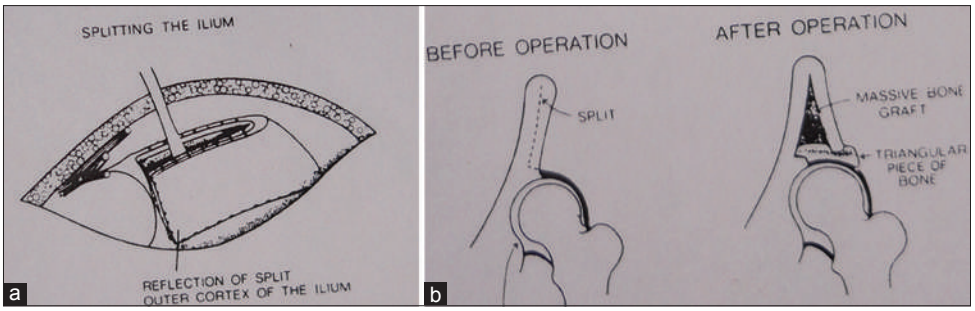

Figure 7: Schematic diagram of steps of tectoplasty. (a) The outer cortex of ilium is split away from the inner cortex and reflected outwards. The cavity thus created is filled up with bone graft. (b) Sectional diagram to show the aim of the operation (reproduced from Saito *et al.*[24])

from Saito *et al*. J Bone Joint Surg 1986; 68: 55-60)]. After raising the outer table of the iliac bone at the lateral edge of the affected acetabulum, as a proximally-based flap, bone grafts are inserted in the space to provide a congruous, nonabsorbable roof for the femoral head [Figure 8a and b].

Prognosis

Outcome of treatment depends upon the stage of the disease at the time of presentation. Synovial involvement alone will show a very good result with chemotherapy and functional exercises. There is always some residual deformity with late presentation. Campbell and Hoffman[16] observed relationship between radiological type and results with treatment. Good results were observed with "normal type" and "Perthes type;" whereas the "travelling acetabulum type," "dislocation type," "mortar and pestle" type showed bad prognosis. With modern diagnostic facilities, the patients are being diagnosed early along with very effective antitubercular drugs, hence the number of patients with advanced radiological changes are going down. On the other hand there is a worldwide threat of an untreatable epidemic of multidrug resistant TB with the global explosion of HIV and irrational treatment in some parts of the world.[11] In HIV positive patients, the prognosis also depends upon the stage of HIV infection and CD counts. The good nutritional status and control of any co morbidities helps in minimizing the chances of recrudescence.

Management in children

The aim of management is to have a painless, mobile hip with anatomy of the hip joint as near to normal as possible. The late secondary osteoarthritis is always a concern despite the healing of the disease. For this reason, early detection and management is even more important in this age group. With pathological subluxation and dislocation, it may be impossible to obtain a congruous hip. Further, a fixed hip in nonanatomical position puts the other hip, spine and knee in mechanical disadvantages with resulting consequences.

The cornerstone of management is early diagnosis. Once suspected clinically, radiological examination of both

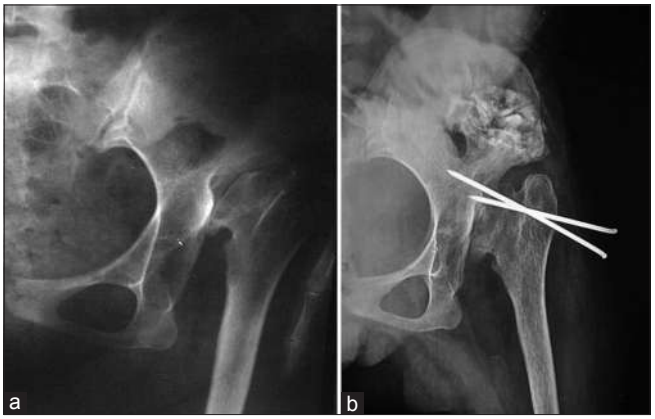

Figure 8: X-ray left hip anteroposterior view showing (a) old healed tubercular arthritis hip with dislocation. (b) Tactoplasty after pulling the head down. For initial six weeks, temporary stabilization is provided by k wire fixation, to be removed around 6 weeks

hips and lungs should be analyzed critically. The other investigations like complete blood count, erythrocyte sedimentation rate, C-reactive protein, Mantoux test are either supportive or to exclude pyogenic and other types of arthritis. Since the bone and joint TB is secondary to primary pathology somewhere else in the body, investigations should also aim to find the primary site of lesion, like lungs, lymph nodes, etc., The diagnosis of the primary site may not be possible many a times. Shiv *et al*. recommends USG of the hip to confirm fluid inside before patient is subjected to arthrotomy or drainage.[34] however, in our opinion absence of fluid, is not a contraindication for arthrotomy. Analysis of joint aspirate may help in excluding some of the other causes of painful hip in children like septic arthritis, transient synovitis, hemarthrosis, etc., In children, arthrotomy for diagnosis purpose is usually not required; however, if joint is opened as part of management strategies, the tissue should be subjected for microbiological, histological, and PCR.

The management in children as in adults depends upon the stage at presentation. Moon *et al*.[20,22] introduced a working classification system based on the joint stability, cephalocotyloid morphology and its anatomical relationship. Synovitis and early arthritis are treated by nonoperative

measures. In addition to anti tubercular chemotherapy, skin traction/skeletal traction in mild to severe deformity is sufficient in most of the cases. We prefer the traction, since assisted movements of the hip joint can be started earlier. Whenever there is an issue of compliance with continuous traction as in very young children or if joint is very painful, hip spica can be applied for 4-6 weeks to reduce the pain before movements are started. The management in advanced joint destruction, wandering acetabulum or with pathological subluxation and dislocation is difficult and controversial.[31,35] Our opinion is that though the majority of the hips can be made painless eventually by ATT and traction alone, however, an arthrotomy and surgical debridement will give early resolution of the disease. It can also take care of deformities. For example, with anterolateral approach to the joint, one can correct the flexion deformity of the hip. In children, we should try to preserve the viable bone as much as possible. Children have great potential for regeneration and remodeling. In the current scenario, we do not recommend excision arthroplasty or arthrodesis before skeletal maturity. Instead, a stabilization procedure can be done to provide stability. Moon *et al*. recommended early variation osteotomy to restore a normal cephalocotyloid relation of the travelling acetabulum secondary to hip TB in children.[22]

Conclusion

The TB of hip is still a common condition in developing countries. Early presentations are pain around hip and limp. Later the patient presents with deformities, shortening of limb and restriction of movements. The constitutional symptoms may or may not be present in all the cases. Diagnosis is mainly clinicoradiological, however, supportive blood investigations and imaging modalities like USG and MRI are helpful. Histological proof may not be necessary in all the cases in the endemic zones for TB. The management depends upon the stage of clinical presentation and the severity of destruction as visible radiologically. From conservative therapy in the form of ATT and traction to debridement and joint replacement, a variety of surgical procedures have been described. On an average 2-5% of patient's report back with reactivation of the disease within about 20 years after the apparent clinical healing of the first lesion.

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Management of Perthes' disease

Benjamin Joseph

Abstract

The main complication of Perthes' disease is femoral head deformation. Evidence from the literature highlights two important factors related to the cause and timing of this complication. (1) Extrusion of the femoral head appears to be a major factor that leads to femoral head deformation. (2) Deformation of the femoral head occurs in the latter part of the stage of fragmentation. The likelihood of preventing femoral head deformation is over 16 times higher if extrusion is reversed or prevented by the early stage of fragmentation than if done later. Several treatment options have been described in children who present later in the course of the disease but the outcomes of all these measures do not compare with those of early intervention.

Key words: Containment, femoral head deformation, Perthes' disease
MeSH terms: Prognosis treatment protocols, legg-calve, perthes, hip, children

Introduction

Perthes' disease was described over a 100 years ago, but the aetiology of the disease has not been established, and there is no consensus on the optimal treatment. The major emphasis of this article is to highlight a rational approach of treatment that aims to prevent the femoral head from getting deformed by intervening early in the course of the disease. Treatment options later in the course of the disease have also been mentioned.

Aim of treatment

Perthes' disease is a self-limiting disease of children characterized by interruption of the blood supply to the capital femoral epiphysis resulting in necrosis of the epiphysis. The vascular occlusion is temporary; complete re-vascularization of the epiphysis occurs over a period of 2-4 years if the child is under 12 years of age at onset of the disease.[1,2] During the process of re-vascularization the necrotic bone is completely replaced by healthy new bone.[3,4] In some children the disease heals without any sequelae and consequently no treatment is needed in these children. However, treatment is needed in a significant proportion of children in whom the femoral head is likely to get deformed while epiphyseal re-vascularization occurs. Secondary degenerative arthritis is likely to develop in mid-adult life if the femoral head does get deformed. The aim of treatment of these susceptible children should be to prevent the femoral head from getting deformed.

In order to achieve this aim, we need to understand what causes the femoral head to get deformed and when during the evolution of the disease irreversible deformation of the femoral head occurs.

Pathogenesis and Timing of Femoral Head Deformation

The bone necrosis that follows the vascular occlusion triggers changes in the soft tissue of the hip joint which include synovitis,[5-7] articular cartilage hypertrophy[8] and hypertrophy of the ligamentum teres.[9] These soft tissue changes and muscle spasm cause the femoral head to extrude out laterally of the acetabulum. Stresses of weight-bearing and muscular contraction pass across the acetabular margin onto the extruded part of the avascular femoral head. Unlike normal healthy bone, the avascular bone is not capable of withstanding these physiological stresses and the trabeculae collapse; this results in irreversible femoral head deformation.[10,11] Extrusion appears to be a prime factor that predisposes to femoral head deformation; the greater the extrusion, the greater the propensity for femoral head deformation. If more than 20% of the width of the epiphysis extrudes outside the acetabulum irreversible femoral head deformation is almost inevitable.[12,13]

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The natural evolution of Perthes disease can be clearly identified on plain radiographs. The disease passes through the stages of avascular necrosis, fragmentation, and reconstitution (Stages I-III) before the disease finally heals (Stage IV).[14] The stages of avascular necrosis, fragmentation, and reconstitution can be further divided into early and late stages [Stages Ia, Ib, IIa, IIb, IIIa and IIIb – Figure 1].[13] In untreated children femoral head extrusion increases as the disease progresses; in the initial stages of the disease the increase in extrusion is gradual but extrusion abruptly increases in the late stage of fragmentation (Stage IIb), often exceeding the critical 20%.

There is evidence that the femoral head deformation occurs during the late stage of fragmentation or in the early part of the stage of reconstitution.[13] This vital knowledge enables us to divide the disease into an early part (i.e., before femoral head deformation begins) and the late part (i.e., after the femoral head has begun to deform). It follows that treatment aimed at preventing femoral head deformation must be instituted in the early part of the disease if it is to be effective. It needs to be emphasized that any treatment instituted at the late stage of fragmentation (Stage IIb) or thereafter is not preventive but either remedial or salvage in nature.

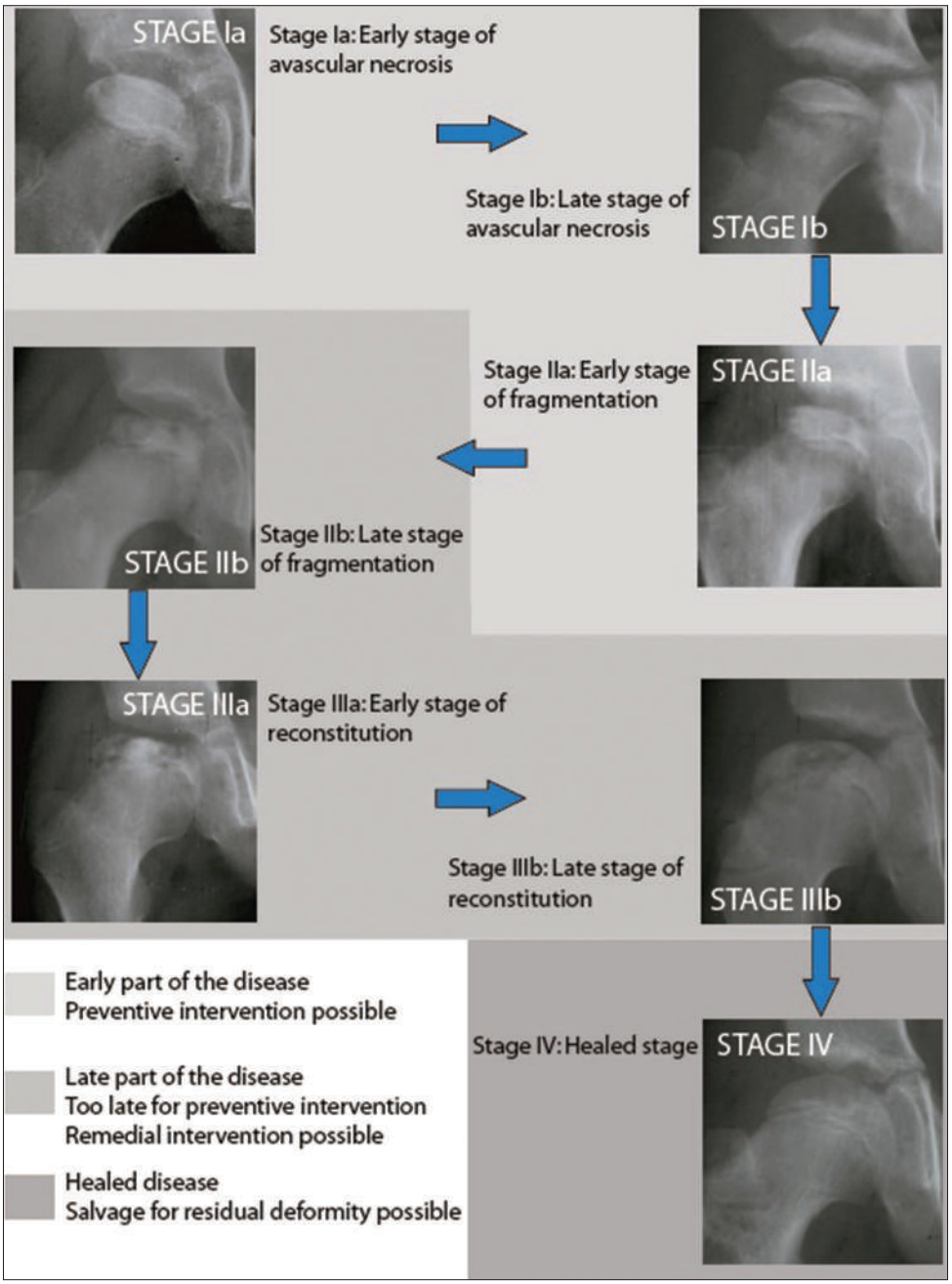

Figure 1: The stages of evolution of Perthes' disease. The early part of the disease is from the onset till Stage IIa (early fragmentation stage). The late part of the disease is from Stage IIb to Stage IIIb. Intervention aimed at preventing femoral head deformation is only feasible during the early part of the disease

Treatment of Perthes': Early in the Course of the Disease

Treatment early in the course of the disease (i.e. from the onset to the early stage of fragmentation) attempts to prevent the femoral head from bearing forces across the acetabular margin by either preventing or reversing extrusion of the femoral head by "containment."

Containment is the term used to describe any intervention that places the antero-lateral part of the femoral epiphysis well into the acetabulum thereby protecting the vulnerable part of the epiphysis from being subjected to deforming stresses. Containment can be achieved by two different methods; the first involves keeping the hip in abduction and internal rotation or in abduction and flexion by casting, bracing or by surgery on the femur. Alternatively, containment can be achieved by an osteotomy of the pelvis that re-orients the acetabulum such that it covers the antero-lateral part of the femoral epiphysis (e.g. Salter osteotomy, triple innominate osteotomy) or by creating a bony shelf over the extruded part of the epiphysis [Figure 2].

Extrusion invariably occurs sooner or later in children over the age of 7 years at the onset of the disease[13,15] and hence containment should be ensured as soon as the disease is diagnosed. In children under 7 years at the onset of the disease extrusion may or may not occur; these children need to be monitored closely with anteroposterior and frog-lateral radiographs, every 3 or 4 months and containment ensured as soon as extrusion is identified without any delay. Most children who are under the age of 5 years at the onset of the disease have a favorable prognosis but some fare badly.[16,17] Containment will be needed even in these young children if extrusion occurs.[17]

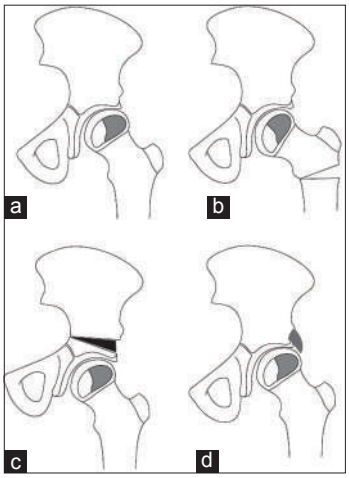

Figure 2: Schematic diagram of surgical options for containment of an extruded avascular femoral epiphysis (a) include proximal femoral varus osteotomy (b) innominate osteotomy (c) and shelf procedure (d)

Though the importance of containment in the early part of the disease was emphasized repeatedly by several authors this has often been ignored.[18-22] It is important that their advice is followed as the odds ratio of avoiding femoral head deformation is 16.58 times higher if containment is achieved early in the disease (Stage IIa or earlier) than if it is achieved late in the disease (Stage IIb or later).[23]

The range of motion should be restored before effective containment can be achieved. Skin traction for a week usually restores motion. If this fails a broom-stick cast in wide abduction can be applied under general anesthesia and retained for 6 weeks; hip motion improves once the cast is removed.

The effect of surgical containment lasts throughout the course of the disease, but the containment effect of bracing or casting is present only as long as the device is worn. Since the propensity for femoral head deformation persists till the early stage of reconstitution (Stage IIIa) the brace or splint must be worn till the disease has progressed beyond this point but need not be continued till complete healing of the disease has occurred.[24]

The author advocates avoiding weight-bearing in addition to containment as some reports suggest that combining weight relief with containment may be beneficial.[25]

Treatment Planning

The factors to take into consideration to decide the treatment include:

- The age of the child at the onset of symptoms
- The presence of extrusion of the femoral head
- The range of motion of the hip
- The stage of evolution of the disease.[26]

The outline of treatment that takes these variables into consideration is shown in Table 1.

Two factors widely used for treatment planning, the status of the lateral pillar (Herring's grading) and the extent of epiphyseal involvement (Caterall's grouping) have not been included in the decision-making scheme outlined in table. This is because treatment needs to be initiated well before the stage of fragmentation when these two variables can be identified with some degree of certainty.[27]

Table 1: Outline of decision-making for treatment of Perthes' disease early in the course of the disease

Variable	Contain	Don't contain
Age	>7 or <7 with extrusion	<7 (no extrusion)
Stage of evolution of the disease	Stage Ia, Ib, IIa	Stage IIb, IIIa, IIIb, IV
Extrusion	Present	Absent (<7 years)
Range of hip motion	Normal	Restricted

Children may not qualify for containment based on the decision-making outline shown in Table 1; these include children who do not need containment as the prognosis is good (e.g., a 6-year-old child in Stage IIa with no extrusion) and children who are denied containment since it is too late for containment to be of benefit (children in Stage IIb or later). Both these groups of children need no active intervention but should be followed up till skeletal maturity to evaluate their outcome.

What is the effect of containment?

Several studies suggest that children over the age of 6 years at onset of the disease and in whom more than half the epiphysis is avascular are likely to benefit from containment.[28-36] The chances of retaining a spherical femoral head with minimal coxa magna are greater when containment is performed.

Contrary to earlier views that surgical containment has no effect on the healing process[37,38] it has been shown that the duration of the disease is significantly shortened with a third of children by-passing the stage of fragmentation when a varus osteotomy is performed in the stage of avascular necrosis.[32]

How much of containment is needed?

Kim *et al*. suggest that a modest varus angulation of 10-15° is sufficient to obtain adequate containment by a femoral varus osteotomy;[39] the author prefers to create a varus angulation of 20° [Figure 3].[26,32]

Excellent containment can be obtained with the triple pelvic osteotomy; however, there is a risk of over-coverage and pincer impingement. The acetabular fragment must not be rotated so far as to increase the CE angle beyond 44° when a triple pelvic osteotomy is performed.[40]

There are no studies that attempt to determine how large a shelf is required to provide adequate containment without causing impingement.

Treatment of Perthes' : Late in the Course of the Disease (Remedial Surgery)

Treatment in the late part of the stage of fragmentation or in the early part of the stage of reconstitution attempts to minimize the effects of early deformation of the femoral head that has already occurred. At this stage, some children have a reduced range of motion (particularly abduction) and attempted abduction results in hinging.[41] A valgus femoral osteotomy overcomes the hinging and brings a more congruent surface of the femoral head under the acetabulum.[42] The operation should be performed in the advanced stage of reconstitution rather than in the late part of the fragmentation stage because sufficient reconstitution of the femoral head should have occurred enough to withstand weight-bearing stresses without getting deformed.[42] A valgus osteotomy will increase uncovering of the femoral head, and this can be addressed with a shelf procedure.[41] However, the shelf procedure should be delayed in the younger child as the acetabular cover may improve spontaneously once the abnormal forces on the lateral rim of the acetabulum while hinging are relieved by the valgus osteotomy.[41]

The valgus osteotomy when performed for hinge abduction relieves pain and improves functional scores but only in a small proportion of hips (~10%) will the femoral head remain spherical and end up as Stulberg Class I or II (spherical head); the majority will fall into Class III and IV (non-spherical).[41,42] The role of containment at this phase of the disease remains uncertain.[43,44]

Arthrodiatasis and epiphyseal drilling

Apart from containment (which is most widely practiced) some surgeons have attempted arthrodiatasis or joint distraction with an external fixator in an attempt to unload the hip and facilitate the restoration of epiphyseal height.[45,46] The reported results have not been sufficiently encouraging to recommend this as the procedure of choice.[46] Yet another

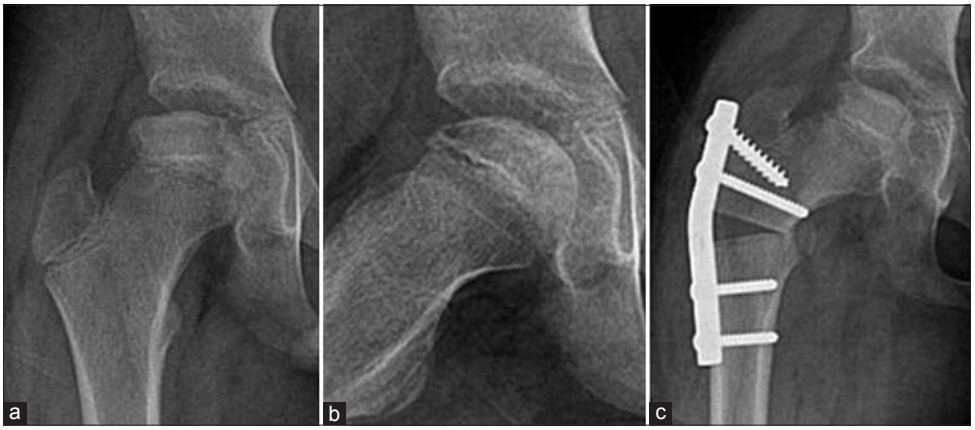

Figure 3: Anteroposterior (a) and frog leg lateral (b) radiographs of the hip of an 11-year-old boy with Perthes' disease in the early stage of the disease. An open wedge varus osteotomy with 20° of angulation has been performed (c)

approach has been to drill the epiphysis in the hope that this will hasten re-vascularization; reports on the long term outcome of this method of treatment are awaited.[47]

Treatment of the Sequelae of the Disease (Salvage Surgery)

In recent times, there has been enthusiasm to attempt to re-shape the deformed femoral head and the acetabulum following Perthes' disease by safe surgical dislocation of the hip.[48-50] Abnormalities such as cam impingement, pincer impingement, functional retroversion and greater trochanteric and lesser trochanteric impingement have all been noted and addressed. The surgical procedures performed on young adults are included under what is termed as "joint preserving surgery."[48] Reduction of pain, increased joint motion and improved strength of the hip abductors have been reported after such intervention. Survival analysis demonstrated that 61% of the patients had not undergone a total hip replacement 8 years after the surgery, while 39% had already undergone hip replacement by this time. It remains to be seen how much longer the surviving hips will function to decide if these procedures do really preserve the hip. A longer followup is clearly needed to answer this question particularly because a study from Norway noted that a third of young adults undergoing total hip replacement for degenerative joint disease secondary to Perthes disease had undergone 'joint preserving surgery' prior to the hip replacement.[51]

Treatment of established degenerative joint disease following Legg-Calvé-Perthes disease

Total hip replacement is required once secondary degenerative arthritis develops.[52] The surgery may need to be modified to deal with structural changes in the proximal femur and the acetabulum that follows Perthes' disease. A higher rate of complications had been noted in some series, but the survival rate of the prosthesis is good.[53-55] Responses to a standard health-related quality of life questionnaire showed that the patients who underwent total hip replacement for the sequelae of Perthes' disease had reduced quality of life.[53] These observations underscore the overwhelming reason for early preventive intervention in order to preserve the sphericity of the femoral head during the early part of Perthes' disease.

Future Trends

The treatment planning outlined here is based entirely on plain radiographic evaluation of the disease. Recent reports suggest that newer methods of magnetic resonance imaging (MRI) such as perfusion MRI may hold promise in treatment planning and currently studies evaluating the efficacy of these imaging techniques are underway.[56,57]

Conclusion

Treatment of Perthes disease should aim at preventing femoral head deformation, thereby minimizing the risk of secondary degenerative arthritis. This is possible in a large proportion of instances if the hip is contained early in the course of the disease.

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Treatment of neglected femoral neck fracture

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Abstract

Intra-capsular femoral neck fractures are seen commonly in elderly people following a low energy trauma. Femoral neck fracture has a devastating effect on the blood supply of the femoral head, which is directly proportional to the severity of trauma and displacement of the fracture. Various authors have described a wide array of options for treatment of neglected/nonunion (NU) femoral neck fracture. There is lack of consensus in general, regarding the best option. This Instructional course article is an analysis of available treatment options used for neglected femoral neck fracture in the literature and attempt to suggest treatment guides for neglected femoral neck fracture. We conducted the "Pubmed" search with the keywords "NU femoral neck fracture and/or neglected femoral neck fracture, muscle-pedicle bone graft in femoral neck fracture, fibular graft in femoral neck fracture and valgus osteotomy in femoral neck fracture." A total of 203 print articles were obtained as the search result. Thirty three articles were included in the analysis and were categorized into four subgroups based on treatment options. (a) treated by muscle-pedicle bone grafting (MPBG), (b) closed/open reduction internal fixation and fibular grafting (c) open reduction and internal fixation with valgus osteotomy, (d) miscellaneous procedures. The data was pooled from all groups for mean neglect, the type of study (prospective or retrospective), classification used, procedure performed, mean followup available, outcome, complications, and reoperation if any. The outcome of neglected femoral neck fracture depends on the duration of neglect, as the changes occurring in the fracture area and fracture fragments decides the need and type of biological stimulus required for fracture union. In stage I and stage II (Sandhu's staging) neglected femoral neck fracture osteosynthesis with open reduction and bone grafting with MPBG or Valgus Osteotomy achieves fracture union in almost 90% cases. However, in stage III with or without AVN, the results of osteosynthesis are poor and the choice of treatment is replacement arthroplasty (hemi or total).

Key words: Femoral neck, neglected, nonunion
MeSH terms: Femoral neck, neglected diseases, fractures ununited

Introduction

Intra-capsular femoral neck fractures are seen commonly in elderly people following a low energy trauma. 2-3% of all femoral neck fractures occurs in adults younger than 50 years and is often the result of high-energy trauma. Femoral neck fracture continues to be considered as an unsolved fracture in view of poor prognosis and variable outcome reported after different procedures.[1] In developing countries the fracture often remains untreated as the patients do not seek treatment due to nonavailability of treatment facility or may be treated primarily by osteopaths or operated under suboptimal theatre conditions with poor quality implants. The problem gets compounded and the outcome deteriorates further in such situations.

Femoral neck fracture has a devastating effect on the blood supply of the femoral head, which is directly proportional to the severity of trauma and displacement of the fracture.[2] The intra-capsular hematoma is also implicated with development of avascular necrosis (AVN) of femoral head.[2] Femoral neck fractures in young adults are associated with higher incidences of osteonecrosis, with the rate reported in the literature from 12% to 86%. Early anatomical reduction and stable internal fixation restores the vascularity and reduces the incidence of AVN.[3] Nonunion and AVN of the femoral head are the main complications following femoral neck fractures. The reasons for such complications include precarious vascularity, shearing forces at the fracture site, inadequate reduction and inadequate fixation.[3] The nonunion (NU) is complicated by resorption at fracture ends leading to significant shortening of the femoral neck.

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Various authors have described a wide array of options for treatment of neglected/NU femoral neck fracture.[4-34] There is lack of consensus in general, regarding the best option. This instructional course article is an analysis of available treatment options used for neglected femoral neck fracture in the literature and an attempt to suggest treatment guidelines for neglected femoral neck fracture.

Materials and Methods

We conducted a Pubmed search with the keywords "NU femoral neck fracture, neglected femoral neck fracture, muscle-pedicle bone graft in neglected femoral neck fracture, fibular graft in femoral neck fracture and valgus osteotomy in femoral neck fracture." A total of 203 published papers were obtained as the search result. Forty eight papers considered fresh cases of femoral neck fracture, while 18 presented outcome of hemi/total hip arthroplasty as the treatment option in fresh and neglected cases, 4 were case reports, 9 were review articles or instructional course lectures, 8 were on pediatric femoral neck fracture, (71 were not related to the NU femoral neck fracture) and no abstract or full papers were available in 12 papers, hence were excluded from the analysis. The papers that dealt with fractures of the neck femur more than 3 weeks old in adults (prospective and retrospective) were chosen for this article. A total of 33 articles were considered. All these articles thereafter were categorized into four subgroups based on treatment options, (a) treated by muscle-pedicle bone grafting (MPBG), (b) closed/open reduction internal fixation and fibular grafting (c) open reduction and internal fixation with valgus osteotomy, (d) miscellaneous procedures. The data was pooled from all groups for mean neglect, the type of study (prospective or retrospective), classification used, procedure performed, mean followup available, outcome, complications, and reoperation if any.

Results

Muscle pedicle bone graft (8 studies)

Six full papers and two abstract were analyzed.[4-11] Seven studies[4-6,8-11] were prospective, and 1 was retrospective.[7] These studies included 368 patients [Table 1]. The average age was 35.58 years (n = 198) in series where the mean age was described. In all studies, X-ray was the main investigating modality. None of the study used any particular classification system described for neglected or un-united femoral neck fracture. The mean neglect averaged at 6.45 months (range 3 weeks-9 months) in 166 cases (These are those cases of studies in which range were mention). The techniquess used were Tensor fascia lata based muscle pedicle bone graft (n = 48), anterior trochanteric pedicle graft (n = 3) and quadratus femoris based graft (n = 317). The average followup was at 49.15 months (n = 156), in remaining mean followup was not described. The average time to union was 8.1 months (n = 135). There were overall 16 NUs, 3 AVN and 13 varus malunion in 201 patients (16% complications) where results were described, whereas in 167 cases the complications were not described.

Open/closed reduction with fibular grafting (7 studies)

5 were prospective[13-15,17,18] and 2 retrospective studies.[12,16] The total number of patients were 406 [Table 2]. The mean neglect mentioned in 4 studies averaged at 20.48 weeks (n = 119). The average age of the patients was 35.7 years (n = 138). Radiograph was the principle investigation in all the studies. Sandhu *et al.* (n = 236)[18] used a classification system proposed by the author himself for NU neck of femur. All the studies performed open or closed reduction and fixation with one or two fibular auto-grafts, however in the study by Elgafy *et al.*,[12] six patients underwent fibular allograft fixation along with cannulated cancellous screw (CCS). The average time to union was at 22.45 weeks (n = 170). The average followup was not known for two study, one study by Azam *et al.*[16] reported (n=28) the minimum followup of 36 months. The average followup in rest of the four studies was 66.93 months (n = 119). Roshan and Ram[17] (n = 32) did not report any complications. There were 33 NU and 11 AVN reported in 374 patients (11.3% complications).

Valgus osteotomy (11 studies)

The valgus osteotomy was performed below the level of the fracture site except in one study by Pingle[24] (n = 29), where the closing wedge osteotomy was performed at the level of fracture, and a wedge of bone was removed, with its apex at the nonunion site [Table 3]. The osteotomy entered the fracture, and the wedge of bone was grafted into the NU site. The mean neglect was 20 weeks (n = 73, mentioned in 3 studies).[25,27,29] The average age of the patients was at 33.99 years (n = 285).[19-21,25-29] The principle investigation done was X-ray in all these studies. None of the studies used any particular classification system for NU of femoral neck fractures. The mean followup was 52.38 months (n = 293). The mean time to union was 16.86 weeks (9 studies, n = 138).[19-24,27-29] Complications in 3 studies (n = 69) were not reported.[22-24] There were 22 NU and 21 AVN (n = 285) in remaining 8 Studies (15% complications).

Miscellaneous procedures

This group included 7 studies[30-36] in which techniques other than that mentioned above or a combination of techniques was used [Table 4]. The study by Ayoub and Gad[32] used the classification of Sandhu *et al.*[18] (Type I, n = 20 and Type II, n = 16). Three studies (n = 84) reported outcome of bone grafting at the fracture site, with

Table 1: Data from studies on MPBG

Author	Type of study	Number of patient	Average age (years)	Technique	Follow-up (years)	Time to union	Mean neglect	Complications	Functional result
Bhuyan[5] (2012)	Prospective	48	32.9	ORIF+TFL MPBG±multiple drilling and cortico-cancellous bone grafting	4.4	Not mentioned	86 days	NU (*n*=3) AVN (*n*=2) Var (*n*=2)	HHS 19 E 22 G 5 F 2 P
Vallamshetla *et al.*[7] (2010)	Retrospective	42	34	ORIF+QF MPBG±cortico cancellous BG	Not mentioned	6 months	9 months	NU (*n*=6) Var (*n*=9) LLD (*n*=9)	Not mentioned
Gupta *et al.*[9] (2008)	Prospective	32	45	ORIF+QF MPBG	3.4	Not mentioned	>3 weeks (29)	NU (*n*=2) F. drop (*n*=2) scrotal sensory loss (*n*=1) Var (*n*=1)	Salvatti and Wilson E15, G4 S4 P6
Gupta[8] (2007)		20	24	ORIF+QF MPBG	5.10	4.9 months	7.5 months	AVN (*n*=1) Var (*n*=1)	93 final average HHS
De and Balasubramaniam[10] (1991)	Prospective	3	Not mentioned	Anterior trochanteric muscle pedicle graft	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Baksi[6] (1986)	Prospective	56	42	ORIF with MPBG	2.14	3-6 months in 42 8-10 months in 7	6.3 months	NU (*n*=5)	Not mentioned
Meyers *et al.*[11] (1973)		150	Not mentioned		Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Nair *et al.*[4] (2013)	Prospective	17	Not mentioned	QF	Not mentioned	8 months	Not mentioned	Not mentioned	Not mentioned

ORIF=Open reduction and internal fixation, MPBG=Muscle pedicle bone grafting, TFL=Tensor fascia lata, QF=Quadratus femoris, AVN=Avascular necrosis, NU=Nonunion, HHS=Harris hip score, LLD=Limb length discrepancy, Inv=Investigation, E=Excellent, G=Good, S=Satisfactory, F=Fair, P=Poor, Var=Varus, F.drop=Foot drop

Table 2: Data on fibular graft

				Fibular graft					
Author	**Type of study**	**Number of patient**	**Average age (years)**	**Technique**	**Follow-up**	**Time to union**	**Mean neglect**	**Complications**	**Functional result**
Elgafy *et al.*[12] (2011)	Retrospective	19	46	Fibula Auto (*n*=13) Allo (*n*=6)	Not mentioned	4.8 months auto 13.3 months Allo	Not mentioned	NU (*n*=4) Auto NU (*n*=4) Allo	Not mentioned
LeCroy *et al.*[13] (2002)	Prospective	22	28.7	Free vascularized fibular grafting	84.7 months	9.9 months	18.3	NU (*n*=2)	HHS average 78.9
Xie *et al.*[14] (2012)		13	30.9	ORIF+free vascularized fibular grafting	51.2 months	4.8 months	6.7 months	Var (*n*=9)	HHS average 55.5
Azam *et al.*[16] (2009)	Retrospective	32 (28 followed)	37.8	CR/OR IF with 2 CCS and fibular strut graft	3 years Min.	5.2 months	16.4 weeks	NU (*n*=3) AVN (*n*=6) Var (*n*=4)	Anglen E 5 G 14 P 6
Roshan *et al.*[17] (2006)	Prospective	32	18-50	OR+2 CCS+1 free fibular graft	6.1 years	19.2 weeks	3-6 months		HHS 87.1 (mean)
Sandhu *et al.*[18] (2005)	Prospective	236	Not mentioned	CRIF+CCS+fibular graft	Not mentioned	Not mentioned	Not mentioned	NU (*n*=20)	Not mentioned
Nagi *et al.*[15] (1998)	Prospective	52	35.1	OR+CCS+free fib graft	58.8 months	16.7 weeks	5.1 months	NU (*n*=4) AVN (*n*=5) Var (*n*=11)	Not mentioned

ORIF=Open reduction and internal fixation, CRIF=Closed reduction internal fixation, CR=Close reduction, OR=Open reduction, IF=Internal fixation, CCS=Cannulated cancellous screw, AVN=Avascular necrosis, NU=Nonunion, HHS=Harris hip score, Auto=Autograph, Allo=Allograft, Var=Varus

Table 3: Data on valgus ostelotomy

Valgus osteotomy									
Author	**Type of study**	**Number of patients**	**Average age (years)**	**Technique**	**Follow-up**	**Time to union**	**Mean neglect**	**Complications**	**Functional result**
Varghese *et al.*[25] (2013)	Retrospective	40 (32 FU)	43	Valgus intertrochanteric osteotomy	5 years	Not mentioned	6 months	NU (*n*=3)	HHS 82 average
Bansal *et al.*[26] (2013)	Prospective longitudinal observational study	30	35.4	Valgus osteotomy with double angle barrel plate	1-5 years	Not mentioned	>3 weeks	NU (*n*=2)	Askin Bryan index 11 E 15 G
Gavaskar *et al.*[27] (2013)	Prospective longitudinal observational study	11	41	Sliding subtroch osteotomy+DHS	Not mentioned	10 weeks	6 months	Not mentioned	Oxford hip score
Kainth *et al.*[29] (2011)		22	33	CR+valgus osteotomy for singh ind. >3 <3 + fibular. graft and no osteotomy	19 months	20 weeks	12 weeks	NU (*n*=1) AVN (*n*=2)	Askin Bryan E 2 G 17 P 3
Khan *et al.*[20] (2009)	Prospective	16	36.4	Valgus osteotomy+ double angle barrel plate+DHS	19 months	14.7 weeks	>3 weeks	Implant cut out (*n*=2)	Not mentioned
Magu *et al.*[21] (2009)	Retrospective	48	48.1	Modified Pauwels' intertrochanteric osteotomy	6.1 years	Not mentioned	Not mentioned	NU (*n*=4) AVN (*n*=2)	Not mentioned
Sringari *et al.*[22] (2005)	Prospective	20	Not mentioned	Valgus osteotomy+double angle blade plate	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Kalra *et al.*[23] (2001)		20	Not mentioned	Valgus osteotomy	30 months	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Pingle[24] (2014)	Prospective	29	Not mentioned	Valgus osteotomy	66 months	6 months	Not mentioned	Not mentioned	Not mentioned
Raaymakers *et al.*[28] (2008)	Prospective	66	49.5	Valgus osteotomy	110 months	Not mentioned	Not mentioned	NU (*n*=8) AVN (*n*=13)	Not mentioned
Gupta *et al.*[19] (2014)	Prospective	60	35	Valgus osteotomy	42 months	3.9 months	Not mentioned	NU (*n*=2) AVN (*n*=4)	Not mentioned

DHS=Dynamic hip screw, AVN=Avascular necrosis, NU=Nonunion, HHS=Harris hip score, CR=Close reduction, E=Excellent, G=Good, P=Poor

Table 4: Data on combined procedures

Author	Type of study	Number of patient	Average age (years)	Technique	Follow-up	Time to union	Mean neglect	Complications	Functional result
Huang[33] (1986)	Not mentioned	16	16-43	CRIF/ORIF/augment osteo/BG	2-8 years	Not mentioned	Not mentioned	AVN (*n*=4)	Not mentioned
Ayoub and Gad[32] (2013)	Not mentioned	36	26.8	ORIF with CCS+BG±bone marrow	25.3 months	19.6 weeks	44.6 days	NU (*n*=2) AVN (*n*=2) Var (*n*=4)	Not mentioned
Sen *et al.*[35] (2012)	Prospective	22	Not mentioned	Angle blade plate+fibular grafting	3.2 years	Not mentioned	11.2 months	AVN (*n*=1) NU (*n*=1)	Not mentioned
Garg[31] (2011)	Prospective	32	38	Neck reconstruction (AIIMS box technique)	Minimum of 10 years	16 weeks	Not mentioned	AVN (*n*=1)	Not mentioned
Chen and He[36] (2008)	Prospective	28	37.6	Iliac crest graft+vascular pedicles from lateral circumflex iliac	35.8 months	4-8 months	8.6 months	NU (*n*=3), AVN (*n*=7)	HHS: 49.6 (mean)
Kapoor *et al.*[30] (2012)	Not mentioned	23	Not mentioned	ORIF with DHS+Valgus osteotomy+fibular grafting	2-13 years	Not mentioned	Not mentioned	AVN (*n*=4)	Not mentioned
Gadegone *et al.*[34] (2013)	Prospective	41	45.41	Valgus osteotomy+ fibular strut grafting	32.5 months	16.82 weeks	14 weeks	NU (*n*=2)	Not mentioned

ORIF=Open reduction and internal fixation, CRIF=Closed reduction internal fixation, CCS=Cannulated cancellous screw, BG=Bone graft, DHS=Dynamic hip screw, HHS=Harris hip score, AVN=Avascular necrosis, NU=Nonunion

average age at 32.4 years.[31,32,36] One of these studies is described as the AIIMS Box technique[31] (n = 32). The average time to union in this study was 16 weeks, where simple bone grafting at the fracture site led to the union by 19.6 weeks (n = 36). The mean neglect mentioned only by Ayoub *et al.*[32] was at 44.6 days. In all there were 7 AVNs, 2 NU and 4 Varus Malunion (n = 84, 15.5%). The valgus osteotomy and fibular autografting were combined in n = 86 patients (3 studies).[30,34,35] The average age was 45.41 years (n = 41) in one study. No particular classification system was used by any of the studies. The average followup was at 35.25 months (n = 63). The average time to union was mentioned only in the study by Gadegone *et al.* as 16.82 weeks (n = 41).[34] The mean neglect was at 7.35 months (n = 63). There were 5 cases of AVN and 3 NU amongst the total of 86 patients (9.25%). Chen and He[36] reported 28 patients in whom Iliac crest corticocancellous grafting was done along with vascular pedicles from lateral circumflex iliac artery. The mean neglect of the patients was 8.6 months, and mean followup of 35.8 months. The average time to union was 4-8 months, and there were 3 incidents of NU and 7 incidents of AVN (n = 28).

Discussion

Pathoanatomy

The medial circumflex femoral artery (MCFA), lateral circumflex femoral artery (LCFA) and the obturator artery form the main blood supply to femoral head.[1] The obturator artery supplies the femoral head through the ligamentum teres. The LCFA gives rise to the inferior metaphyseal artery and supplies infero-anterior femoral head. The largest contributor to the femoral head, especially the superolateral aspect of the femoral head is the MCFA. The lateral epiphyseal artery complex arises from the MCFA and courses along the posterosuperior aspect of the femoral neck before supplying the femoral head. These terminal branches supplying the femoral head are intra-capsular. Fracture displacement disrupts the terminal branches to the femoral head and leads to development of osteonecrosis.[37-39]

Classification

Pauwel's and Garden's classification systems are the two most commonly used radiological classification system for fresh femoral neck fractures. These classifications describe for fresh fractures and cannot be used reliably to predict the outcome in cases of NU femoral neck fracture.

The changes that occur at the fracture site once the fracture remains untreated are (a) absorption of femoral neck (b) fracture surfaces get smoothened (c) the fracture gap is increased and (d) the head of the femur can develop

AVN. These changes occur in variable severity depending on the length of neglect. Pauwel and Garden's classification do not consider these variables and hence are unsuitable to be used for classifying neglected femoral neck fracture.

X-ray of pelvis including both hip joints in the identical position should be taken to classify neglected femoral neck fracture. The length of the proximal fragment is measured from upper margin of fovea centralis to the midpoint of fracture margin. Sometimes the absorption of the proximal fragment is more marked in the center than the periphery giving it the shape of a cup or moon. This may not be clearly seen on routine anteroposterior X-ray of the hip and can be better appreciated on computed tomography (CT) scan or magnetic resonance imaging (MRI). AVN of the head of the femur may be seen earlier on MRI than on plain X-ray of the hip. Sandhu[40] described a classification system for NU/neglected femoral neck fracture incorporating these changes at various stages. Based on these changes, he classified the neglected femoral neck fracture into 3 types (described as 3 stages).

The radiological findings are:

Stage I

a. Fracture surfaces are still irregular (irregular or jagged)
b. The size of the proximal fragment is 2.5 cm or more
c. Gap between the fragments is 1 cm or less
d. Head of the femur is viable with no sign of AVN on X-ray or MRI.

The presence of good size femoral head fragment allows good hold of implant while performing internal fixation, and very little resorption of neck and absence of AVN promotes fracture healing.

Stage II

a. Fracture surfaces are smooth and sclerosed
b. The size of the proximal fragment is 2.5 cm or more
c. The gap between the fragments is more than 1 cm but <2.5 cm
d. The head of the femur is viable.

If either sclerosed and smoothened proximal end or a fracture gap more than 1 cm is observed it can be labeled as stage II. The freshening of fracture surfaces by drilling or curettage while performing open reduction is indicated along with bone grafting. The proximal fragment is big enough for good and stable purchase by implant, hence suitable for osteosynthesis.

Stage III

a. Fracture surfaces are smoothened out
b. The size of the proximal fragment is <2.5 cm
c. The gap between the fragments is more than 2.5 cm
d. The head of the femur shows signs of AVN. The presence of any of the latter three, that is, proximal fragment <2.5 cm,(inadequate for good hold of implant) or fracture gap more than 2.5 cm or head of femur has AVN are placed in stage III marks the fracture unsuitable for osteosynthesis.

Neglected femoral neck fracture presents with shortening, severe external rotation of the lower extremity, upward displacement of the trochanter, with or without soft tissue contracture. Head and neck would have undergone variable degree of absorption. Plain X-rays are adequate to make a clinical diagnosis and stage the neglected femoral neck fracture. CT scan may be useful to see the bony appearance of stippled area and bony sclerosis, trabecular resorption, microfracture and subchondral collapse and presence of AVN. Bone scan may be indicative of AVN, but MRI is most sensitive modality to diagnose AVN.[41]

Treatment

The goal of treatment in neglected fracture NOF is to achieve a painless, mobile and stable hip.[29] The treatment depends on the age and physical status of the patient, duration of NU, viability and spherocity of the femoral head, amount of resorption of the femoral neck and potential limb length inequality. Various options of management are described in the literature, all with variable outcomes in various series. They are grouped as

(a) Osteosynthesis with or without vascularized or nonvascularized bone grafting
(b) Osteotomy, displacement or angulation type
(c) Osteosynthesis with muscle pedicle bone grafting
(d) Replacement (hemiarthroplasty or THR).

(a) Closed/open reduction, internal fixation and single or double fibular grafting

In this procedure closed or open reduction and CCS fixation of the fracture is performed after freshening the fracture surfaces. Some of the authors[12-18] used open reduction of fracture with freshening of fracture surfaces and placed cancellous autograft alongwith fibula. Fibula being cortical bone provides mechanical strength besides stimulating the union and getting incorporated as a biological graft. Once the graft is revascularized, the osteoblasts stimulated by bone morphogenic protein replace the resorbed bone. If this bone is appropriately stressed, the graft acquires sufficient strength to handle the load.[16] Nonvascularized fibular strut graft along with cancellous screws provides a dependable and technically less demanding alternative procedure for neglected femoral neck fractures in young adults. Vascularized fibular graft are reported to give superior result; however, it consists of microvascular anastomosis that is technically more demanding. Leung and Shen[12] obtained 100% union and satisfactory clinicoradiographic

result at 5-7 years followup using vascularized iliac bone graft augmented by screw fixation. One or two guidewires are placed to guide a tunnel for fibula. First a tunnel is created by triple reamer and later one or two fibulae are placed (with fixation done by two CCS at least). The use of nonvascularized fibular strut graft is technically less demanding. In the present search thirty-three NUs were reported out of 374 cases while AVN was reported in 11 cases (3%), with an overall complication rate of 11.3%.

(b) Valgus intertrochanteric osteotomy

Mcmurray Osteotomy used to be commonly described and performed procedure.[44] It is a displacement osteotomy. In general one-third of the neglected fracture NOFs unite while in the remaining it provided an armchair effect, improving the ambulation. The displacement osteotomy (like McMurrary osteotomy) makes future hip replacement difficult, hence are no longer performed. None of the authors performed McMurray's Osteotomy in the available search.

Pauwel's V-Y osteotomy is an inter-trochanteric ostreotomy which starts at the base of the greater trochanter and goes to the point just above the lesser trochanter. A suitable wedge of about 20°-30°is excised from the lateral half or 2/3rd of femur, thus giving the shape of V-Y to the osteotomy.[19-22] The distal fragment is abducted to close the gap created by excision of the wedge and is fixed with dynamic hip screw or 135° blade plate or double angle blade plate. Hence, the fracture line which was vertical gets converted into horizontal and the shearing forces get converted into compressive forces.

Other osteotomy is a simple lateral closed wedge valgus osteotomy (done just at or below the level of lesser trochanter) where a wedge of bone is excised and the osteotomy is closed. This may be combined with open reduction, freshening of fracture surfaces and bone grafting. Valgus inter-trochanteric osteotomy is an alternative line of treatment for these patients. Pauwels and Müller advised Y-shaped wedge-closing – wedge-opening osteotomy to treat pseudo-arthrosis of the femoral neck. The Y-shaped osteotomy reduces the area of contact of the osteotomy surfaces. On the other hand, simple V-shaped wedge removing osteotomy provides broad osteotomy surfaces that ensure good bony contact on closure of the osteotomy and lateralization of the femoral shaft. Valgus inter-trochanteric osteotomy results in rotation of the upper segment of the femur in a clockwise manner for the left hip and counterclockwise for the right hip. The osteotomy line becomes obliquely situated, running downwards and laterally, and its lateral end is displaced distally, resulting in lengthening. Lengthening is usually desirable to compensate for the shortening that is present in these cases. The femoral shaft is now displaced medially and becomes vertically oriented after the osteotomy. Osteotomy fixation with a double-angled plate will maintain this deformed position. On the other hand, fixation with a single-angled blade plate will pull the femoral shaft laterally and distally to the plate along the slope of the obliquely situated osteotomy line.[21] This will result in correction of the medialisation of the femoral shaft and also restore the normal inclination of the femur to the sagittal plane. These effects have a positive influence on the knee joint in preventing the valgus strain and overloading. In this analysis 22 out of 285 cases who underwent valgus osteotomy remained un-united, while 21 out of 285 cases developed AVN. The combination of various procedures has also been described with success.[30-36] In a single article by Pingle J *et al*.[24] Lateral closing wedge osteotomy based laterally was performed approximately 4 cm below and directly opposite the nonunion site and parallel to the pins into the nonunion site. The proximal cut of osteotomy was made parallel to the proximal pins and the distal cut of the osteotomy was angled to get the desired wedge laterally.

(c) Muscle pedicle bone graft

The fracture surfaces are freshened, and the fracture is accurately reduced and fixed with cancellous screws. A piece of bone about 2.5-3.0 cm long and about 1.0-1.5 cm wide is harvested. The graft is placed across the femoral neck fracture and the head. The graft may be secured with a screw. Various muscle-pedicle based grafts are described. Posterior approach is used for Quadratus Femoris based MPBG. Tensor Fascia Lata and Gluteus medius based MPBG is done in lateral or supine position by lateral or anterolateral approach.[5-10]

Myoperiosteal grafting for inducing osteogenesis is reported for where the Quadratus Femoris pedicle is lifted with a strip of periosteum from neck and is placed across the fracture. The author reported 20 neglected fracture NOF with a mean delay of 7.5 months (range 2-18 months). 100% fracture union was reported in a mean of 4.9 months and with a mean followup of 70 months (range 14-144 months). The preoperative AVN was seen in 7 cases and did not progress in 6. Delayed collapse and flattening of the femoral head occurred in one. The author also opined that anatomical reduction is not mandatory for fracture union, provided its vascularity has been restored.[8] A muscle-pedicle bone graft seems to accelerate the union of fresh intra-capsular fractures.[11,42] Meyers and Harvey[11] reported the results of their technique for delayed union. 9 years later Baksi[43] reported encouraging results with muscle-pedicle bone graft in the treatment of posttraumatic AVN of the femoral head whether the fracture was united or not.[43] The placement of the muscle-pedicle bone graft behind the femoral head and neck served several purposes: it acted as a strut across

the posterior cortical defect; it prevented posterior tilt of the femoral head; and it acted as a viable vascular inlay graft encouraging osteosynthesis and revascularization of the femoral head. Originally Baksi had described fixing the graft with pins and threads, however in later series screws were used for fixation. In the present analysis, the fracture united in 92% cases with 3 out of 201 reporting AVN and 13 out of 201 developing malunion.

(d) Replacement arthroplasty

Hemireplacement can be performed when the acetabulum is normal, and age of the patient is more than 75 years, and life expectancy is about 5 years.[1,42] This operation is of short duration. The hemiarthroplasty can become painful after sometime due to loosening or acetabular erosions. Hemiarthroplasty can be performed with a cemented modular stem so that modular bipolar can be later converted to THA. Total hip arthroplasty is indicated in younger patients of 55 years or less. More in stage III neglected fracture NOF or when osteosynthesis and osteotomy has failed to achieve fracture union. It allows early rehabilitation and lasts longer than hemiarthroplasty. After THA the patient is not allowed to squat and sit crosslegged. Dislocation (1-5%), infection (1%), periprosthetic fracture (1%) and aseptic loosening are other complications.

The problem with the data available in the literature is manifold: (a) The choice of procedure is not correlated with the length of neglect (b) no classification system is used as a result, each series has clubbed cases of all duration of neglect, that is, from 3 weeks to 11 months and reported the outcome. The mechanical and biological disturbance at fracture site will be different with length of neglect. Hence, it is appropriate to use classification proposed by Sandhu *et al*. we propose a guideline of treatment depending on the duration of neglect.

Neglected fracture NOF less than 4 weeks

It is usually staged I by Sandhu's classification. At this stage closed or open reduction and internal fixation is the preferred line of management. One may consider adding bone grafting at NU site if open reduction is contemplated. The fracture with vertical fracture line (Pauwel's Type II or III) would require a valgization osteotomy. The implant chosen may be CCSs. However, if valgization osteotomy is undertaken then nail plate assembly is the intended construct. The rate of fixation failure and NU are reported as 10%. It is advisable to follow the patient on a long term basis for the risk of developing AVN and secondary osteoarthritis. Poor reduction and improper placement of the screws is a major factor for failure of union at NU site.

Neglected fracture NOF between 4 weeks and 3 months

Generally, these NU are either stage II or sometimes stage I, The choice of treatment is open reduction and internal fixation with bone grafting (vascularized or nonvascularised) or valgization osteotomy. The extreme valgus position after osteotomy should be avoided. The angulation osteotomy is to be fixed with angle hip screws and side plates. Good results are also reported with open reduction and internal fixation with compression screws and free fibular graft. However complications like fibular graft breakage and screw penetration into joint do occur.

Neglected fracture NOF between 3 and 6 months

Generally, these NUs are stage II, however could be stage III also. In all these cases where the head fragment is vascular, open reduction, freshening of fracture surfaces, bone grafting at NU site and internal fixation by CCS and MPBG could be a good strategy. Which muscle to choose for MPBG and the consequent approach could be the surgeon's choice.

Hip arthrodesis may be considered for very young patients. However, the procedure is not preferred by patient or surgeons. In an established case with AVN in stage III one may have to resort to hemiarthroplasty or THR.

Neglected fracture NOF more than 6 months

These fractures are stage III, hence prosthetic replacement (hemi or total) is generally preferred. However, if still in stage II with a vascular femoral head, a hip preserving surgery may also be considered.

Conclusion

The outcome of neglected femoral neck fracture depends on the duration of neglect, as the changes occurring in the fracture area and fracture fragments decides the quality of biological materials required for fracture union. In Sandhu's stage I and stage II neglected femoral neck fracture osteosynthesis with open reduction and bone grafting with MPBG or Valgus Osteotomy achieves fracture union in almost 90% cases. However, in stage III with or without AVN, the results of osteosynthesis are poor and the choice of treatment is replacement arthroplasty (hemi or total).

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Management of femoral head osteonecrosis: Current concepts

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Abstract

Osteonecrosis of femoral head (ONFH) is a disabling condition of young individuals with ill-defined etiology and pathogenesis. Remains untreated, about 70-80% of the patients progress to secondary hip arthritis. Both operative and nonoperative treatments have been described with variable success rate. Early diagnosis and treatment is the key for success in preserving the hip joint. Once femoral head collapses (>2 mm) or if there is secondary degeneration, hip conservation procedures become ineffective and arthroplasty remains the only better option. We reviewed 157 studies that evaluate different treatment modalities of ONFH and then a final consensus on treatment was made.

Key words: Avascular necrosis, femur head, hip, osteonecrosis, treatment
MeSH terms: Avascular necrosis of bone, femur head, treatment protocols, osteonecrosis

Introduction

Osteonecrosis of the femoral head (ONFH) is caused by inadequate blood supply leading to death of the osteocytes. Subsequently it progresses to collapse of the femoral head and advanced joint destruction. ONFH thus leads to significant disability in the most productive years of life and is one of the common causes of hip arthroplasty in young individuals. Both traumatic and nontraumatic etiologies have been described for ONFH. The common causes include corticosteroid medications, fractures and dislocations of hip joint and chronic alcohol intake. In about 30% patients, it is idiopathic [Table 1]. Bilateral presentation is frequently seen and males are more commonly affected.[1] Contralateral hip may be affected in about 55% of the patients within 2 years.[2] About 75% of patients with other sites of involvement will have concurrent ONFH.[3]

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At an early-stage of ONFH, the hip joint is painless. However, it becomes painful and there is limitation of hip range of movement with advancement of disease. Multiple diagnostic and treatment modalities have been described for ONFH but none of them are completely accurate and effective. Earliest X-ray findings of ONFH take at least 2 months to develop, but may take as long as 6 months. Sclerosis and cystic changes are early radiographical changes. With progression of disease, there is asphericity of femoral head (femoral head collapse) and joint space reduction (secondary arthritis). Magnetic resonance imaging (MRI) is the most sensitive diagnostic modality for ONFH. MRI has sensitivity of 90-100% and specificity of 100% in diagnosis of avascular necrosis (AVN).[4] It is also useful for early detection of asymptomatic AVN.[5] The characteristic appearance of the infarcted area is a hypo-dense on T1 image surrounded by a single hypo-dense line separating normal and osteonecrotic bone. T2 image shows another line within this line representing increased vascularity in granulation tissue. The appearance of the interface is more important in the diagnosis, and the density of the necrotic central part will change with the change in fat content due to death of adipocytes and appearance of reparative tissue. MRI can help in identifying patients at risk of collapse of the femoral head. Presence of bone marrow edema, increased fat content in the proximal femur and joint effusion on MRI are important prognostic factors. Dynamic MRI may be the future investigation for early prediction of vascular insult to femoral head.[6,7] Altered hemodynamic changes in the vascular phase of bone scintigraphy may be seen as early as first 24 h of vascular insult. Classical finding is increased uptake in the reparative interface where vascular tissue is invading the dead bone, and new bone is

depositing. This surrounds the area of increased uptake by the dead trabeculae. Bone scan will thus detect the lesion before conventional radiograph. It is also helpful to detect disease at multiple sites in the skeleton. Most commonly used isotope is Tc-99m. Studies have shown that bone scintigraphy of the hip has lower resolution and sensitivity in the diagnosis of osteonecrosis compared to MRI.[8,9] Disadvantages include radiation exposure, poor morphometric details and expertise needed for interpretation. It is less useful than MRI in ruling out other differential diagnosis for osteonecrosis. It has the advantage in patients where MRI may not be feasible, such as, cardiac pacemakers, intracranial clips and claustrophobia.

There are many classification systems that describe the clinical and radiological severity/progression of ONFH. The Ficat and Arlet-staging system is still one of the most commonly used systems [Table 2]. It is based on radiological findings, but does not consider the extent of necrosis.[10] Quantification of the size of the lesion is helpful in predicting the collapse of the femoral head. Kerboul *et al*.[11] estimated the extent of necrosis radiographically in the early-stages by measuring the sum of arc of area of the femoral head involved on anteroposterior and lateral radiographs. Clinical outcomes were better if this value was <200°. These measurements have also been obtained on mid-sagittal and mid-coronal MRI scans and is useful in predicting outcomes.[12] Steinberg *et al*.[13] added quantification of femoral head involvement to the classification system, but could not gain wide popularity as it was difficult to apply. The Association Research Circulation Osseous (ARCO) system of classification incorporated features of both the Ficat and Arlet system and the Steinberg classification [Table 3].[5]

The natural history of ONFH is a progression to subchondral fracture leading to femoral head collapse and secondary osteoarthritis.[1,2] Accordingly, the treatment can be broadly categorized into two types; treatment in the precollapsed or early collapsed stage <2 mm and treatment after advanced collapse or osteoarthritis of hip joint. Numerous nonoperative treatment modalities and hip preserving surgical procedures have been described for precollapsed and early collapsed stage. Once joint collapse occurs or degeneration starts, the treatment for joint preservation becomes more complex and outcome is poor. This review will discuss the current evidences for treatment of ONFH.

Materials and Methods

A Pubmed/Medline search was conducted (between January 1st 1980 and June 30th, 2014) to identify all randomized control trial, meta-analysis, systematic reviews, prospective and retrospective studies published on the

Table 1: Common etiologies of avascular necrosis of the femoral head

Disordered lipid metabolism
Systemic steroid administration
Habitual alcohol use
Hyperlipidemia
Pancreatitis
Interruption of arterial supply
Trauma: Fractures and dislocations of the hip
Iatrogenic: Following surgical intervention around hip
Embolic
Gauchers disease
Sickle cell disease
Dysbarism (caissons disease)
Coagulation disorders (thrombotic)
Thalassemia
Polycythemia
Myeloproliferative disorders
Thrombolytic and hypofibrinolytic states
Ionizing radiations
Miscellaneous and multifactorial
Slipped capital femoral epiphyses
Legg-Calve-Perthes disease
Congenital hip dislocation
Gout
Systemic lupus erythematosus
Rheumatoid arthritis
Organ transplantation
Pregnancy
Cytotoxic agents
HIV

HIV=Human immunodeficiency virus

Table 2: Ficat and Arlet classification of femoral head osteonecrosis

Stage	Findings
1	Normal radiograph
2	Femoral head has normal sphericity, but there are signs of bone remodeling such as cystic and osteosclerotic regions
3	Subchondral collapse or flattening of the femoral head
4	Degenerative change is shown in acetabulum with reduction in joint space

Table 3: ARCO classification of femoral head osteonecrosis

Stage	Findings
0	All diagnostic studies normal, diagnosis by histology only
1	Plain radiographs and computed tomography normal, magnetic resonance imaging positive and biopsy positive, extent of involvement A, B, or C (<15%, 15-30%, and >30%, respectively)
2	Radiographs positive but no collapse, extent of involvement A, B, or C
3	Early flattening of dome, crescent sign, computed tomography or tomograms may be needed, extent of involvement A, B, or C, further characterization by amount of depression (in millimeter)
4	Flattening of the femoral head with joint space narrowing, possible other signs of early osteoarthritis

ARCO=Association Research Circulation Osseous

treatment of ONFH. The MeSH terms used in different combinations were "AVN, ON, nonoperative treatment, bisphosphonate, extracorporeal shock wave therapy (ESWT), electromagnetic therapy, hyperbaric oxygen, core decompression (CD), stem cell, bone-graft, tantalum rod, osteotomy, arthroplasty." The searches were limited to English language and human species. The references of these studies and systematic reviews were also searched for inclusion of other relevant studies in this review.

Result

Number of articles retrieved with the above search strategy has been mentioned in Table 4. In total 157 studies were reviewed, and a consensus of treatment was planned.

(A) Nonoperative treatment

Nonoperative management of ONFH includes restricted weight-bearing, pharmacological agents and biophysical modalities of treatment.[7] The goal of drug treatment in the precollapsed stage is to improve hip function, provide pain relief, prevent radiographic progression to subchondral fracture and collapse, and allow healing of the necrotic lesions.[14-16]

Nonweight bearing

Restricted weight-bearing using cane, crutches or a walker is effective in early-stages ON hip (Ficat and Arlet Stage-I and II) when the osteonecrotic lesion is <15% and located far from the weight-bearing dome (medial lesions).[16] Mont *et al*.[17] reviewed 21 studies (n = 819 patients) based on restricted weight-bearing treatment and observed satisfactory clinical result (no further surgery) in 22% patients after 34 months. Radiological progression was seen in 74% patients. There was no difference in outcomes among patients following full, partial, and nonweight-bearing regimens in the study. In a systematic review (level II evidence), Mont *et al*.[18] again reported that 59% (394 of 664 hips) of asymptomatic hips had onset of symptoms or disease progression to collapse after 7 years (range, 0.2-20 years). The investigators reported increased risk of collapse in sickle cell disease (73%; 29 of 40 hips) and minimal risk of collapse in systemic lupus erythematous (SLE) (17%; 10 of 59 hips). 32% patients with small or medium-sized lesions (<50% of head involvement) progressed to symptoms or collapse, whereas large lesions had 84% of chance of progression. It was stressed that progression to advanced-stage depends largely on location, size of the lesion and etiology. Small size lesion may show spontaneous regression.[19] In 21st century, this modality of treatment cannot be accepted as a standard isolated modality of treatment and may be an additive treatment to medical or surgical management.

Bisphosphonates

Bisphosphonate inhibits the osteclastic activity in the osteonecrotic lesion site and thus promotes bone healing. It prevents the onset of subchondral fracture or collapse in early ON hip, and in advanced conditions when already collapse has occurred it delays the need of total hip replacement (THR) surgery.[20-30] Agarwala *et al*. have reported the benefits of alendronate (10 mg/day or 70 mg/week) in ON hip at <1-year, 4 years and 10 years followup.[20-22] At an average followup of 4 years, Agarwala *et al*.[21] reported radiographic progression to collapse in 12.6% (27 of 215 hips) of hips in Stage-I and 55.8% (72 of 129 hips) of hips in Stage-II (Ficat and Arlet). Over all radiological progression was seen in 46% (99 of 215) of hips in Stage-I, 54% (70 of 129) of Stage-II hips and 20% (10 of 51) of Stage-III hips. The proportions of hips requiring THR were 2%, 8% and 33% for Staged-I, -II and -III ONFH respectively compared with 65%, 69% and 87% respectively as reported by Mont and Hungerford in untreated hips.[31] Agarwala and Saha[22] in a recent publication of 53 hips (in 40 patients) at 10 year followup reported a 29% collapse rate in the precollapse-stage of ON (10 of 34 hips) following 3 years of continuous alendronate use at 70 mg weekly. The investigators thus concluded that the natural history of untreated ON with more than 70% collapse rate was favorably altered with alendronate use.

In level II, prospective comparative study Nishii *et al*.[23] also found the lower rate of collapse and lesser hip pain after 1-year in ON hip patients receiving alendronate (14 patients with 20 hips, 5 mg daily for 1-year) than patients not receiving alendronate.

Lai *et al*.[24] reported similar efficacy of alendronate in the treatment of nontraumatic ON hip at early-stages (Steinberg Stage-II or III). In a randomized control trial, the authors reported 2 of 29 hip collapse in the alendronate group and 19 of 25 hip collapse in the control group (no treatment or placebo) at 2 years. Radiographic progression was observed in 14% patients in the treatment group compared with 80% in the placebo group. One hip in the alendronate group underwent total hip arthroplasty (THA), whereas 16 hips in the control group needed THA ($P < 0.001$).

A recent report by Chen *et al*.[25] provided conflicting evidence about bisphosphonate treatment in ONFH. In this prospective, randomized, double-blinded, placebo-controlled trial (level I evidence), there were 65 hips in Stage-IIC and IIIC (University of Pennsylvania classification). They did not notice any significant difference in radiographic disease progression, quality-of-life improvement, and prevention of THA between the alendronate and the placebo groups after 2 years. However, the investigators thought that the study was underpowered to detect statistical significance despite

Table 4: Search strategy of pubmed and extracted articles for review

Key words	Search details	Total hits	Number of articles evaluating treatment
Bisphosphonate, femoral head, osteonecrosis	((“diphosphonates”MeSH Terms OR “diphosphonates”All Fields OR “bisphosphonate”All Fields) AND (“femur head”MeSH Terms OR (“femur”All Fields AND “head”All Fields) OR “femur head”All Fields OR (“femoral”All Fields AND “head”All Fields) OR “femoral head”All Fields) AND (“osteonecrosis”MeSH Terms OR “osteonecrosis”All Fields)) AND ((“1980/01/01”PDAT : “2014/05/30”PDAT) AND “humans”MeSH Terms AND Englishlang	134	11
Extracorporeal shock wave therapy, femoral head, osteonecrosis	(ExtracorporealAll Fields AND (“shock”MeSH Terms OR “shock”All Fields) AND waveAll Fields AND (“therapy”Subheading OR “therapy”All Fields OR “therapeutics”MeSH Terms OR “therapeutics”All Fields) AND (“femur head”MeSH Terms OR (“femur”All Fields AND “head”All Fields) OR “femur head”All Fields OR (“femoral”All Fields AND “head”All Fields) OR “femoral head”All Fields) AND (“osteonecrosis”MeSH Terms OR “osteonecrosis”All Fields)) AND ((“1980/01/01”PDAT : “2014/05/30”PDAT) AND “humans”MeSH Terms AND Englishlang)	8	9
Electromagnetic therapy, femoral head, osteonecrosis	((“electromagnetic phenomena”MeSH Terms OR (“electromagnetic”All Fields AND “phenomena”All Fields) OR “electromagnetic phenomena”All Fields OR “electromagnetic”All Fields) AND (“therapy”Subheading OR “therapy”All Fields OR “therapeutics”MeSH Terms OR “therapeutics”All Fields) AND (“femur head”MeSH Terms OR (“femur”All Fields AND “head”All Fields) OR “femur head”All Fields OR (“femoral”All Fields AND “head”All Fields) OR “femoral head”All Fields) AND (“osteonecrosis”MeSH Terms OR “osteonecrosis”All Fields)) AND ((“1980/01/01”PDAT : “2014/05/30”PDAT) AND “humans”MeSH Terms AND Englishlang)	17	8
Hyperbaric oxygen, femoral head, osteonecrosis	hyperbaricAll Fields AND (“oxygen”MeSH Terms OR “oxygen”All Fields) AND (“femur head”MeSH Terms OR (“femur”All Fields AND “head”All Fields) OR “femur head”All Fields OR (“femoral”All Fields AND “head”All Fields) OR “femoral head”All Fields) AND (“osteonecrosis”MeSH Terms OR “osteonecrosis”All Fields)) AND ((“1980/01/01”PDAT: “2014/05/30”PDAT) AND “humans”MeSH Terms AND Englishlang)	9	5
Enoxaparin, femoral head, osteonecrosis	((“enoxaparin”MeSH Terms OR “enoxaparin”All Fields) AND (“femur head”MeSH Terms OR (“femur”All Fields AND “head”All Fields) OR “femur head”All Fields OR (“femoral”All Fields AND “head”All Fields) OR “femoral head”All Fields) AND (“osteonecrosis”MeSH Terms OR “osteonecrosis”All Fields)) AND ((“1980/01/01”PDAT : “2014/05/30”PDAT) AND “humans”MeSH Terms AND Englishlang)	8	4
Avascular necrosis, osteonecrosis, core decompression, femoral head	((“osteonecrosis”MeSH Terms OR “osteonecrosis”All Fields OR (“avascular”All Fields AND “necrosis”All Fields) OR “avascular necrosis”All Fields) AND (“osteonecrosis”MeSH Terms OR “osteonecrosis”All Fields) AND coreAll Fields AND (“decompression”MeSH Terms OR “decompression”All Fields) AND (“femur head”MeSH Terms OR (“femur”All Fields AND “head”All Fields) OR “femur head”All Fields OR (“femoral”All Fields AND “head”All Fields) OR “femoral head”All Fields)) AND ((“1980/01/01”PDAT : “2014/05/30”PDAT) AND “humans”MeSH Terms AND Englishlang)	209	48
Stem cell, femoral head, osteonecrosis	(“stem cells”MeSH Terms OR (“stem”All Fields AND “cells”All Fields) OR “stem cells”All Fields OR (“stem”All Fields AND “cell”All Fields) OR “stem cell”All Fields) AND (“femur head”MeSH Terms OR (“femur”All Fields AND “head”All Fields) OR “femur head”All Fields OR (“femoral”All Fields AND “head”All Fields) OR “femoral head”All Fields) AND (“osteonecrosis”MeSH Terms OR “osteonecrosis”All Fields)) AND ((“1980/01/01”PDAT : “2014/05/30”PDAT) AND “humans”MeSH Terms AND Englishlang)	56	14
Bone graft, femoral head, osteonecrosis	(“bone transplantation”MeSH Terms OR (“bone”All Fields AND “transplantation”All Fields) OR “bone transplantation”All Fields OR (“bone”All Fields AND “graft”All Fields) OR “bone graft”All Fields) AND (“femur head”MeSH Terms OR (“femur”All Fields AND “head”All Fields) OR “femur head”All Fields OR (“femoral”All Fields AND “head”All Fields) OR “femoral head”All Fields) AND (“osteonecrosis”MeSH Terms OR “osteonecrosis”All Fields)) AND ((“1980/01/01”PDAT : “2014/05/30”PDAT) AND “humans”MeSH Terms AND Englishlang)	380	69
Tantalum rod, femoral head, osteonecrosis	((“tantalum”MeSH Terms OR “tantalum”All Fields) AND rodAll Fields AND (“femur head”MeSH Terms OR (“femur”All Fields AND “head”All Fields) OR “femur head”All Fields OR (“femoral”All Fields AND “head”All Fields) OR “femoral head”All Fields) AND (“osteonecrosis”MeSH Terms OR “osteonecrosis”All Fields)) AND ((“1980/01/01”PDAT : “2014/05/30”PDAT) AND “humans”MeSH Terms AND Englishlang)	11	11
Osteotomy, femoral head, osteonecrosis	((“osteotomy”MeSH Terms OR “osteotomy”All Fields) AND (“femur head”MeSH Terms OR (“femur”All Fields AND “head”All Fields) OR “femur head”All Fields OR (“femoral”All Fields AND “head”All Fields) OR “femoral head”All Fields) AND (“osteonecrosis”MeSH Terms OR “osteonecrosis”All Fields)) AND ((“1980/01/01”PDAT : “2014/05/30”PDAT) AND “humans”MeSH Terms AND Englishlang)	535	58
Avascular necrosis, osteonecrosis, total hip replacement, hip arthroplasty	((“osteonecrosis”MeSH Terms OR “osteonecrosis”All Fields OR (“avascular”All Fields AND “necrosis”All Fields) OR “avascular necrosis”All Fields) AND (“osteonecrosis”MeSH Terms OR “osteonecrosis”All Fields) AND (“arthroplasty, replacement, hip”MeSH Terms OR (“arthroplasty”All Fields AND “replacement”All Fields AND “hip”All Fields) OR “hip replacement arthroplasty”All Fields OR (“total”All Fields AND “hip”All Fields AND “replacement”All Fields) OR “total hip replacement”All Fields) AND (“hip”MeSH Terms OR “hip”All Fields) AND (“arthroplasty”MeSH Terms OR “arthroplasty”All Fields)) AND ((“1980/01/01”PDAT : “2014/05/30”PDAT) AND “humans”MeSH Terms AND Englishlang)	818	68

a numerical reduction in the rate of disease progression (61% vs. 66%) and THA conversion (12.5% vs. 15.2%) in the alendronate group.

Even though the efficacy of alendronate is proven in early-stages ONFH, the doses required and duration of therapy is yet to be clearly established. There are reports of jaw necrosis and subtrochanteric fractures with the longterm use of bisphosphonate.[20-30] Most of the studies on the efficacy of this drug in ONFH are underpowered and without the control group. With these limitations and potential side effects, the surgical treatment is still favored.[32] With the current evidence, alendronate in ONFH patients can be used in a dose of 70 mg weekly for 3 years in Stage-I, II and III (Steinberg classification).[20-30,32]

Anticoagulants, statins and other vasodilators

Hypofibrinolysis and thrombophilia leading to venous stasis and reduced arterial flow, thus causing increased intraosseous pressure and hypoxic bone death have been postulated as a major and common etiological factor for ON.[33,34] Systemic anticoagulation therapy started before irreversible segmental collapse of the femur head may arrest or, speculatively, sometimes reverse the process of ischemic ON.[32-35] In a prospective study, Glueck *et al*.[35] reported outcome of enoxaparin therapy in Ficat Stage-I or II ON hip after 2 years (mean 3 years, range, 2-4 years) of followup. But they included patients of ON hip with either hypofibinolytic or thrombophilic or combined disorders. They observed 95% of hips (19 of 20 hips) with primary ON and 20% (3 of 15 hips) of patients with secondary ON (secondary to corticosteroid use) with no progression of the disease after enoxaparin treatment (60 mg/day for 3 months). In another recent retrospective study of 36 patients with bilateral idiopathic ON having at least one hip in the precollapsed stage (Ficat and Arlet Stage-I and II), Chotanaphuti *et al*.[36] observed no evidence of radiographic progression ($P = 0.042$) in 57.7% (15 of 26 hips) of hips in patients receiving enoxaparin therapy (6000 units 3 months) compared to 21.7% (5 of 23 hips) of hips in patients not receiving any treatment at the end 2 years. Only 7 patients (14 hips, 38.9%) had coagulation disorder in the enoxaparin group compared with 5 patients (10 hips, 27.8%) in the control group. Anticoagulant therapy has shown clear benefit in these two small studies[35,36] and has prevented the progression of ON from precollapsed stage to advanced-stage in idiopathic ON and/or corticosteroid-induced ON.

Lipid lowering agents are also helpful in ONFH particularly in steroid-induced ON.[37] Steroid causes hyperlipidemia which increases the fat content of the femoral head also.[37,38] It increases intracortical pressure and lead to sinusoidal collapse and osteonecrosis. Statins are lipid-clearing agents that dramatically reduce lipid levels in blood and tissues. Pritchett[39] reported that after mean followup of 7.5 years, only 1% of patients taking high-doses of corticosteroids and statin drugs developed ONFH whereas the prevalence was 3-20% in patients receiving high-dose corticosteroids without statins. But Ajmal *et al*.[40] did not find any significant reduction in ON between patients taking steroid and statin versus steroid without statin (4.4% vs. 7%). Further, large randomized studies are needed to establish its efficacy in ONFH. Another vasodilator named Iloprost (a prostacyclin derivative) has also shown benefit after 1-year treatment in patients of osteonecrosis and bone marrow edema.[41] Recently adrenocorticotropic hormone has also shown protection against ONFH induced by steroid. The proposed mechanism of action of this drug is based on enhancement of osteoblastic activity and stimulation of vascular endothelial growth factor that enhance neovascularization in the femoral head.[42] These drugs are still under trial and need larger study for regular use as a prophylactic agent.

Extracorporeal shock wave therapy

The exact mechanism how ESWT benefits in ONFH remains unknown. However, researchers believe that it enhances neovascularization by stimulating the expression of angiogenic growth factors.[26,28,43-49] In a randomized clinical trial, Wang *et al*.[44] compared ESWT (one episode of ESWT therapy, 23 patients with 29 hips) to CD with nonvascularized fibular grafting (VFG) (25 patients with 29 hips) in early-stages of ONFH. There was a significant improvement ($P < 0.001$) in pain, as well as hip function (Harris hip score HHS) and a nonsignificant ($P = 0.04$), but definite decrease in lesion size in ESWT group compared to CD and fibular graft group at the end of 2 years. 79% of patients in ESWT group improved whereas only 29% patients had improvement in bone-grafting group. The same investigators[46] reported the long term outcome (mean, 8.5 years; range, 7.7-8.8 years) of the above two groups of patients. They reported that patients with ESWT had significantly better clinical outcomes (pain score and HHS, 76% vs. 21% good or fair; $P < 0.001$) and decreased need for THA (24% vs. 64%; P 5.002) compared with the surgery group. MRI also revealed significant decrease in lesion size and bone marrow edema in ESWT group compared to the surgery group ($P < 0.05$).

In another randomized clinical study, Wang *et al*. compared ESWT alone (25 patients, 30 hips) to combined ESWT and alendronate therapy (ESWT followed by alendronate 70 mg/week for 1-year, 23 patients, 30 hips). There was significant but statistically similar improvement in pain, function and lesion size in both the groups at the end of 1-year. The authors concluded that the addition of alendronate to ESWT did not provide additional benefit.[30]

Ludwig *et al.*[47] (*n* = 22 patients) reported significant improvement in pain (visual analogue score VAS 8.5 to 1.2), function (HHS 43.3-92) and lesion size (size decreased or healed in 10 of 14 successfully treated patients) after 1-year of ESWT in ARCO Stage-I to Stage-III ONFH. Hsu *et al.*,[28] in a prospective randomized study of 98 early ON hips compared the ESWT to a cocktail regimen consisting of ESWT, hyperbaric oxygen, and alendronate. At 2 years followup (range, 1.5-4 years), the overall results (clinical, radiograph and MRI) showed 74% improved, 16% unchanged and 10% worsened in cocktail group; and 79.2% improved, 10.4% unchanged and 10.4% worsened in ESWT group ($P = 0.717$). THR was performed for 10% of cocktail group and 10.4% of ESWT group ($P = 0.946$). MRI showed a significant reduction in bone marrow edema and a trend of decrease in the size of the lesions in both groups, however, no difference was noted between the two groups. Wang *et al.*[48] in a randomized trial of 55 hips with ARCO Stage-I to III ON reported no significant difference in pain ($P = 5$ 0.4), hip function ($P = 5$ 0.1), and the need for THA ($P = 5$ 0.8) with ESWT (6000 impulses at 28 kV at each session) in patients with SLE and a non- SLE control group at minimum of 2 years' followup.

Vulpiani *et al.*[49] evaluated the outcome of ESWT in early-stages ONFH (ARCO I to III). At 1-and 2 years followup, all 10 patients (100%) in Stage-I, 9 of 11 patients (81.8%) in Stage-II and 4 of 15 patients (26.7%) in Stage-III reported excellent or good results on Roles and Maudsley score. Patients from ARCO Stage-I group and Stage-II group achieved significantly better results (pain, HHS and Roles and Maudsley score) than patients from ARCO Stage-III group ($P < 0.005$). Within 2 years, 10 of the 15-II ON hip needed arthroplasty. ARCO Stages I and II lesions were unchanged on radiographs and on MRI. They concluded that ESWT in ARCO Stages I and II slows down the worsening of the grade of the ONFH and improve clinical features. Short followup and small studies on ESWT are the major limitations for its restricted use.

Pulsed electromagnetic therapy

Pulsed electromagnetic therapy is thought to favorably affect early-stage ON through stimulation of osteogenesis and angiogenesis similar to ESWT.[26,50-56] Massari *et al.*,[55] 37 in their retrospective analysis of 76 hips treated with electromagnetic field stimulation in Ficat Stage-I to III, reported that the 94% of hips in Stage-I and II avoided the need for THA with a significantly higher proportion of hips in Stage-III progressing to THA at a mean followup of 2 years. At present, evidence in favor of electromagnetic stimulation is limited and further research is needed to explore its potential role in early-stage ON.

Hyperbaric oxygen

Hyperbaric oxygen improves oxygenation, reduces edema by causing vasoconstriction, and induces angioneogenesis; thus causing a reduction in intra osseous pressure and improvement in microcirculation.[28,29,57-59] Reis *et al.*,[57] observed normal MRI in 13 hips after hyperbaric oxygen treatment (100% oxygen at 2-2.4 atmospheric pressure for 90 min by mask for 100 days) to 12 patients with 16 ONFH, all with Steinberg stage 1 disease. Camporesi *et al.*[58] also reported clinical improvement at followup of 7 years in the study of 19 patients randomized to receive 30 treatment doses of either hyperbaric oxygen or hyperbaric air for a total period of 6 weeks. None of the hyperbaric oxygen group patients needed THA till the time of final followup. Because of limited data, the use of hyperbaric oxygen in ONFH is controversial.

(B) Operative treatment

Surgical treatment for precollapsed stage ONFH involves hip preserving procedures (CD, nonvascularized bone-graft, vascularized bone-graft) whereas prosthetic hip surgery is reserved for advanced-stage of collapse and arthritic hip.

Core decompression

Core decompression is the most commonly performed surgical procedure for treatment of early ONFH. It decreases the intraosseous pressure in the femoral head and increases blood flow to the necrotic area, thus augmenting neobone formation [Figures 1 and 2]. It has been considered as the only cost-effective surgical procedure for ONFH,[60,61] but the success of the treatment is largely dependent on the etiology and radiographic parameters such as lesion size, location or collapse of the lesion.[62,63] The overall success rate as defined by the need for further surgery has varied between 40% and 80% across multiple studies at 2-7 year followup.[60-69] Conventional core decompression (CD) was performed using 8-10 mm cannula or trephine which had the potential risk of subtrochanteric fracture and hip joint penetration.

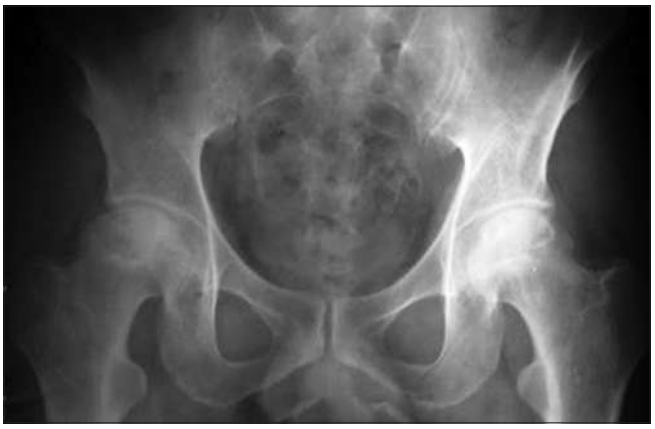

Figure 1: Radiograph of pelvis with both hip joints anteroposterior view showing a bilateral idiopathic osteonecrosis of hip in early stage

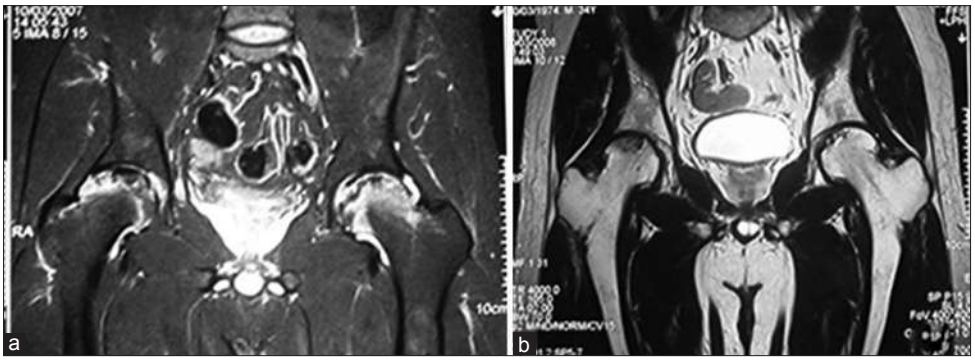

Figure 2: Magnetic resonance imaging of the same patient demonstrates edema inside femoral head as well as effusion in the hip joint (a-preoperative) and, after 1-year of core decompression the lesion has diminished in size, the edema has subsided and hip joint effusion is resolved (b-postoperative 1-year)

But the technique of CD has improved overtime.[66,67] The procedure of CD by multiple small drillings was presented in the annual ARCO meeting by Kim *et al*., in 2004.[65] They compared the results of the efficacy of two decompressive methods (multiple drilling MD vs. conventional CD) for the treatment of precollapse ONFH in a consecutive series of 54 patients. They reported that radiographically and clinically, high failure was significantly related to the larger size and laterally located lesion in both groups. The average preoperative and the last HHS was 73.7-86.7 in single CD and 74.6-87.0 in MD. The group who had undergone MD had significantly longer time before the collapse (mean 42.3 months vs. 22.6 months, $P = 0.011$) and the lower rate of collapse within 3 years after operation (55.0% vs. 85.7%). In a systematic review, Marker *et al*.[67] compared the outcome of recent technique of CD to that of old conventional technique. Recent technique of CD had a better result than old conventional technique. There were 1337 hips treated before 1992 and 1268 hips between 1992 and 2007. The proportion of patients surviving without additional surgery increased ($P < 0.001$) from 59% (range, 29-85%) in the earlier studies to 70% (range, 39-100%) in the more recent reports. Similarly, the radiographic success also increased ($P = 0.027$) from 56% (range, 0-94%) for the pre-1992 cohort to 63% (range, 22-90%). Stratification by Ficat stage showed there were fewer ($P < 0.001$) patients who were Ficat stage III after 1992. CD thus is an effective procedure for early ONFH mainly in Ficat stage I and II. Recent technique of CD involves MD of the necrotic lesion of femur head which is an easy, simple and safe procedure. A recent study by Al Omran[68] also reported similar observation as noted by Marker *et al*. in their review. In his series 61 patients underwent a classical 8 mm drilling and 33 patients underwent 3.2 mm diameter MD. They observed significant improvement in outcome in both groups of patients, but there was no difference in the outcome between the groups at the end of 2 years (100% improvement in pain and HHS of Ficat stage I patients both groups $n = 19$, 80% in CD vs. 78% in MD group had better pain and HHS in Stage-IIA $n = 39$, 52% in CD and 52.8% MD had improved pain and HHS in Stage-IIB $n = 36$). In a retrospective study, Song *et al*.[69] reported the outcome of MD in 163 hips as a treatment for Ficat stage I to III ON. They reported clinical success (defined as HHS >75 and no need of additional surgery) in 79% (31 of 39 hips) of Stage-I hips and 77% (62 of 89 hips) of Stage-II hips. 88% (52 of 59 hips) hips with small to medium-sized lesions required no additional surgical procedure at a mean followup of 7.2 years (range, 5-11.2 years).

Mont *et al*.[66] reported 71% successful outcome (32 of 45 hips) following MD (2-3 perforations) with 3 mm steinmann pin. They observed better outcome in small and medium size lesions of Stage-I compared with large lesions and Stage-II disease. Current recommendation is that CD should be performed with 3.2 mm drill bit with multiple perforation (at least 3). This is an established modality of treatment for early-stage ONFH. This procedure can be safely performed under image intensifier with percutaneous method with minimal risk of subtrochanteric fracture or inadvertent hip joint penetration [Figures 1 and 2].

Mesenchymal stem cells implantation or growth factor based treatment strategies

To augment osseous regeneration in the necrotic lesion site, the applications of osteogenic or angiogenic precursor cells with or without growth factor is an alluring possibility. Adult tissue derived mesenchymal stem cells (MSCs) application represents a highly promising option for treatment of ONFH in the precollpased stage [Figures 3].[70] Many researchers have documented decreased quantity of endothelial progenitor cells and colony forming units in patients suffering from ONFH.[71,72] Besides that, there is impaired migratory capacity of endothelial progenitor cells and increased cellular senescence resulting in decreased angiogenesis in patients of ONFH.[70] All these reasons justify the potential role of stem cells or growth factors in treatment of precollapsed ONFH. MSCs implantation has capability to differentiate into

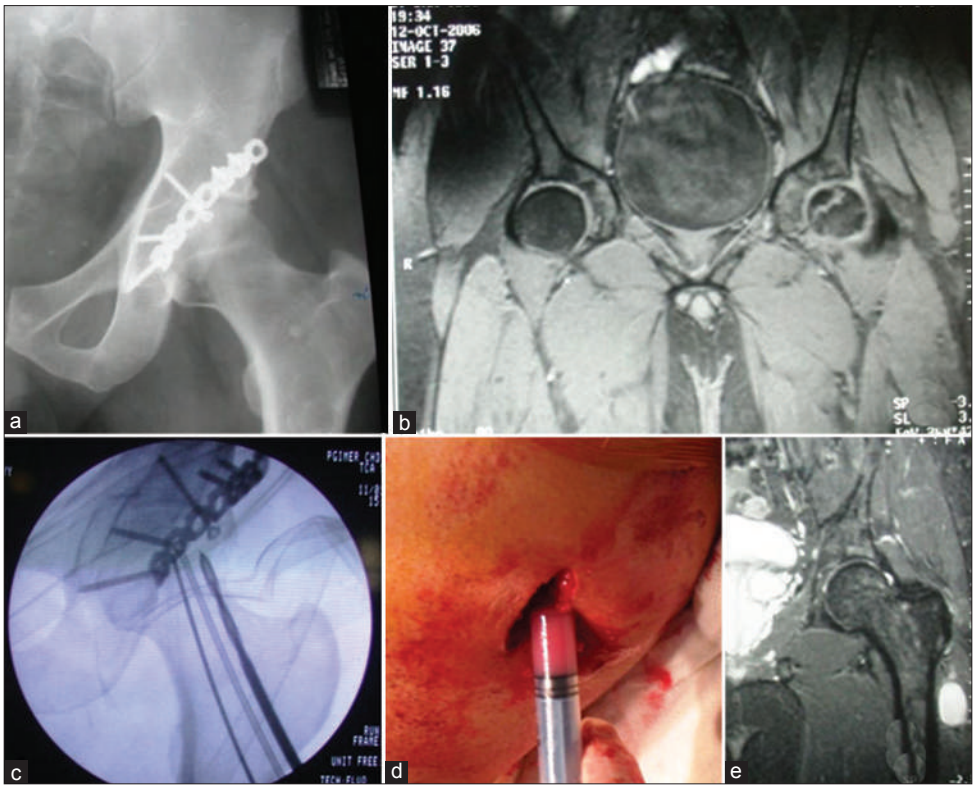

Figure 3: (a) Plain x-ray anteroposterior view of left hip in a 32-year old young patient showing posttraumatic AVN in its early stage (b) MRI of both hips showing early avascular changes (c) Intraopartaive photographs demonstrating core decompression and (d) bone marrow concentrate instillation inside the core tract. (e) After 15 months, the necrotic lesion has completely healed

multiple cell lineages including the osteoblast, chondrocytes and adipocytes. This property of stem cells has been observed in an experimental dog model while evaluating its effect in ON.[73] However, the efficacy of stem cells in healing ON lesion is because of the osteoblastic differentiation ability or secondary to release of growth factors or cytokines remains unclear. In addition, augmentation of neovascularization or angiogenesis property of stem cells have been described by many researchers which ascribes another reason for its potential role in the treatment of ON.

Mesenchymal stem cells can be implanted either as bone marrow concentrate mononuclear cells [Figure 3c and d] or *ex vivo* culture expanded bone marrow-derived stem cells.[70] Application of stem cells in ONFH was pioneered by Hernigou *et al*.[74-76] The authors injected the mononuclear cells fractions of the bone marrow aspirate from the iliac crest and injected into the necrotic area. Nine out of 145 patients with early-stage ONFH (Steinberg stage I or II) and 25 out of 45 patients with advanced ONFH (Steinberg stage III or IV) required THR.[62] Subsequently Gangji *et al*.,[77,78] Yan *et al*.[79] and Deltro *et al*.[80] also proved the safety and efficacy of MSCs in ONFH.

In a prospective, randomized and double blind trial, Gangji *et al*.[81] reported the outcome of isolated CD and the autologous bone marrow implantation at followup of 5 years. In 24 ON hips at ARCO Stage-I and II, they observed significant improvement in pain and lower rate radiographic progression in bone marrow implantation patients (23%, 3 of 13 hips) compared to CD cohort (73%, 8 of 11 hips). However, they did not notice a significant difference in both the groups in terms of the need of subsequent THA (15% in bone marrow implantation group vs. 27% in CD). A retrospective study by Liu *et al*.[82] reported the outcome of CD and hydroxyapatite/polyamide implantation with or without bone marrow MSCs implantation. At the end of 2 years, they observed better-clinical success (HHS and pain score) and radiographic improvement in stem cells group. 21.4% (6 of 28 hips) of ON hips in bone marrow group collapsed compared to 59.3% (16 of 27 hips) in CD group. In another comparative prospective randomized study, Zhao *et al*.[83] reported significantly lower radiographic progression to collapse in the bone marrow group (23%, 10 of 44 hips) than the CD (4%, 2 of 53 hips) group at 5 years followup in ARCO Stage-I and II ONFH. Within each stage of disease, the author reported significant improvement in HHS and radiographic necrotic volume in the bone marrow group compared to CD ($P < 0.05$). Sen *et al*.,[84] in a recent randomized control trial of 51 hips with ARCO Stage-I and II ON comparing CD with a bone marrow mononuclear cell instillation, reported significant improvement in pain, deformity, and hip survival in the bone marrow concentrate ($P < 0.05$) group after 2 years.

The efficacy of ex vivo expanded autologous bone marrow-derived stem cells have been studied in few small studies.[85,86] Kawate *et al*.[85] reported the outcome of VFG combined with a synthetic β-TCP ceramic and cultured bone marrow-derived MSCs in 3 patients with advanced-stages of steroid-induced ONFH (Steinberg stage III or IV). There was no progression in any patients within 34 month followup. Noth *et al*. also observed promising result with similar treatment.[87]

The growth factors secreted by osteogenic cells, platelets, and inflammatory cells (bone morphogenetic proteins BMPs, insulin-like growth factor-1 and -2, transforming growth factor-β1 (TGF-β1), platelet-derived growth factor, and fibroblast growth factor-2) are functionally involved in bone healing.[70] Lieberman *et al*.[88] treated 15 patients (17 hip joints at Ficat stage II or III) with CD and allogenic, antigen-extracted, autolyzed fibula grafts, combined with 50 mg of recombinant human BMP-2 and noncollagenous protein. Radiographic progression of the disease was prevented in 14 of 17 hips at an average of 53 months (range, 26.94 months). Only one of 15 hips, that were classified as Ficat stage IIA developed collapse. The other two hips that progressed already had collapse of the femoral head before the procedure.

Mont *et al*.[89] used a triphasic bone substitute consisting of demineralized bone matrix, processed allograft bone chips, and a thermoplastic carrier plus the addition of BMP-7 for ONFH in 19 patients (21 hips). A successful clinical outcome (HHS >80) was observed in 86% percent at mean followup of 48 months. In another retrospective study, Seyler *et al*.[90] used autologous, nonvascularized bone-grafts loaded with BMP-7. There were 33 patients (39 hips: 22 at Ficat stage II and 17 at Ficat stage III) with ONFH. At the mean time of 36 months, only four of 22 Ficat stage II hips and 11 of 17 Ficat stage III hips needed THR. In several other animal models, the efficacy of BMP-2, BMP-7 and 14 have been evaluated in ONFH. However, the studies on the efficacy of growth factors are still in its preliminary stage. Lack of the control group, small patient numbers and short duration of followup are the major limitations to consider these treatments as a definite modality of management.

The regenerative medicine also widens its application in ONFH in all its stages. Few researchers have used cartilage regenerative technique such as osetochondral graft implantation, mosaicplasty, autologus chondroctes transplantation and acellular matrix application for treatment of ONFH in its advanced-stage (Ficat III and IV, ARCO III and IV).[91-94] Gagala *et al*.[95] recently reported the outcome of autologous osteochondral transfer in ONFH of 20 patients with 21 hips. Seven patients with ARCO IIA and IIB were treated with Osteo Articular Transfer System alone, 13 patients with ARCO IIC, III and IV were treated with OATS and morselized bone allograft. Hip survival in OATS group was 85.71% after 4 years (one conversion to THR) and 61.54% in OATS/allograft group after 3 years (five conversions to THR). Cartilage regenerative techniques include a surgical dislocation of the hip anteriorly to access the osteochondral defect, thus, it is more invasive and surgically demanding. Very few cases have been reported with the above methods, and it has shown variable results; thus, it is very difficult to comment on the efficacy of these techniques.

Nonvascularized bone graft

Nonvascularized bone-grafts (usually tibial autograft and fibular autograft or allograft) are used to support subchondral bone and articular cartilage after removal of the necrotic lesion from the femoral head. The osteoconductive and osteoinductive properties of bone-graft help in healing of the osteonecrotic lesion. This modality of treatment has been reported to be successful in precollapse, and early postcollapse (<2 mm collapse) ONFH when the articular cartilage is relatively undamaged. The surgeons commonly adopt this procedure in Ficat stage I and II ONFH when CD fails.[32] Three methods of bone-grafting technique have been described: Phemister technique (grafting through CD track), trap door (grafting through a window created in the femoral head) and light bulb procedure (grafting through a window created in femoral neck or femoral neck-head junction). Although these modalities of treatment is rarely been used now a days as an isolated procedure, many researchers now use these techniques in combination with growth factors and various bone-graft substitutes.[32] The position of bone-graft within the necrotic lesion or at the transition zone between necrotic lesion and normal bone has not shown any difference in the outcome, but the type of graft (tibail autograft is better than fibular graft) has a definite impact on the outcome.[91-96,97] Still though, the findings of finite-element analyses recommend the graft to be placed as close as possible to the subchondral bone, and in the lateral part of head.[98]

Many studies have reported encouraging results with the use of nonvascularized bone-graft (70-90% excellent result at 2-7 years followup)[98-104] but few studies have shown a high rate of radiological progression (Nelson and Clark,[105] Dun and Grow.[106]). Seyler *et al*.[90] reported 83% survivorship in stage I and II ON and 78% survivorship at a minimum follow up of 2 years in 39 hips using the light bulb procedure. In a retrospective study (80 hips in 65 patients), Keizer *et al*.[97] used tibial autograft and fibular allograft in 18 and 62 patients of ONFH respectively. Of the 78 hips available for evaluation, 42 patients (54%) had clinical failure (secondary surgery or a poor Merle d'Aubigné and Postel score (<8

points) at a mean of 4.5 years. Kaplan–Meier survivorship analysis with clinical and radiological end-point showed a mean survival rate of 55% at 5 years and a mean of 33% at 10 years. Survivorship analysis with revision surgery as an end-point showed a mean survival rate of 66% (95% confidence interval [CI], 55-77) at 5 years and of 52% (95% CI, 39-65) at 10 years. When survivorship analysis was stratified according to Ficat stage, it showed a mean survival rate of 83% for stage 0, 0% for stage I, 80% for stage IIA, 63% for stage IIB, 54% for stage III and 56% for stage IV at 5 years. On comparative evaluation, tibial autograft showed a significantly better survival than fibular graft (P = 0.002). At 6 year followup, the survival rate for tibial graft was 75% (95% CI, 54-96) compared to fibular allograft which showed a mean survival rate of 42% (95% CI, 30-55).

The effect of autologous nonvasculairized fibular graft in combination with BMP-7 was evaluated by many investigators.[88,89,107] Use of cancellous chips admixed with BMP-7 during nonvascularized grafting via a trapdoor technique avoided the need for the secondary procedure in 80% of stage II and III ONFH.[76,77] Papanagiotou *et al*.[107] in a recent study treated 7 hips which were in precollapsed stage (5 Steinberg stage II and 2 Steinberg stage III). Five hips maintained the sphericity of head and two failed (needed THR) after an average followup of 4 years (2-5.5 years). The author observed a marked improvement of function (mean HHS increase of 49.2) and decrease of pain level (mean VAS decrease of 5) in these five hips.

Porous tantalum implant

Porous tantalum implants provide structural support like that of bone-graft and avoid the risks of infectious complications and donor site morbidity as reported with the use of allograft and autograft respectively. These rods are highly porous (>80% volume) and thus allow secure and rapid bone growth.[108-114] With the addition of bone marrow, growth factors, or bisphosphonates, the efficacy of porous tantalum rod can be further imporved.[111,112]

Veillette *et al*.,[108] prospectively evaluated 54 patients (60 hips) in whom ONFH was treated with CD and insertion of a porous tantalum rod. At the mean followup of 24 months, 15.5% (*n* = 9 patients) of patients needed THA. The overall survival rates were 91.8% at 12 months, 81.7% at 24 months, and 68.1% at 48 months. The absence of chronic systemic diseases resulted in a survival rate of 92% at 48 months. Varitimidis *et al*.[115] prospectively evaluated 27 patients who were treated with tantalum rod in nontraumatic ONFH. At the mean followup of 38 months (15-71 months), 13 of 26 hips remained at the same radiographic stage, and 13 deteriorated. Mean HHS improved from 49 to 85, 6 patients needed THA. Survivorship, with conversation to THA, was 70% at 6 years. The authors concluded that tantalum rod implantation is a safe "buy-time" technique, especially when other joint salvage procedures are not an option. But he stressed on careful patient selection (early-stage disease) and careful rod insertion for favorable results.

Tsao *et al*.[113] reported early clinical results of these implants and observed better survival rates (92% at 48 months) than hips treated with CD and VFG. Shuler *et al*.[109] reported a survival rate of 86% after 39 months after insertion of the tantalum implant, and 6 weeks protected weight-bearing. Nadeau *et al*.[116] reported a survival rate of 78% after 12 months and overall success rate of 45%. The reason behind less success rate is because of inclusion of patients with advanced collapse. Tanzer *et al*.[112] reported the results of a retrieval analysis of 15 clinically failed porous tantalum implants that were associated with little bone ingrowth and insufficient mechanical support of subchondral bone. Floerkemeier *et al*.[110] reported 44% survival after implantation of a tantalum rod in ONFH (19 patients with 23 hips) at mean followup of 1.45 years. Thirteen hips needed THA. The authors concluded that treatment of the early-stage of ONFH with CD combined with the implantation of an osteonecrosis intervention rod seems to be no better and no worse than simple CD. Furthermore, the procedure is associated with increased costs and a prolonged operation time. However, the author did not notice any difficulty in removing implant while converting to THR as warned by many surgeons before in their reports. At this stage, porous tantalum rod cannot be considered as a standard mode of treatment in ONFH.

Vascularized bone graft

Vascularized bone-grafting is a recommended modality of treatment for early ONFH (Ficat stage I to III).[117-122] The graft provides a viable structural support (eg., vascularized iliac crest graft, vascularized fibula graft) and prevents joint collapse Figure 4.[117-125] As the vascularity is preserved, and the graft has inherent osteogenic potential, it augments bony healing in the necrotic lesion site. However, the

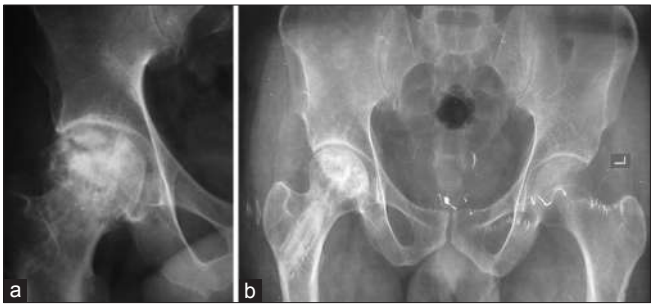

Figure 4: (a) X-ray (R) hip joint anteroposterior view showing advanced stage osteonecrosis of hip treated with vascularized fibular graft, (b) X-ray pelvis both hip joints anteroposterior view (b) after 11 years showing the lesion has healed and femoral head has maintained the sphericity

outcome is less rewarding in large lesions where the involvement is more than 50% of the femoral head, and the collapse is more than 2 mm. Patients with a history of smoking, alcoholism, peripheral vascular disease or other risk factors should not be considered for the procedure. The major demerit of this technique is its surgical complexity and increased surgical duration.[117-125]

Muscle pedicle bone graft

Meyers (1978) 117 first reported the application of muscle pedicle bone-graft for treatment of ONFH. They observed good result in all patients with Stage I and II disease but only in 33% patients in advanced disease (Ficat III and IV disease) at 6 months to 2 years followup. Lee and Rehmatullah[118] reported 70% success rate with muscle pedicle bone-graft in idiopathic ONFH. Baksi (1991)[119] reported the outcome of 68 hips (61 patients) treated with many types of muscle pedicle bone-graft at 3-12 years (mean, 7 years) followup. Of the several types of muscle pedicle bone-grafts used, the tensor fascia lata anteriorly, and the quadrates femoris posteriorly were preferred. About 83% patients had good or excellent results.

Vascularized Iliac crest graft

The method described is recommended for treatment in the Ficat stage II and early-stage III, when necrosis does not yet involve the complete femoral head. Iwato *et al.*[120] observed 74% success rate (17 of 23 hips) with vascularized iliac crest graft use in ONFH. Most of the patients had no femoral head collapse preoperatively, but more than 50% progressed to radiographic collapse at a mean followup of 3 years. Eisenschenk *et al.*[126] reported stable disease after 5 years followup in 56% of ONFH patients treated with iliac crest graft perfused by the circumflexed ilium profunda artery. Matsusaki *et al.*,[121] used vascularized pedicle iliac bone-graft combined with trans-trochanteric anterior rotational osteotomy in patients with extensive necrosis in whom the necrotic area occupied more than two-thirds of the weight-bearing zone of the femoral head. There was significant clinical improvement and no disease progression in 12 of 17 hips (71%) after mean followup of 50.7 months. They concluded that vascularized pedicle iliac bone-graft combined with trans-trochanteric anterior rotational osteotomy to treat AVN of the femoral head is promising for joint preservation. In a retrospective study, Babhulkar[127] reported only one progression to collapse (treated with THR) in 31 patients after treatment with CD and iliac crest with deep circumflex iliac vessels. He included patient with nontraumatic ONFH in ARCO stage IIB and IIIC only and followed them up till 5-8 years.

Vascularized fibular graft

Fang *et al.*[128] reviewed six articles on vascularized fibular graft (VFG) used as a treatment of ONFH published between January 1980 and April 2012. In this meta-analysis of six studies (n = 984 patients), there were 122 conversions to THA (16.5%) from 740 patients who were treated with VFG. In the remaining 244 patients treated with other methods (CD, non-VFG, and vascularized iliac graft), there were 104 conversions to THA (42.6%). VFG can achieve lower conversion rate than the other three methods (odd ratio [OR] 0.19; 95% CI, 0.13-0.28; P = 0.001; I2 = 24%). Among patients evaluated with radiographs for progression to collapse in 3 of these studies (n = 122 patients), a total of 14 of 84 (16.7%) hips treated with VFG collapsed, and a total of 56 of 88 (63.6%) hips treated with non-VFG collapsed. The result favored vascularized grafting more than nonvascularized grafting (OR, 0.09; 95% CI, 0.01-0.57; $P < 0.05$). In precollapse phase (steinerg I and II), VFG had got a better hip salvage than other three methods (CD, N-VFG, vascularized iliac grafting). Among the 270 hips, a total of 16 of 163 (9.8%) hips treated with VFG failed, and a total of 43 of 107 (40.2%) hips treated with non-VFG failed (OR, 0.17; 95% CI, 0.09-0.33; P = 0.001; I2 = 5%). In precollapse and early postcollapse phase (Steinberg II and III) 116 of 705 (16.5%) hips treated with VFG failed, total of 83 of 194 (42.8%) hips treated with non-VFG failed (OR, 0.17; 95% CI, 0.11-0.26; $P < 0.001$). A total of 30 complications (23.8%) were reported in 126 VFG treated patients and 13 complications (8.9%) in 146 patients treated with CD, non-VFG, and vascularized iliac graft (n = 272 total patients followed, P = 0.01). However, in the weighted test for overall effect, this difference does not reach significance (OR, 3.44; 95% CI, 0.81-14.62; P = 0.09).

Urbaniak *et al.*[129] in their study of 103 hips treated with vascularized fibula grafting, reported 91% survivorship in stage II and 77% survivorship in stage III at a final followup of 5 years. Yoo *et al.*[128] also reported excellent results, with 89% survivorship in 124 hips in stage II and III at a minimum of 10 years' followup (mean, 13.9 years; range, 10-23.7 years). Eward *et al.*[130] recently reported the long term followup data (mean, 14.4 years; 10.5-26 years) on 65 hips with precollapse-stage ON treated with vascularized fibula grafting; 75% of the hips survived without the need for THA at a minimum 10 year followup. The investigators noted that demographic and radiographic factors were not associated with changes in graft survivorship.

Proximal femoral osteotomy

The underlying principle behind proximal femoral osteotomies in ONFH is to rotate the necrotic femur head away from the load-bearing area and replace it with the uninvolved healthy portion of the head. It also reduces the intraosseus venous pressure and improves vascularity. There are mainly two types of osteotomy described: Trans-trochanteric rotational osteotomy and intertrochanteric varus or valgus osteotomy (combined with

flexion or extension). The success rates of these osteotomies have been reported between 70% and 93%.[15,32,131-135]

Jacobs *et al.*[136] had 73% success rate at 5.3 years followup after intertrochanteric osteotomy in ONFH. Maistrelli *et al.*,[137] reported satisfactory results in 71% of ON hips after 2 years of intertrochanteric varus or valgus osteotomy and it dropped to 58% at 8.2 years. After 10.2 years followup, Gallinaro and Masse[138] observed success rate in 62.5% of cases after flexion osteotomy. Flexion valgus osteotomy with autogenous bone-grafting has shown a survival rate of 87% without replacement arthroplasty 10 years after operation.[139]

The success rate of rotational osteotomy has been described in 78% of patients after 3-16 years followup.[136] Zhao *et al.*,[140] in their study of 73 hips at a mean followup of 12.4 years (range, 5-31 years), reported that 91.8% (67 of 73 hips) of the hips remained intact and did not need conversion to a THA following curved trans-trochanteric varus osteotomy. There was a significant improvement in HHS after surgery, and the mean postoperative intact ratio was 57.2% (range, 27-100%). To prevent progressive collapse they reported that the cutoff for the postoperative intact ratio was 33.6% (sensitivity, 82.9% and specificity, 100%; $P = 0.001$). Moreover, to prevent collapse and joint space narrowing, the cutoff intact ratio was reported to be 41.9% (sensitivity, 88.9%; specificity, 92.1%; $P = 0.001$). Sakano *et al.*[141] similarly reported that, in their series of 20 hips, 90% (18 hips) did not collapse or require conversion to a THA following trans-trochanteric varus osteotomy at a mean followup of 4 years (range, 0.7-4.1 years). The mean postoperative intact ratio was 61%, and the reported mean elevation of the greater trochanteric was 1.2 cm (range, 0.5-2 cm). Ito and colleagues recently reported the longterm results of varus half wedge osteotomy in 34 hips at a mean followup of 18.1 years (range, 10.5-26 years). Overall, 74% (25 hips) had satisfactory results with a mean HHS of more than 80 points despite having a mean limb length discrepancy of 19 mm (range, 8-36 mm). The investigators concluded that the varus osteotomy of the proximal femur provides favorable longterm outcomes in the presence of more than one-third of normal superolateral bone.

The major point against limited acceptance for the above osteotomy technique is because of its technical complexity. All these articles are from single surgeon's series and are of level IV evidence. The technique has never been compared to any other method of treatment and hence it is difficult to establish the superiority of this technique to other methods described. Osteotomies are best suited to patients not being treated with longterm steroids, with minimal osteoarthritic changes, with no loss of joint space or acetabular involvement and small combined necrotic angle (Kerboul's angle <200).[15,32]

Arthroplasty

Patients with ONFH may need THR when all other modalities of treatment have failed, or joint is arthritic secondary to advanced collapse (more than 2 mm). THR is considered as a last resort of treatment because ONFH victims are usually young adults whose functional demands are high and also, there is a high possibility of the need of revision arthroplasty in such patients. Polyethylene wear and osteolysis leading to aseptic loosening are major concerns. Literature has reported 8-37% of aspectic loosening following THR in ONFH.[32] With the introduction of third generation ceramic bearings, porous materials and high cross-linked polyethylene, the survivorship of THR has increased.[142]

Bipolar arthroplasty is no more an acceptable treatment option for ONFH. Young patients, high incidence of protrusion acetabuli, increased rate of loosening and better THR bearings are major reasons for its unacceptability. Revision rate ranging from 13.9% to 27.6% have been reported with bipolar hemiarthroplasty in ONFH after average followup of more than 5 years.[142-146]

Limited femoral resurfacing arthroplast is also a treatment option in ONFH patients with Ficat and Arlet Stage-III disease, a combined necrotic angle of >200° or >30% involvement, femoral head collapse of >2 mm, and no evidence of damage to the acetabular cartilage.[15,32] Although it had shown satisfactory results for up to 10 years, a few recent studies has shown less predictable outcomes of these procedures with overall hip survivorship reaching 75.9% at 3 years.[147] In another study by Cucklere *et al.* 31% failure was noted in a mean followup of 4.5 years (18 failure of 59 hips).[148]

Better implant designs have improved the outcome of THR in ONFH. In a systematic review of 67 studies (3277 THR in 2593 patients) Johannson *et al.*[149] reported mean survivorship of 97% at 6 years followup in patients operated after 1990. Stratification of the patients as per their associated risk factors demonstrated higher revision rate in sickle cells disease, Gaucher disease and end-stage kidney disease or transplant patients. The revision rate was lower in patients with SLE, idiopathic or after heart transplant. With the poly on poly bearings (n = 172 THR), Min *et al.*[150] reported 100% survivorship at 7.2 years followup. In a study by Kim *et al.*,[151] ceramic head on polyethylene bearing has shown 100% survivorship (excluding infection) at an average 8.5 years followup. Furthermore, when literature was analyzed to search for the component which commonly fails, cup wear or loosening was found to be more common then stem loosening. Kim *et al.*[151] ($n = 148$ THRs), reported 98% stem survivorship (cemented and cementless) but only 85% cementless cup survivorship after 17.3 years. Issa *et al.* have expected a still better survivorship with the introduction of tantalum or titanium porous acetabular cup recently.[142]

The surgeons sometimes expect difficulty in performing a THR in ONFH. Previous surgery with altered hip biomechanics, presence of hardware, bone/fibula grafts, screw track, scar and fibrosis around hip may evoke potential problem. However, many studies have reported that the medium term result of THR is not affected by previous surgery in ONFH.[152-156] Helbig *et al*.[157] demonstrated no complications or component loosening, at a mean followup of 54 months in the series of 15 hips, that were converted to THR after they had previous CD. In a study of 15 failed trans-trochanteric rotational osteotomies that were converted to THR, Kawasaki *et al*.[152] reported no significant differences in implant survivorship, stability, or HHS compared with a matching group of 16 hips that had only undergone a primary THR at a mean followup of 5 years. Ball, Le Duff, and Amstutz compared 21 failed hip resurfacings that were converted to a standard THR, with 64 standard THRs (both cohorts included osteonecrosis patients), and reported no differences in aseptic loosening, dislocations, HHS or complications between the two groups.[155] Issa *et al*.[158] evaluated 92 hips in 87 patients who had failed prior hip preserving surgery (35 hips that had previous resurfacing, 9 hips that had a hemi-resurfacing, 29 hips that had a nonvascularized bone-grafting, and 19 that had a CD). These patients were compared with 121 hips in 105 osteonecrosis patients who underwent THR and had no prior surgical interventions. At a mean followup of 75 months, they reported no significant differences in survivorship, clinical, and radiological outcomes among the groups.

As described earlier, patients who have sickle cell disease, Gaucher disease, or end-stage kidney failure and/or posttransplantation have been reported to be at an increased risk for revision following THA. However, even in these high-risk groups, outcomes of THR have improved over time.[142,159] Issa *et al*.[160] evaluated 42 THRs for osteonecrosis in 32 sickle cell patients who had a mean age of 37 years compared with 102 THRs in 87 nonsickle cell osteonecrosis patients who had a mean age of 43 years. At a mean followup of 7 years (3-10.5), they reported no significant differences in aseptic implant survivorship (95% vs. 97%), HHS (87 vs. 88), and SF-36 physical (43 vs. 44) or mental component scores (59 vs. 58) between the two patient cohorts respectively. Marulanda *et al*.[161] compared the outcomes of two types of peri-operative management (conservative or aggressive protocols) in three patients who had sickle cell anemia and had undergone 31 separate orthopedic surgeries for ONFH. In the conservative protocol, patients received packed red blood cells preoperatively to increase the hemoglobin level to a minimum of 10 g/dL. Fresh frozen plasma or packed

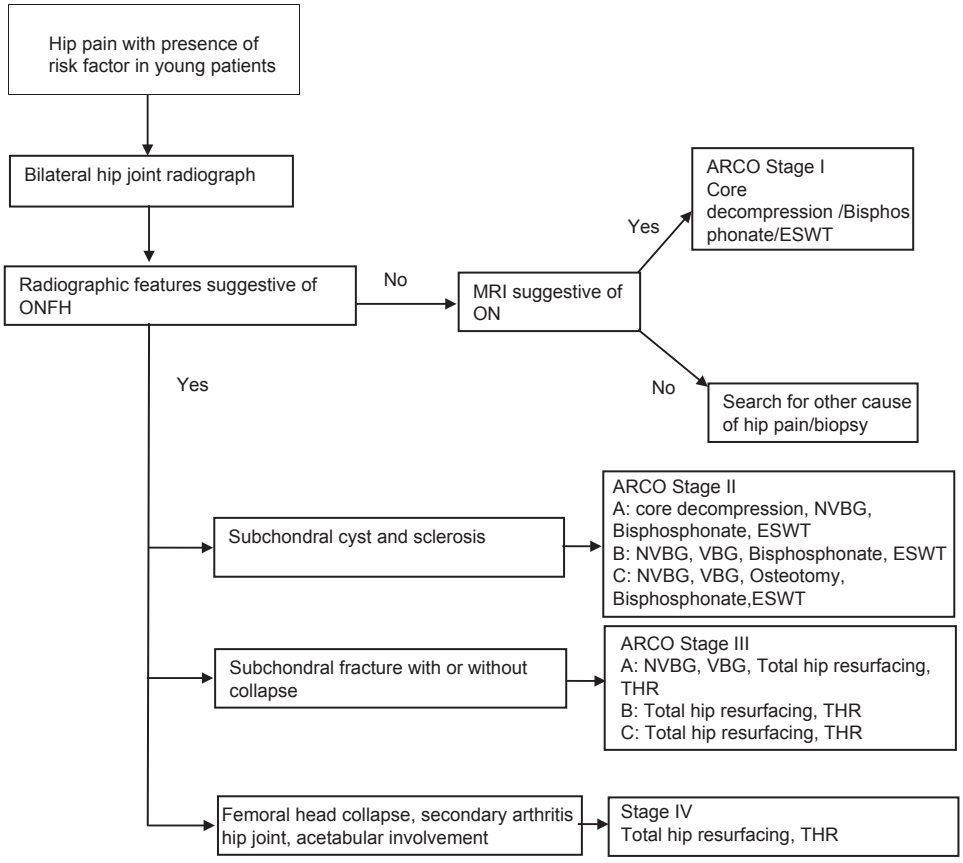

Figure 5: An algorithm of ONFH management

red blood cells were given only when excessive bleeding occurred intraoperatively. In the aggressive protocol, patients received preoperative packed red blood cells with the goal of keeping hemoglobin levels between 9 g/dL and 11 g/dL, and of lowering the hemoglobin S levels to <30%. Fresh frozen plasma was given when patients' Factor VII levels were less than 30%. They reported although both protocols were safe in managing these patients, the most aggressive protocol had resulted in lower rates of postoperative complications, transfusions, and the need to resort to supplementary oxygen.

Chang *et al*.[162] evaluated 74 hips in 52 patients who underwent THR for ONFH after kidney transplantation with cementless THRs. They reported 96.6% cumulative implant survivorship at a mean followup of 10.2 years, which is comparable with survivorship due to other causes of THR. In the light of these findings, the outcomes of THR even in these high-risk patients are improving, potentially due to improved medical and surgical management, as well as the use of modern prosthetic designs, including cementless acetabular and femoral fixation.

Conclusion

Symptomatic hip osteonecrosis is a disabling condition with poorly understood etiology and pathogenesis. Numerous treatment options for hip osteonecrosis have been described including nonoperative modalities, joint preserving procedures, and THR. Nonoperative or joint preserving treatment may improve outcomes when an early diagnosis is made before the lesion has become too large, or there is radiographic evidence of femoral head collapse. The presence of a crescent sign, femoral head flattening, and acetabular involvement indicate a more advanced-stage disease in which joint preserving options are less effective than THR. The algorithm of ONFH management as presented is an effective treatment strategy which is practically feasible and based on sound evidence [Figure 5].

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Symposium-ICL-2014

Limb salvage: When, where, and how?

Ajay Puri

Abstract

From an era where amputation was the only option to the current day function preserving resections and complex reconstructions has been a major advance in the treatment of musculoskeletal sarcomas. The objectives of extremity reconstruction after oncologic resection include providing skeletal stability where necessary, adequate wound coverage to allow early subsequent adjuvant therapy, optimising the aesthetic outcome and preservation of functional capability with early return to function. This article highlights the concepts of surgical margins in oncology, discusses the principles governing safe surgical resection in these tumors and summarises the current modalities and recent developments relevant to reconstruction after limb salvage. The rationale of choice of a particular resection modality and the unique challenges of reconstruction in skeletally immature individuals are also discussed. Striking the right balance between adequate resection, while yet retaining or reconstructing tissue for acceptable function and cosmesis is a difficult task. Complications are not uncommon and patients and their families need to be counseled regarding the potential setbacks that may occur in the course of their eventual road to recovery, Limb salvage entails a well orchestrated effort involving various specialties and better outcomes are likely to be achieved with centralization of expertise at regional centers.

Key words: Bone tumor, megaprosthesis, reconstruction
MeSH terms: Bone neoplasm, prosthesis, reconstructive surgical procedure

Introduction

The last few decades have seen rapid strides in the field of musculoskeletal oncology. Amputation no longer remains the only option to achieve local control in malignant bone and soft tissue tumors of the extremity. Function preserving alternatives in these lesions have now become the norm without compromising on overall disease survival and have resulted in a documented improvement in overall quality of life of patients compared with those with an amputation.[1] Various studies have confirmed that limb salvage is superior to amputation in preserving function.[2,3] Although certain species such as starfish or salamanders are capable of regenerating whole extremities, in humans surgeons need to rely on advances and innovations in biological and mechanical reconstruction for restoration of function after major resections for tumors.[4] The advent of better imaging modalities, more effective chemotherapy, improved radiotherapy techniques, a better understanding of anatomy with continuous refinement in surgical techniques and advances in prosthesis design and materials have all played a part in enabling this goal.

Though the number of limb salvage surgeries undertaken for malignant tumors of the extremity has increased the principles that govern surgical resection of bone and soft tissue tumors have remained unchanged. Limb salvage is recommended only if:

1. The ability to achieve adequate margins is not compromised. An adequate margin is one that would result in an acceptably low rate of local recurrence of the tumor. If the surgeon is unable to achieve adequate margins in his endeavor to salvage the limb then an amputation is preferred
2. The salvaged limb will provide function superior to that offered by a prosthetic limb after an amputation. A desensate salvaged limb with inadequate motors defeats the very purpose of limb salvage, which aims at improving the patient's quality of life.

Balancing these two opposing goals can often be a Herculean challenge, especially in patients with large tumors. Kawaguchi's concept of "barrier effects" has helped surgeons better understand evaluation of margins of resection.[5] Though conventionally quantitative parameters were used to define resection margins Kawaguchi converted anatomical

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Stem cell therapy in spinal trauma: Does it have scientific validity?

Harvinder Singh Chhabra, Kanchan Sarda

Abstract

Stem cell-based interventions aim to use special regenerative cells (stem cells) to facilitate neuronal function beyond the site of the injury. Many studies involving animal models of spinal cord injury (SCI) suggest that certain stem cell-based therapies may restore function after SCI. Currently, in case of spinal cord injuries, new discoveries with clinical implications have been continuously made in basic stem cell research, and stem cell-based approaches are advancing rapidly toward application in patients. There is a huge base of preclinical evidence *in vitro* and in animal models which suggests the safety and clinical efficacy of cellular therapies after SCI. Despite this, data from clinical studies is not very encouraging and at times confounding. Here, we have attempted to cover preclinical and clinical evidence base dealing with safety, feasibility and efficacy of cell based interventions after SCI. The limitations of preclinical data and the reasons underlying its failure to translate in a clinical setting are also discussed. Based on the evidence base, it is suggested that a multifactorial approach is required to address this situation. Need for standardized, stringently designed multi-centric clinical trials for obtaining validated proof of evidence is also highlighted.

Key words: Spinal cord injury, stem cells, neurologic recovery, clinical trials
MeSH terms: Spinal cord injury, stem cell research, clinical trial

Introduction

Spinal cord injury (SCI) is the most devastating ailment that can afflict mankind. A complete injury causes permanent loss of sensation and movement in the affected limbs and trunk, loss of bowel, bladder and sexual functions, thus causing extreme psychological stress.[1] It not only causes disability, but also has a profound impact on the social and economic prospects of the individual and the whole family.[2] The high aggregated costs of treatment and prolonged hospitalizations are an economic burden not only to the individual's family, but also to the society.

Accidents are the main cause for SCI and youth in their prime of life are the most commonly affected.[3] Till date, there is no established therapeutic intervention capable of restoring significant neurological function after SCI. With recent advances in stem cell research there has been a tremendous hope for the development of new treatments for many serious diseases amongst researchers, clinicians and the individuals suffering from such diseases. Rigorous scientific and medical evidence is a must to harness the potential of these cells to create a standard mode of therapy which may then be offered as a clinical alternative to other existing standard therapies. In the following passages, we attempt to cover the evidence base for regeneration and repair after SCI. Both preclinical and clinical studies have been critically analyzed for graft survival, axonal regeneration, safety and sensory and motor functional recovery. Finally, we discuss the necessity for multi-disciplinary approaches using combinatorial strategies to achieve robust cellular regeneration associated with neurological and functional improvement.

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Pathophysiology of the spinal cord

Spinal cord injury is caused by direct mechanical damage to the spinal cord that usually results in complete or incomplete loss of neural functions such as mobility and sensory function.[4] The nature and extent of the injury varies widely, depending on the site of injury and its severity. A primary injury refers to a mechanical trauma to the spinal cord leading to a disruption of the spinal cord tissue. SCI can result from contusion, compression, penetration or maceration of the spinal cord.[5] The most common injury mechanism is contusion of the spinal cord at the moment of injury, and the prolonged

compression caused by vertebral bony structures and soft tissues that have become dislodged.[6] During the injury process, the spinal cord might be hyper-bent, over-stretched, rotated, and lacerated,[7] but the white matter is usually spared.[8] The primary injury to the spine triggers a number of pathophysiological processes, which may lead to a prolonged secondary injury phase.[9] These pathophysiological processes are the key determinants of the final extent of neurological deficits.[4,10] The secondary phase can be divided into the immediate (≤2 h), acute (≥2-48 h), sub-acute (≤14 days) intermediate (≤6 months) and chronic stages (≥6 months) of SCI. The pathophysiological processes, which are most affected relate to three major bodily systems - the nervous system, the immune system and the vascular system.[11]

The pathophysiological changes that occur within these different phases are distinct. (1) Acute phase: Edema, ischemia, hemorrhage, reactive oxygen species production and lipid peroxidation, glutamate-mediated excitotoxicity, ionic dysregulation, blood-spinal-cord barrier permeability, inflammation, demyelination, neuronal cell death, and neurogenic shock. (2) Sub-acute phase: Macrophage infiltration, microglial activity, astrocyte activity and scar formation, and initiation of neovascularization. (3) Chronic phase: Wallerian degeneration, glial scar maturation, cyst and syrinx formation, cavity formation, and schwannosis. The end of spontaneous post-SCI changes is identified as a pathophysiological phenomenon with solid glial scar formation, syrinx formation, and neuronal apoptosis. There is retraction and demyelination of spared axons, which may induce permanent loss of sensorimotor functions that is unresponsive to treatment.[12] To select the best time-point for therapeutic cell transplantation, an understanding of the timeline of secondary damage cascades is important.[13]

The persistence of secondary injury mechanisms leads to further neuronal cell death and the interruption of the descending and ascending axonal tracts culminating in glial scarring. The scar forms a hostile environment for axon regeneration due to secretion of molecular inhibitors of axon growth as well as physical impenetrability.[14] The intrinsic capacity for regrowth of CNS axons over long distances if provided permissive environment suggests that the failure of CNS neurons to regenerate is due to the defects lying in the environment rather than within the CNS neurons.[15] A multitude of regenerative (cell growth and survival) as well as nonregenerative (physical and biochemical) events need to function in tandem to restore functionality of the neuron.[16]

Targets for repair

Based on the pathophysiology of SCI, several targets for intervention have been proposed to minimize damage and promote repair and regeneration.[14,16] The same are summarized in Figure 1. Based on these targets several physicochemical and cellular strategies have been employed at preclinical and/or clinical level to evaluate their safety and efficacy [Figure 2].

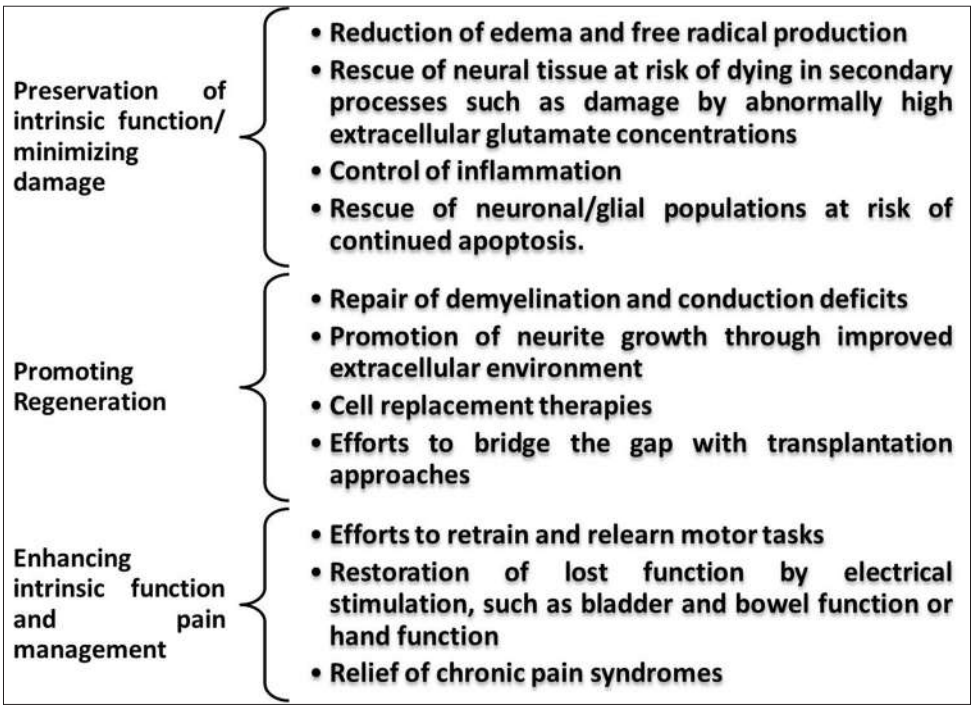

Figure 1: Schematic diagram showing targets for Intervention after spinal cord injury (SCI): Potential targets for repair and regeneration after SCI are listed in the left pane and the proposed approaches to achieve these targets are listed in their right

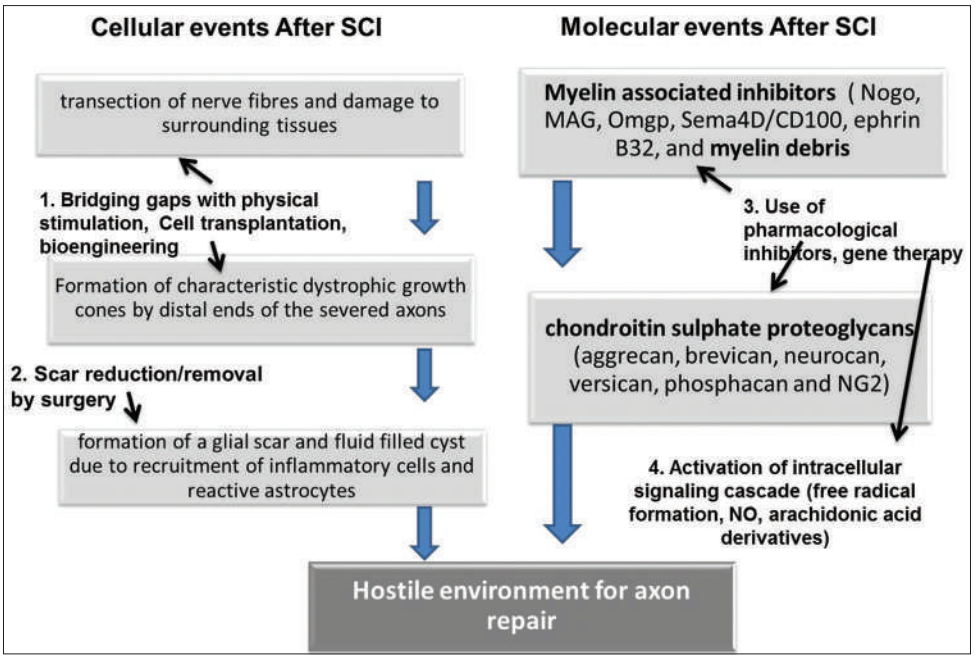

Figure 2: Strategies to promote regeneration after spinal cord injury (SCI). The cellular and molecular events which result in the creation of a hostile environment for axon repair following SCI are delineated. The strategies (1–4) employed to promote neuronal repair and regeneration by providing a permissive environment along with the level at which they act

In order to promote functional recovery, stem cell transplantation must suppress the inflammatory response, inhibit neuronal apoptosis and necrosis, enhance neuronal regeneration, and promote axon regeneration and remyelination.[17]

Materials and Methods

We searched MEDLINE for the search term "(stem cell OR stem OR hematopoietic OR mesenchymal) AND (SCI OR hemisection OR contusion injury OR dorsal column injury OR complete transection OR corticospinal tract injury) from 1st January 2000 to 28th February 2014. Our initial search retrieved 2076 articles, of these 1494 were animal studies, and 981 were human studies. If required, recovered papers were reviewed for further relevant references. Further cross-referencing was undertaken with EMBASE, Cochrane Library, ongoing trials databases and Google and Google Scholar to corroborate findings and resolve discrepancies, if any.

Preclinical evidence

Cell transplantation after SCI may promote neuronal regeneration and function by (1) Secreting neurotrophic molecules at the lesion site; (2) acting as a scaffold for axonal regeneration; (3) replacing the lost/damaged cells.[18]

A number of cell populations have been tested for their safety and efficacy after SCI. These include

- Embryonic cells
- Umbilical cord cells
- Mesenchymal cells
- Hematopoietic cells
- Olfactory ensheathing glial cells
- Progenitor cells
- Schwann cells (SCs)
- Induced pluripotent stem cells (iPSCs).

A large volume of preclinical evidence exists indicating the efficacy of cell transplantation in case of animal models of SCI and is discussed below.

Embryonic stem cells

Embryonic stem cells (ESCs) are pluripotent stem cells derived from the inner cell mass of the early embryo.[19] They can replicate indefinitely and differentiate into all three germ layers and generate all cell types of the body. ESCs were the first population of cells tested for its regenerative potential. The cells could differentiate into neuronal cell types both *in vitro* and *in vivo* in animal models. However, due to their capability to differentiate into all cell types they were found to be tumorigenic.[20] In recent times, instead of direct transplantation, derivatives of these cells have been used to analyze their potential for neuronal regeneration. Several groups have derived neural progenitor/stem cells, motor neurons, oligodendrocyte progenitor cells, and olfactory ensheathing cells (OECs) from ESCs *in vitro*, and then transplanted these cells into various animal models to study restoration of neural function. The transplanted population in these cases have a restricted potential to

differentiate and are generally progenitor cell populations derived from the pluripotent ESC. The use of such restricted population thus reduces the risk of tumorigenesis. Such stem cell-derived neuronal progenitor cells (NPCs) are hailed to be a promising population for neuronal repair. Such NPCs may possess variable characteristics depending on how they were derived.

Kumagai *et al*.[21] generated two primary and secondary neurospheres from the ESCs and demonstrated that only the secondary neurospheres were effective in promoting functional recovery in the rodent sub-acute SCI model. This functional recovery was attributed to paracrine secretion from the transplanted gliogenic neurospheres rather than direct cell replacement. Other populations derived from ESCs include motor neurons,[22] neural stem cells (NSC),[23] NPCs, [24] GABAergic neurons,[25] oligodendrocyte progenitor cell (OPC) populations.[26] These populations have demonstrated various degrees of functional restoration in animal models. Table 1 describes in brief the cell populations derived and their effect upon transplantation in animal models.

Due to the efficacy of neuronal regeneration and neuronal function promotion by the ESC derived NSCs, a variety of engineered ESC-NSC populations have been developed for SCI by several groups. These include, ESC-NSC expressing neural cell adhesion molecule L1.[31] Transplantation of L1-overexpressing substrate adherent ESC-derived neural aggregates into a mouse SCI model resulted in an increased number of surviving cells, enhanced neuronal differentiation, reduced glial differentiation, and increased tyrosine hydroxylase expression as compared to wild type cell aggregates.[32]

Similarly, engineered cell population expressing neurogenins, a family of a basic helix-loop-helix transcription factors involved in specifying neuronal differentiation, have been reported by several groups. Perrin *et al*. and Shapiro *et al*. utilized Neurogenin-2 expressing ESC-derived NPCs and reported full restoration of weight support and significant improvement of functional motor recovery in rats after severe spinal cord compression injury. Partial restoration of serotonin 5HT1A receptor expression, which plays a major role in locomotion and is particularly affected after SCI, was also observed.[33,34]

Successful differentiation of human ESC-derived NPCs (hESC-NPCs) with collagen scaffolds into neurons and glia was observed in the hemisection rat model.[24] The transplanted cells also promoted hindlimb locomotor recovery and sensory responses with observed migration of transplanted stem cells toward the lesion site.[24] Niapour *et al*. reported that co-transplantation of hESC-NPCs and SCs resulted in significant motor function recovery as compared to control and single transplantation groups.[35] This study suggested that the co-transplantation might be a feasible strategy to enhance neuronal differentiation and suppress glial differentiation and thus promote functional recovery.

Table 1: Cell population derived from ESCs and their effect upon transplantation in animal models

Cell population derived	Animal model	Effect upon transplantation	References
Primary and secondary neurospheres	Rat subacute SCI model	Axonal growth promotion, remyelination, angiogenesis, and significant locomotor functional recovery by secondary neurospheres only	21
Motor neurons derived from a co-culture of endothelial cells and ESCs treated with retinoic acid and sonic hedgehog	Adult mouse SCI model	Significant recovery of sensory and motor function	22
Longterm self-renewing rosette-type neural stem cells	Mouse SCI model	Enhanced remyelination and axonal regeneration and survival of endogenous neurons	27
ESC-derived motor neuron progenitors	Adult rat SCI model	Enhanced sprouting of endogenous serotonergic (5-HT) projections, enhanced survival of endogenous neurons, enhanced gross tissue sparing, and decreased phosphorylation of stress-associated protein kinase which can result in apoptosis, immune activation, and inflammation	28
ESC - derived GABAergic neurons	Hemisection rat model	Significant reversal of decreased PWTs after intrathecal transplantation	25
ESC-derived oligodendrocyte progenitor cells	Rat contusion SCI model	Improved axon remyelination and motor function	26
ESC-derived oligodendrocyte progenitor cells	Contusion SCI model in rats during the acute phase after injury	Survival, migration and integration into the spinal cord tissue	29
ESC-derived oligodendrocyte progenitor cells	Cervical contusion rat model	Significantly improved forelimb stride length and a reduced demyelination and more oligodendrocyte remyelinated axons than Schwann cell remyelinated ones in transplanted group	30

ESCs=Embryonic stem cells, SCI=Spinal cord injury, 5-HT=5-hydroxytryptamine, PWTs=Paw withdrawal thresholds

Embryonic Stem Cell-derived populations have been utilized for combinatorial strategies also. Combination of motor neuron progenitors along with ESC-OPCs in a complete transection SCI rat model[36] resulted in significantly better BBB scores with significantly higher amplitude of motor evoked potential (MEP) in electrophysiological evaluation as compared to individual populations. Salehi *et al*., in another combinatorial study, transplanted OECs and ESC - derived motoneurons into contused SCI rats.[37] They reported significantly better regeneration and functional restoration as compared to that observed when individual populations were transplanted. Illes *et al*. have reported the presence of intrinsically active neurons (IANs) in neuronal populations derived from mouse ESCs. They proposed that presence of such IAN populations in cell grafts may be a prerequisite to attain functional activity following interventions involving transplantation of neural tissues.[38] Lee TH has reported a substantial improvement of motor function due to transplantation of mouse ESCs in a rat model of clip-compression SCI.[39]

Induced pluripotent stem cells

Although ESCs possess great potential due to their ability to differentiate into all cell types that are useful for therapeutic purposes, such as transplantation, they raise significant ethical concern as most of the ESCs arise from human embryos. Recent discovery that somatic cells can be reprogrammed to a pluripotent state may be used to circumvent these concerns. The reprogrammed cells called iPSCs, exhibit functional similarities to ESCs and present an exciting area of research.

These cells have been used to derive cell populations equivalent to those derived by ESCs and tested in case of SCI.

Like ESCs, long term self-renewing rosette-type NSC population has been derived from iPSC (lt-iPSC-NSCs).[23] This population possesses stable neuronal and glial differentiation ability and capacity of generating functional mature neurons *in vitro*. [23] Upon transplantation into the mouse SCI model, enhanced remyelination and axonal regeneration along with survival of endogenous neurons was observed.[27] iPSC derived GABAgeric neurons have been tested in the hemisection rat model and were found to significantly reverse decreased paw withdrawal thresholds.[25] This indicates that this may be a potential solution for the loss of sensory function after SCI.

In a recent study, Sareen *et al*. have reported survival, migration and integration of human neural progenitor cells generated from iPSCs in nude rats. The authors have proposed that the iPSC derived NPC may be an alternative to human fetal tissue derived NPCs.[40]

Mesenchymal stem cells (MSCs)

Mesenchymal stem cells are stromal cells that have the ability to self-renew and also exhibit multilineage differentiation. This self-renewing, multipotent stem cell population was initially identified from the bone marrow (BM). According to the statement of International Society for Cellular Therapy, the definition of multipotent MSCs must (1) Adhere to plastic when cultured in standard conditions; (2) they must express CD105, CD73, and CD90, and lack the expression of CD45, CD34, CD14, or CD11b, CD79a, or CD19 and HLA-DR surface molecules; and (3) they must be able to differentiate to osteoblasts, adipocytes and chondroblasts *in vitro*. MSCs have been reported to differentiate into osteoblasts, chondrocytes, adipocytes, neural cells and myoblasts, *in vitro*.[41,42] Due to their multipotent nature, source availability and comparative safety, these cells have been advocated as a promising cell source for repair. MSCs have been reported to evince spontaneous neuronal differentiation when implanted into both irradiated mice[43,44] and humans.[45] Furthermore, allogeneic MSCs were reported to be well tolerated after intradermal injection in horses.[46,47] Mezey *et al*.[44] and Brazelton *et al*.[43] infused BM cells intraperitoneally in rats and have reported neuronal differentiation in the brain of host animals.

Transplantation of MSCs in SCI animal models has been reported to promote sensorimotor function recovery and bladder function recovery via neural lineage differentiation, neurotrophic paracrine effects and posttrauma inflammation regulation.[48-50] Abrams *et al*. observed that the injury-induced sensitivity to mechanical stimuli was significantly attenuated upon MSC injection in contusion SCI rats.[51] They also reported improvement of locomotor function in SCI rats after transplantation of MSCs.

The major limitations in the therapeutic *in vivo* application of MSCs for SCI is their low survival rate after graft, the lack of neural differentiation, glial scar formation, cystic cavity formation, the inhibitory cellular environment and the transplantation time-point.[48,52,53]

Furthermore, significant effects on the outcome are observed depending upon the route of transplantation of MSCs. Intravenous (IV) transplantation of MSCs was reported to result in significantly better BBB motor score as compared to intralesional transplantation in SCI rats.[54] Similarly, IV cell administration in severe contusive SCI rats in acute and sub-acute phase resulted in significant locomotor recovery.[55] Intrathecal co-administration of NPCs and MSCs did not lead to any migration to the injury site.[56]

Implantation of MSCs into the spinal cord or lesion site has not been reported to promote neuronal

differentiation.[52] However, Boido *et al*. have reported, significantly reduced lesion volume and improved hindlimb sensorimotor functions after transplantation of mouse MSCs into the lesion cavity of compression SCI mouse model.[53] Similar results have been reported by Gu *et al*. after transplantation of BM MSCs into the epicenter of the injured spinal cord of rats [54] In such cases, it is hypothesized that the engrafted MSCs may generate a favorable environment for functional recovery through modulating the post-SCI inflammatory response and by having neurotrophic paracrine activity.[53] The therapeutic effects of MSC transplantation on the sensorimotor deficits in animal SCI models have been clearly confirmed by a large number of studies.[52-54,57]

In order to overcome the limitations of direct MSC transplantation, several strategies have been employed that include pretransplantation neural differentiation, neurotrophic gene transduction, glial cell co-transplantation, and tissue engineering.[51,53,56,58] Rostral and caudal injection of neural modified human bone-marrow derived MSCs to the T-8 lesion immediately after SCI in the rat model resulted in significantly improved locomotor function.[15,58-65] Transplantation of neurally differentiated rat MSCs (NMSCs) into the epicenter of a contusive lesion resulted in the recovery of motor function as well as significantly shortened initial latency, N1 latency and P1 latency of the SSEPs.[58,66] Co-transplantation of autologous neural differentiated and undifferentiated MSCs in the contusion lesion cavity at T8–T9 level of rats' spinal cord reported a significantly higher BBB score as compared to controls.[59]

Genetically modified MScs have been also been tested in some *in vivo* studies. Populations tested include MSCs over expressing basic fibroblast growth factor (bFGF),[60] and Neurotrophin-3 (NT-3) gene.[61]

Song *et al*. have demonstrated improvement of hind limbs' motor function after allograft of bone MSCs in rats with acute injury to their spinal nerve.[67] In another study, Yin *et al*. have reported the antiapoptotic effect of MSC transplantation in adult rats after spinal cord ischemia-reperfusion injury. This suggests that MSCs may affect cell regeneration and repair through control of apoptosis following SCI.[68]

One of the major barriers to spinal cord regeneration is the glial scar, which hampers the movement of regenerating cells and does not support the survival of implanted cells and their neural differentiation. Biological scaffolds are now gaining importance for providing substratum as well as neurotropins to aid cell survival, differentiation and proliferation. Platelet-rich plasma scaffolds in combination with BDNF have been shown to support survival and neural differentiation of human MSCs.[69] Gelatin sponge (GS) scaffold system, which was constructed by ensheathing GS with a thin film of poly-(lactide-co-glycolide) (PLGA), also has been reported to support rat MSC adherence, survival and proliferation *in vitro*, and in the rat SCI model, the seeded scaffolds were shown to attenuate inflammation, promote angiogenesis, and reduce cavity formation.[15] Other scaffolds and cell combinations tested include PLGA scaffolds system and human MSCs,[62] a combination of Matrigel and neural-induced adipose-derived MSCs (NMSCs).[70] In recent times, the use of fibrin scaffold along with MSC injection has been reported to result in the formation of longitudinally-aligned layers of MSCs growing over the spinal cord lesion site. This was associated with migration of host neurites into the MSC architecture. Such a strategy provides control over cell integration into the tissue after intraspinal injections hence enhancing localization of the cell graft.[71]

Sources of MSCs other than BM have also been identified by researchers, such as, adipose tissue,[73] amniotic fluid,[76] placenta,[72,73] umbilical cord blood (UCB),[74,75] and in several fetal tissues including liver, lung, and spleen.[76] Of these the MSCs from UCB and adipose tissue are sources choice with many advantages such as ease of collection, availability and proliferative capacity.

Neural stem/progenitor cells

Neural stem/progenitor cells (NS/PCs) were first demonstrated in the subventricular zone of the mouse in 1989[77] and were isolated from the mouse striatal tissue and subventricular zone for the first time in 1992.[78] These cells were capable of self-renewal and generating the main phenotypes (neurons, astrocytes, and oligodendrocytes) of CNS cells *in vitro* and *in vivo*.[79] After transplantation into the injured spinal cord, NS/PCs generate mature neural phenotypes and provide neural functional recovery in some SCI models.[80]

Neural stem/progenitor cells have been transplanted *in vivo* for studying their therapeutic potential after SCI. In most cases, *in vivo* transplanted NSCs have shown a preferential capability of differentiating into glial lineages, especially astrocytes.[80] The direct transplantation of NSCs or NPCs has not been always efficient for functional recovery after SCI. Transplantation of fetal NPCs, derived from fetal rats, into the dorsal column lesion site of adult rats, resulted in only a minor sensory function improvement with no restoration of the motor function recovery.[81] Pretreatment of human NSCs with bFGF, heparin, and laminin before transplantation into the contusion lesion of rats led to an optimized survival rate, neuronal and oligodendroglia differentiation, and improved trunk stability.[82] Tarasenko *et al*.[5] reported that the spinal cord microenvironment can probably change the differentiating fate of grafted NSCs. Transplantation

of NS/PCs obtained from myelin-deficient shiverer mutant mice (shi-NS/PC) into the lesion site of rats demonstrated that the remyelination capability of wt-NS/PCs was vital to motor and electrophysiological functional recovery.[83] Transplantation of the Olig2 expressing NSC into the contused spinal cord has been reported to increase the volume of spared white matter and reduce the cavity volume. This was associated with thickened myelin sheath which may be due to differentiation of NSCs into oligodendrocytes.[84]

Injection of a combination of NSCs and OECs into the spinal cord lesion of rats has been reported to lead to hindlimb locomotor functional recovery.[85] Salazar *et al*. have reported a significant improvement in locomotor recovery in early chronic SCI mouse model after NSC transplantation.[86] They have also demonstrated that the transplanted NSCs differentiated into oligodendrocytes and neurons and that astrocytic differentiation was rare. The authors also reported the integration of transplanted human NSCs with host cells. Emgard *et al*. have reported a neuroprotective effect of human spinal cord derived neural precursor cells in two different rat models of SCI.[87] In a recent study, Nemati *et al*. transplanted adult monkey NSCs into a contusion model of SCI in the rhesus monkey and reported homing of MSCs to the lesion and improved hindlimb performance.[88]

Olfactory ensheathing cells

Olfactory ensheathing cells permit growing axons from neurons of the nasal cavity olfactory mucosa to re-enter the olfactory bulb (OB) of the brain and form synapses with second-order neurons.[87] These cells are present in the olfactory epithelium and are considered as a special class of glial cells which exist in both the peripheral nerve system (PNS) and CNS, and share certain features and functions with astrocytes as well as SCs.[89] By virtue of their cell-specific properties, OECs are more likely to rescue neural function in the injured spinal cord as compared with SCs.

Recent studies have shown that rodent OECs can support axonal regrowth when transplanted into experimental models of SCI[90] and are also able to form myelin sheaths around regenerated or demyelinated axons, thereby permitting rapid saltatory conduction to occur.[90,91] It has therefore been proposed that OECs may be suitable cells for transplant-mediated repair of spinal cord trauma or nonrepairing foci of demyelination (such as may occur in chronic multiple sclerosis). These data indicate that transplanted OECs have a repair repertoire that is similar to that of SCs, but may have advantages over these because of their ability to migrate and integrate within areas of astrocytosis that are characteristic of damaged CNS.[92,93]

Following transplantation into a localized electrolytic lesion of the corticospinal tract in adult rats, OECs supported unbranched, regenerative growth of corticospinal axons and restoration of a corticospinal-dependent paw-reaching function.[90] OECs promoted regeneration after complete transection of the spinal cord[94] and restored rapid and secure conduction across the transected dorsal columns of the rat spinal cord[95]with recovery of motor function.[96] Human OECs were also shown to remyelinate the demyelinated spinal cord of the rat.[95] Other groups have shed doubt on the functional improvements induced by OECs grafts, and have suggested that they are caused by a trophic support mechanism and not the birth of new neurons, which means that the therapeutic potential of OECs after SCI may be limited.[93,97] Centenaro *et al*.[99] and Aoki *et al*.[100] in their olfactory tissue transplantation studies suggest that OECs may be of limited use in promoting recovery after SCI.

The disparity in the results reported by different groups may be attributed to the cell population used, donor, injury models, graft preparation, time of transplantation and the transplantation procedure.[101-104]

To address the issue of the time of transplantation or "transplantation window", Muñoz-Quiles *et al*.[104] compared the motor function recovery after OB derived OEC (OB-OEC) transplantation into completed transection injured rats among sub-acute chronic and nontreatment groups. They reported a 10% higher percentage of recovery in sub-acute transplantation group than the chronic group with motor axons growing beyond into the lesion site, indicating a rostral to caudal the lesion site crossing phenomenon.[104] Based on these finding Li and Lepski in their review, proposed that sub-acute or chronic cellular transplantation to bypass the acute phase after spinal trauma combined with scar ablation may be a potentially effective strategy to achieve regeneration and/or repair after SCI.[105]

Another factor that determines the survival and fate of the transplanted tissue is *in vitro* culture conditions. OECs with longer preculture times were found to be less effective as compared to those with shorter preculture times.[106]

Although the application of OECs for regeneration after SCI has been questioned, several studies support the potential of OECs to be protective/regenerative in nature.[107] OECs have been combined with cAMP treatment[108-111] and laser puncture,[112] genetically modified for NT-3 production, and co-transplanted with other cell types[113] in order to boost the efficacy of OEC transplantation. Although most of such combinations have resulted in better efficacy as compared to OECs alone, a few have failed to do so. Co-transplantation of OECs with MSCs did not lead to any significant

synergistic effects on neural function improvement as compared to OEC alone.[36,114,115]

Schwann cells

Schwann cells were discovered by Theodor Schwann in 1839 and were found to provide myelination of peripheral axons. Schwann cell precursors (SCP) were found in developing stem cells within neural crest. When connected to nervous fibers, SCs or precursors lead to myelination of peripheral axons.[114] In the human and large animals, SCI leads to the formation of a cavity and a glial scar. Due to this, the ends of the regenerating axons at the edge of the scar become dysmorphic and cannot progress further leading to termination of axon regrowth.[116] It has been demonstrated that after SCI, if these injured neurons are grafted into a peripheral neural environment, which facilitates growth and remyelination, they can recover their morphology and electrophysiological function.[117] SCs are an important part of the PNS and are vital for the myelination of peripheral axons. Park *et al*. have reported that transplantation of SCs into a demyelinated spinal cord slice, *in vitro*, promotes survival and secretion of neurotrophic factors which may aid intrinsic neuronal regeneration.[118] SC transplantation has also been reported to lead to remyelination of demyelinated axons and axonal sprouting.[119]

In the past studies, SCs used were isolated from peripheral nerves and cultured *in vitro* to provide enough number of cells for the transplantation. In recent times, alternate sources for SCs have been used. The SCs have been derived from different stem cell populations or neural progenitors like, MSCs[120,121] adipose-derived stem cells,[120] and skin-derived precursors (SKPs).[122] Mesenchymal stem cell-derived SCs were tested by Park *et al*. and Xu *et al*. *in vitro* and were found to support axon remyelination and sprouting.[118,121] Biernaskie *et al*. derived SCs from SKPs which were isolated from the rodent or human skin.[122] Upon transplantation of these SKP-SCs in the murine contused model lesion site bridging effect, increased size of spared tissue, and reduced reactive gliosis was observed which was better in the SKP-SC group as compared to control and SKP only.[121] In addition, significant enhancement of locomotor recovery was observed although there was no restoration of sensory function. Therapeutic potential of SCP in an acute SCI model was tested by Agudo *et al*.[123] They reported a successful integration of the graft into the host tissue, and a robust bridging effect which extended rostrocaudally due to immediate cell injection into the lesion site after surgery.[122] However, no significant difference in motor function was observed between the SCP and control group.

Similar to other cell types, SCs have also been genetically modified and tested. SCs overexpressing chondroitin sulfate proteoglycans have been reported to suppress the expression of glial fibrillary acidic protein and chondroitin sulfate proteoglycan in reactive astrocytes, induce robust migration of astrocytes extending in parallel to the regenerated axons and remyelinate the axons.[1,124] Co-transplantation strategies and use of scaffolds and matrices have revealed that Matrigel and biodegradable scaffolds could promote cell survival and/or axon regeneration; however, functional activity was not significantly enhanced.[125] Co-transplantation of SC and MSC was found to be a promising strategy to enhance cell survival, axon regeneration and functional activity.[126] However, co-treatment of SC with cAMP enhancer and cAMP analog did not exhibit enhanced locomotor function as was reported previously. This could be attributed to experimental group arrangements, consistency of injury severity, appropriated statistics, and animal surgery.[18,30,127,128] Kanno *et al*. have reported improved axonal regeneration and motor function following transplantation of SCs which were genetically modified to secrete neurotrophin in combination with chondroitinase.[129]

Clinical evidence

Based on the vast body of preclinical evidence, scientists and clinicians have been eager to explore the therapeutic effects of cell transplantation on spinal cord patients. Various cell types, different administration strategies, and different kinds of SCI patients have been involved in clinical trials or therapeutic settings. A plethora of patient testimonials and case studies have reported the clinical safety and efficacy of cell transplantation after SCI. However, there is a paucity of data from valid clinical trials. The data from such validated trials report several obstacles that are inherent to human studies including ethical issues differences in anatomy, and differences in underlying pathophysiological processes. Until now, no promising cell therapies that are safe and effective for SCI patients have been achieved.

Bone marrow transplantation for SCI has been the focus of attention in the last few years. There have been extensive preclinical studies which have demonstrated their potential role. Transplanted BMCs were found to improve neurological deficit in CNS injuries model by generating neural cells or myelin-producing cells[92,128] BMCs have been transplanted by direct injection into the injured spinal cord,[129,130] IV injection,[131] intrathecal injection[131] or injection into the spinal artery.[132]

The uses of BMCs for stem cell therapy in SCI subjects has more advantages compared with ESC use and therefore are more widely used. BM stem cell-based therapy is not associated with carcinogenesis, which sometimes occurs in ESC therapy,[134] Immunological rejection or graft-versus-host reactions, caused by allograft,[133] and extensive scientific

data on BMCs has been accumulated from wide-ranging experiences in BM transplantation for hematological diseases.

Moreover, several hypotheses have been proposed to explain the role of BM stem cells in SCI models. First, BMCs improve neurologic deficit by generating either neural cells or myelin-producing cells.[128,135] Second, transplanted BMCs do not differentiate into neurons; rather, they work by guiding axonal regeneration by producing extracellular matrix. Third, transplanted BMCs promote compensatory mechanisms to reorganize neural network, and activate endogenous stem cells.[136] The studies have been summarized in Table 2.

Preclinical studies suggest behavioral efficacy due transplantation of human UCB cells and suggest that benefits may come from secretion of factors by transplanted cells,[53] however, only a few small "open label" human studies have been conducted with varying claims of benefit. Currently, a planned SCI trial by China SCI network is being conducted (ClinicalTrials.gov Identifier: NCT01046786).

The potential use of ESCs and iPSCs in clinical applications has vastly interested both researchers and clinicians. This has also has gained the attention of media. However, several issues remain to be addressed regarding their safety and efficacy.[153-156] One of the most widely publicized trials has been the hESC OPCs, GRNOPC1, within patients who were suffering from complete thoracic level paraplegia with the loss of motor and sensory function.[157,158] To date, there are no serious adverse events in the long term followup reported, however, in November 2011, Geron announced that it had ended its SCI stem cell research program largely due to financial reasons. Though the concept of using ESC or iPSC derived cells for regeneration and repair is very tempting due to reasons of ease of availability and low immunological risks, still a vast body of preclinical evidence is needed before the therapeutic potential of these cells may be tested in a clinical setting.

Human trials published so far have had various flaws in design and documentation. Initiatives of various associations in educating clinicians as well as individuals regarding cellular therapies and clinical trial design in case of SCI go a long way in promoting moral, ethical and scientifically validated use of cellular interventions.[159-163]

A stem cell clinical trial in SCI needs to address several open ended questions with respect to cell population (ESC derived progenitors, MSCs, OECs, etc.), cell dosage (number of cells and number of interventions), subject selection (acute vs. chronic, level of injury) and outcome measures. In our experience, we have not been able to duplicate the efficacy to stem cell interventions in case of chronic[149] as well as acute SCI (unpublished results). The current proof of evidence points in the direction of undertaking trials which include other repair strategies such as predifferentiation, scaffolds, growth factors, etc., along with cell transplantation to achieve repair and regeneration post-SCI. Transplanting partially differentiated "progenitor cell" populations may be more effective than the pluripotent or multipotent populations. Disparity in preclinical evidence data versus clinical evidence.

Despite huge base of preclinical evidence in support of restoration of neuronal function through cellular interventions, the clinical evidence has not been that encouraging. There still remains a huge gap between the "bench" and the "bedside" which remains to be bridged. The factors which contribute to this are:

- Difference in the injuries between the animal models and human SCI
- Choice of the animal model
- Cell population used
- Patient selection criteria
- Spontaneous recovery confounding interpretation of results
- Poor trial design
- Lack of standardized outcome measures in a clinical trial.

Conclusion

The list of experimental therapies that have been developed in animal models to improve functional outcomes after SCI is extensive. There is a vast body of preclinical evidence which supports the therapeutic potential of cell transplant in facilitating spinal cord regeneration and/or repair after SCI. However, preclinical studies have their inherent limitations dependent upon the mechanism of injury and the animal model used. Recent publications on the mechanisms involved in repair and regeneration post-SCI provide valuable insights regarding the potential barriers to regeneration after SCI. These need to be addressed by scientists and clinicians to define new strategies for achieving repair. Basic scientific research should be directed toward providing a rational basis for tailoring specific combinations of clinical therapies to different types of SCI. Functional regeneration should be the primary goal of any approach being tested, and it is important that this is tested by scientifically validated and universally accepted outcome measures and tools. Due to the involvement of multiple cell type and the complexity of SCI, it is becoming increasingly clear that a single approach may not be successful in achieving SCI repair.

Table 2: Summary of published clinical trials on cellular therapy for SCI

Study	Study type	Study population	Cell population	Route of administration	Result	Limitation
Ichim *et al.*[139]	Case report	A 29-year-old and ASIA scale type A classified patient	MSC+CD34 cells	Multiple intrathecal and IV injections	Significant improvements in sensory function and lower limbs muscle strength recovery	Insufficient evidence in the study to support that the recovery was due to cell graft and not spontaneous
Kishk *et al.*[140]	Case controlled	Chronic complete SCI patients	MSCs	Monthly intrathecal administration	No significant improvements over the controls	Not a randomized controlled trial
Bhanot *et al.*[141]	Case report	Chronic SCI patients	Autologous MSCs	At the site of injury after a laminectomy	Equivocal results	Insufficient evidence and poor trial design
Park *et al.*[142]		Six complete acute SCI subjects	Autologous bone marrow cell transplantation in conjunction with administration of granulocyte macrophage-colony stimulating factor		5 subjects showed improvement in AIS grades with no serious complications. Authors conclude procedure to be safe	
Karamouzian *et al.*[143]	Nonrandomized controlled clinical trial	Eleven SCI patients with complete thoracic injuries	Autologous MSCs	Lumbar puncture	No significant improvements over the controls	
Syková *et al.*[144]		20 subjects with complete SCI	Unmanipulated autologous bone marrow	Intraarterial application	Suggested that transplantation within a therapeutic window of 3-4 weeks following injury would play an important role in any type of stem cell SCI treatment	
Yoon *et al.*[145]	Phase I/II open-label and nonrandomized study on 35 complete SCI subjects		Autologous bone marrow cell transplantation in conjunction with the administration of granulocyte macrophage-colony stimulating factor		Acute and sub -acute groups respond better than chronic SCI groups	
Jarocha *et al.*[146]	Preliminary study	Children with chronic SCI			Safety and feasibility of transplantation of autologous bone marrow mononuclear cells	Though the authors claim to a certain degree of neurological improvement due to the cell transplant, this evidence base provided is inconclusive
Huang *et al.*[147]	Prospective clinical study	16 subjects with chronic SCI	Fetal olfactory ensheathing cells		Feasible and safe	No efficacy studied
Lima *et al.*[148]	Pilot clinical study	AIS A subjects 6 months to 6.5-year post injury	Olfactory mucosa autografts	Transplanted into lesions after a myelotomy and scar removal	Feasible, relatively safe and potentially beneficial	Efficacy of the reported procedure could not be replicated in human chronic thoracic SCI
Chhabra *et al.*[149]	Single-blind, controlled pilot study Phase I/IIa	6 AIS A subjects	Olfactory mucosa autografts	Transplanted into lesions after a myelotomy and scar removal	Feasible and is safe up to 1-year post-implantation. No efficacy reported	Small number of trial patients

contd...

Table 2: *Contd...*

Study	Study type	Study population	Cell population	Route of administration	Result	Limitation
Mackay-Sim *et al.*[150]	Single-blind, controlled, Phase I clinical trial	3 AIS A subjects	Olfactory mucosa autografts	Cultured and purified olfactory ensheathing cells from nasal biopsies injected into the spinal cord lesion	Feasible and is safe up to 1-year postimplantation	Small number of trial patients
Lammertse *et al.*[151]	Randomized controlled trial with single-blinded primary outcome assessment	43 participants (26 treatment, 17 control)	Activated macrophages	Injection into the caudal boundary of the SCI	No significant improvement over the control group	
Zhou *et al.*[152]	Case report	6 subjects	Autologous activated Schwann cells	Laminectomy and cell transplantation	Reported recovery	More replicable pre-clinical data, preferably in large animals, is needed before undertaking further clinical studies using the SC population
Saberi *et al.*[153]	A 2-year followup for the safety assessment	4 subjects with chronic SCI	Schwann cells		Suggest the safety of clinical trials for SC therapy	Poor subject selection criteria and post assessments. Transient paresthesia or increased muscle spasm has been reported following transplantation of purified SCs in patients with chronic SCI (28-80 months posttrauma)
Amr *et al.*[154]	Case series of 14 patients	Chronic SCI	Co-transplantation of bone marrow derived MSCs with chitosan-laminin scaffold and peripheral nerve grafts after chronic SCI	Stem cells injected into the whole construct of cord defect and contained using a chitosan-laminin paste	Sensory and neurological improvements	Randomized controlled studies needed to validate data

SCI=Spinal cord injury, MSCs=Mesenchymal stem cells

In the current scenario, the need for multi-disciplinary involvement is essential as a single approach to achieve functionally effective axonal regrowth and sprouting may be ineffective due to the complex nature of SCI and the number of cell populations involved. A multi-factorial approach involving cell populations, scaffolding matrix, growth factor supplementation and scar removal is required to address this situation. Along with this, multi-centric studies involving standardized and validated approach, a stringent trial design with appropriate outcome measures and rehabilitation protocol are a must to understand and achieve the potential of cellular therapy in case of SCI. A clinical trial program with appropriate clinical trial design and ethical conduct is key for achieving this goal.

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Management of thoracolumbar spine trauma
An overview

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Abstract

Thoracolumbar spine fractures are common injuries that can result in significant disability, deformity and neurological deficit. Controversies exist regarding the appropriate radiological investigations, the indications for surgical management and the timing, approach and type of surgery. This review provides an overview of the epidemiology, biomechanical principles, radiological and clinical evaluation, classification and management principles. Literature review of all relevant articles published in PubMed covering thoracolumbar spine fractures with or without neurologic deficit was performed. The search terms used were thoracolumbar, thoracic, lumbar, fracture, trauma and management. All relevant articles and abstracts covering thoracolumbar spine fractures with and without neurologic deficit were reviewed. Biomechanically the thoracolumbar spine is predisposed to a higher incidence of spinal injuries. Computed tomography provides adequate bony detail for assessing spinal stability while magnetic resonance imaging shows injuries to soft tissues (posterior ligamentous complex [PLC]) and neurological structures. Different classification systems exist and the most recent is the AO spine knowledge forum classification of thoracolumbar trauma. Treatment includes both nonoperative and operative methods and selected based on the degree of bony injury, neurological involvement, presence of associated injuries and the integrity of the PLC. Significant advances in imaging have helped in the better understanding of thoracolumbar fractures, including information on canal morphology and injury to soft tissue structures. The ideal classification that is simple, comprehensive and guides management is still elusive. Involvement of three columns, progressive neurological deficit, significant kyphosis and canal compromise with neurological deficit are accepted indications for surgical stabilization through anterior, posterior or combined approaches.

Key words: Spinal injuries, thoracolumbar trauma, management
MeSH terms: Spinal injuries, thoracic vertebrae, lumbar vertebrae, treatment protocols

Introduction

Fractures of the thoracic and lumbar region constitute a spectrum of injuries ranging from the simple undisplaced fractures to complex fracture dislocations.[1] Anatomically and functionally, the thoracic and lumbar spine can be divided into three regions – thoracic spine (T1-T10), thoracolumbar junction (T10-L2) and the lumbar spine (L3-L5). The thoracic spine is functionally rigid due to coronally oriented facet joints, thin intervertebral discs and the ribcage. Thus, it requires huge amounts of energy to produce fractures and dislocations. The narrow spinal canal in this region predisposes to spinal cord damage resulting in a high incidence of neurological deficit. The lumbar spine, on the other hand, is relatively flexible due to the thicker intervertebral discs, sagittal orientation of facet joints and the absence of the rib cage. The relatively lesser incidence of neurological injury in lumbar fractures can be attributed to the large size of the neural canal and the greater resilience of the cauda equina nerve roots. The thoracolumbar junction (T10-L2) is uniquely positioned in between the rigid thoracic spine and the mobile lumbar spine. This transition from the less mobile thoracic spine with its associated ribs and sternum to the more dynamic lumbar spine subjects the thoracolumbar region to significant biomechanical stress.[1,2] Hence, fractures of the thoracolumbar region are the most common injuries of the vertebral column.

Though fractures of the thoracolumbar spine are common injuries, 50% of these are unstable and can result in significant disability, deformity and neurological deficit.

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There are standard classification systems that have been described based on fracture morphology, injury mechanism, neurological deficit and injury to posterior ligamentous complex (PLC). Radiographs are the basic investigation while computed tomography (CT) scan provides information on the extent on bony injury and magnetic resonance imaging (MRI) scan shows injury to the spinal cord and soft tissue structures. However, despite extensive studies on this common injury, controversies still exist regarding the appropriate radiological investigations, the type of Nonoperative treatment, the indications for surgical management, the timing of surgery, approach and type of surgery, need for fusion and the role of spinal canal decompression. This review provides an overview of the epidemiology, biomechanical principles, radiological and clinical evaluation, and evolution of classification system and management principles.

Epidemiology

In an epidemiological study by Hu *et al.* in the Canadian population, the incidence of spinal injuries was 64/100,000 population/year.[3] In North America, the incidence of spinal injuries is more than 160,000 every year.[2] Among the thoracolumbar injuries, 50-60% affected the transitional zone (T11-L2), 25-40% affected the thoracic spine and 10-14% involved the lower lumbar spine and sacrum.[4] Thoracolumbar fractures are more frequent in men, and the peak incidence is observed between 20 and 40 years.[4,5] Neurological injury complicates 20-36% of fractures at the thoracolumbar junction in different studies.[6,7] The chances and extent of neurological deficit depend on the type of fracture. In a multicenter study, the incidence of neurological deficit ranged from 22% to 51% depending on the fracture type (22% in type A, 28% in type B and 51% in type C fractures, according to the AO classification).[8]

Injuries to the thoracolumbar spine are usually the result of high-energy blunt trauma. Sixty-five percent of thoracolumbar fractures occur due to motor vehicle injuries and falls from a height, with the remainder contributed by sports injuries and violence. Since these are high-velocity injuries, thoracolumbar fractures are commonly associated with other injuries like rib fractures, pneumo-hemothorax, and rarely great vessel injuries, hemopericardium and diaphragmatic rupture[9,10] [Figure 1]. Seat-belt (chance) fractures and flexion distraction injuries are often associated with intraabdominal visceral injuries. Long bone fractures and head injuries are also common and can often lead to missed injuries of the spine.[8] Due to such associated "distracting" injuries, the incidence of missed injuries of the thoracolumbar spine has been reported to be as high as 20%, especially in those with high-energy blunt trauma and altered mental status.[11] In a review of 508 consecutive spinal injury patients, Saboe *et al.* identified associated injuries in 47%. Most frequent injuries were head injuries (26%), chest injuries (24%) and long bone injuries (23%).[12]

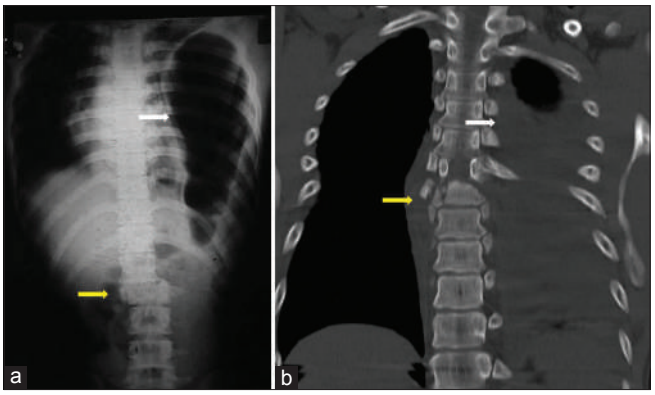

Figure 1: Systemic injuries associated with thoracolumbar fractures. (a) T12-L1 dislocation associated with left diaphragmmatic rupture and herniation of intraabdominal contents. (b) T7-T8 translational injury associated with massive hemothorax on the left side

Diagnosis

Clinical evaluation

Needless to say, any suspected spinal trauma patient in the emergency room should be evaluated following the basic principles of trauma assessment including primary and secondary survey. Once life-threatening injuries are prioritized, a careful history about the injury mechanism and information pertaining to any back or neck pain and neurological symptoms are acquired. Patients typically present with a history of trauma following a road traffic accident, fall from height, a direct blow to the spine or rarely gunshot injuries. Axial, nonradiating back pain of stabbing or aching quality is the most common symptom. Patients with neurological injury complain of weakness, paresthesia or anesthesia below the injury level and urinary retention. Thorough inspection of the spine should be performed after a careful log roll maneuver to look for abrasions, tenderness, local kyphosis and a palpable gap in between spinous processes. Neurological assessment should follow the standard American Spinal Injury Association (ASIA) guidelines[13] [Figure 2]. As the spinal cord ends at the L1-L2 level, and the cauda equina fills the distal canal, varied neurological injury patterns can be observed with thoracolumbar fractures. Neurological injuries above L1 can damage the spinal cord producing a typical upper motor neuron injury. Injuries much below L1-L2 affect only the cauda equina roots involving few or multiple nerve roots resulting in lower motor neuron type injury. Conus medullaris syndrome characterized by exclusive damage to sacral innervations to the bowel and bladder, with intact lumbar nerve roots, is a unique feature of T12-L1 injury [Figure 3].

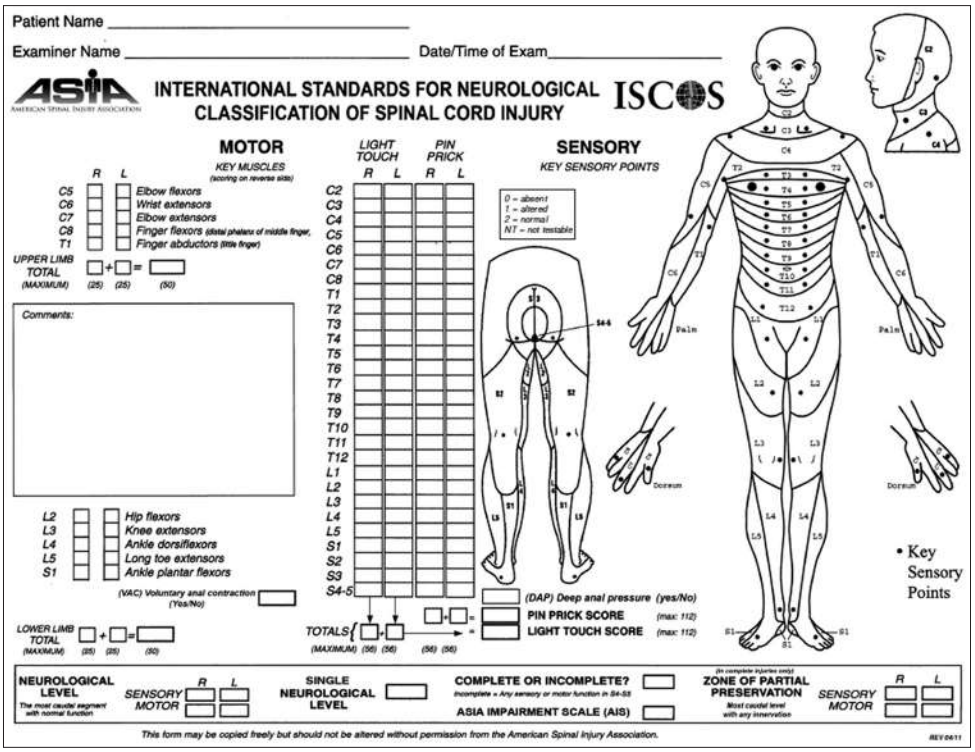

Figure 2: American Spinal Injury Association (ASIA) form for standard neurologic classification of spinal cord injury (from ASIA)

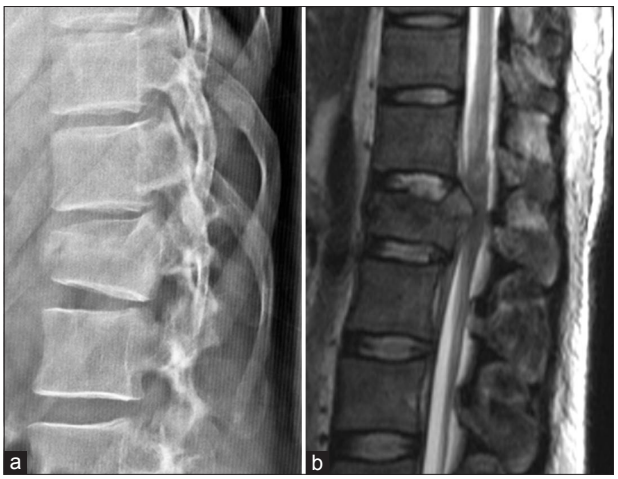

Figure 3: X-ray thoracolumbar spine lateral view (a) and magnetic resonance imaging of conus medullaris syndrome showing fracture of L1 vertebra resulting in injury to the conus medullaris

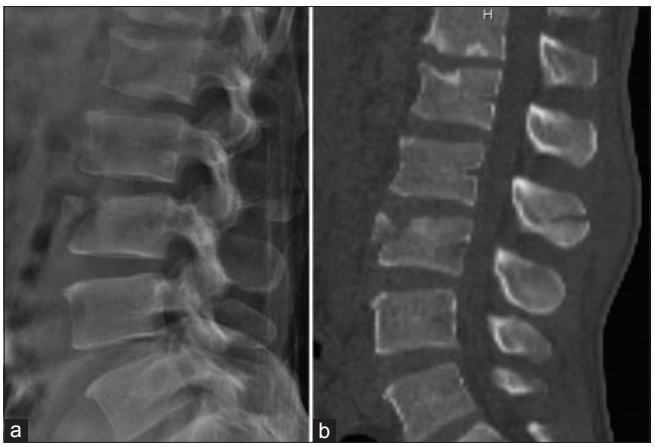

Figure 4: Computed tomography (CT) scan provides excellent delineation of bony injuries. In this patient with A1 injury of the L3 vertbral body seen in the lateral radiograph (a), CT scan showed horizontal split of L2 spinous process indicating a flexion-distraction injury

Radiological evaluation

Standard radiographic evaluation includes antero-posterior and lateral radiographs. Radiographic evaluation should include spinal alignment, presence of any rotation or translation, assessment of the kyphosis, loss of vertebral height, and widened inter-pedicular or inter-spinous distance.[11,14,15] CT scan of the injured area characterizes the fracture further and provides the degree of canal compromise. Approximately, 25% of burst fractures are misdiagnosed as compression fractures if radiographs alone are evaluated[16] [Figure 4]. MRI scan provides information on spinal cord or root injury, presence and extent of cord edema and hemorrhage, and epidural hematoma.[17] Other advantages of MRI are its ability to evaluate injury to the intervertebral discs and PLC, and identify the presence of noncontiguous injuries through screening of the whole spine [Figure 5]. The incidence of noncontiguous spinal fractures is 1.6-23.8%.[18,19] The incidence of a delayed diagnosis of the second lesion ranges from 23.1% to 83.3%.[18,19] Thorough clinical examination of the entire spine to look for bruise and tenderness, radiographs of the other regions of the

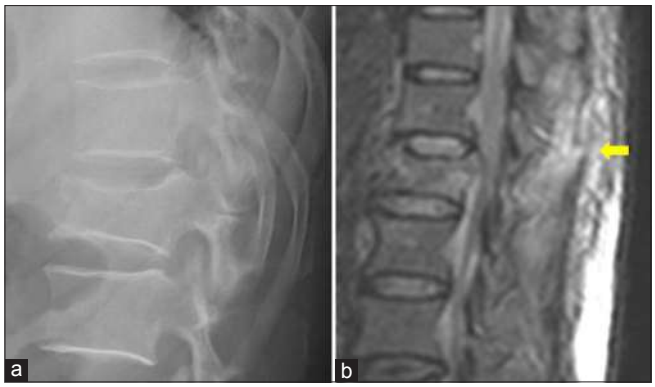

Figure 5: (a) Lateral radiograph of thoracolumbar spine showing a burst fracture of L1 vertebral body. (b) Sagittal magnetic resonance image shows a hyper intense signal of the posterior ligamentous complex (yellow arrow) indicating injury, which is not detected in the radiograph

spine and sagittal MRI screening of the whole spine can potentially avoid missing other injuries.

Classification

Biomechanics of the load bearing and supporting structures of the vertebral column form the basis of understanding the spinal injuries and their classification systems. The classification of thoracolumbar fractures has evolved over the years as the understanding of the spinal biomechanics, mechanism of injury and identification of vertebral stability improved.

Early classification systems described by Boehler (1929) and Jones were descriptive systems, based only on radiographs.[20] Holdsworth revolutionized the thoracolumbar injury classification with the introduction of the "two column concept."[21] Denis believed that the middle column is the key to the stability of the fracture and proposed the "three column concept."[22] Based on the three column concept described by Denis and the possible mechanisms of failure of the columns, McAfee described a simplified system of classifying injuries[23] [Table 1]. This system is simple and includes most injuries observed in clinical practice. In 1994, Magerl analyzed 1445 cases of thoracolumbar injuries and presented a comprehensive AO classification of thoracolumbar fractures based on the mechanism of injury and morphological pattern of the fracture.[6] Despite being a comprehensive classification system, this system was cumbersome with poor inter-observer reliability.

McCormack *et al.* introduced a classification (load sharing classification) to predict the risk of implant failure after posterior short segment fixation for thoracolumbar fractures. This classification intends only to identify fractures that would require supplemental anterior fixation following a posterior surgery.[24] The Thoracolumbar Injury Classification System (TLICS) created by "The Spine Trauma Study Group,"

Table 1: McAfee's classification of thoracolumbar fractures

Wedge compression fractures result from isolated failure of the anterior column due to forward flexion. They rarely are associated with neurological deficit except when multiple adjacent vertebral levels are affected
In stable burst fractures, the anterior and middle columns fail because of a compressive load, with no loss of integrity of the posterior elements
In unstable burst fractures, the anterior and middle columns fail in compression, and the posterior column is disrupted. The posterior column can fail in compression, lateral flexion, or rotation. There is a tendency for posttraumatic kyphosis and progressive neural symptoms because of instability. If the anterior and middle columns fail in compression, the posterior column cannot fail in distraction
Chance fractures are horizontal avulsion injuries of the vertebral bodies caused by flexion around an axis anterior to the anterior longitudinal ligament. The entire vertebra is pulled apart by a strong tensile force
In flexion distraction injuries, the flexion axis is posterior to the anterior longitudinal ligament. The anterior column fails in compression, whereas the middle and posterior columns fail in tension. This injury is unstable because the ligamentum flavum, inter-spinous ligaments, and supraspinous ligaments usually are disrupted
Translational injuries are characterized by malalignment of the neural canal, which has been totally disrupted. Usually all three columns have failed in shear. At the affected level, one part of the spinal canal has been displaced in the transverse plane

is based on three major injury characteristics – mechanism of injury, integrity of the PLC and neurological status. Based on the severity scores within these three categories, a total score is calculated that can be used to guide treatment.[25]

Among these classification systems, the Denis/McAfee classification, AO classification and the TLICS classification are commonly used in clinical practice. Blauth *et al.* have reported that the inter-observer reliability of the AO classification was low (fair agreement, $\kappa = 0.33$), and when the injury was classified into subgroups, the inter-observer reliability decreased further.[26] Oner *et al.*[27] and Wood *et al.*[28] also reported that the Denis classification system ($\kappa = 0.60$ and 0.606) showed higher inter-observer reliability than the AO classification system ($\kappa = 0.35$ and 0.475). Lenarz *et al.* compared the reliability of Denis, AO, and TLICS systems in 97 thoracolumbar fractures and observed that in all the three systems, variation in reliability was present, with the highest reliability occurring in the senior resident group and attending spine surgeon group.[29] The lowest reliabilities were in the nonspine attending orthopedists and junior residents. In each group, the neurologic status had the highest inter observer and intraobserver reliability. They concluded that the TLICS is an acceptably reliable system when compared with the Denis and AO systems.

The AO spine knowledge forum has proposed a recent comprehensive modified AO classification including morphology of the fracture, neurological status, and description of relevant patient-specific modifiers.[30]

The fracture morphology is assessed based on 3 main injury patterns: Type A (compression-injury to the vertebral body without PLC involvement), type B (tension band disruption - the failure of posterior (PLC) or anterior (anterior longitudinal ligament) constraints), and type C (displacement/translation) injuries. Neurologic status is classified as follows: No neurologic injury (N1), radicular symptoms or deficits (N2), incomplete spinal cord injury (SCI) or any kind of cauda equina injury (N3), complete SCI (N4) and unknown neurologic status (NX). Forty cases with a broad range of injuries were classified independently twice by group members and the reliability in the identification of a morphologic injury type was substantial (κ =0.72). The classification appears much simpler and equally comprehensive when compared with the previous AO classification and includes important information about neurology and posterior ligamentous structures. Based on this classification, type A4, B1, B2, B3 and C injuries will need surgical stabilization. The inter/intraobserver reliability of this classification is yet to be studied, apart from the originators.

Management

Medical management

Throughout resuscitation in the emergency room and subsequent care, all efforts must be taken to immobilize spinal injury patients safely and intermittently log roll to prevent pressure sore formation. Stabilization of unstable injured motion segments plays an important role in preventing further injury. In a patient with SCI, injury to neural structures occurs both at the time of injury (primary – nonmodifiable) and in the subsequent period due to vascular dysfunction, edema, ischemia, electrolyte shifts, free radical production, inflammation and delayed apoptotic cell death (secondary – potentially modifiable).[31] Numerous pharmacological agents thought to mitigate the secondary injury have been extensively studied. These include the steroids (antiinflammatory), gangliosides, naloxone (opiate receptor antagonist), calcium channel blockers, free radical scavengers and neurotropic agents.

Steroids were extensively employed in the clinical treatment of SCI beginning in the mid-1960s. In rat SCI models, steroids have been shown to improve neurological recovery.[32] After encouraging "positive" results with the use of high dose steroids in North American Spinal Cord Injury Study (NASCIS) 1 and 2 trials, the NASCIS 3 trial studied the effect of methyl prednisolone within 3-8 h of injury and concluded that better neurological recovery is statistically observed if administered over 24-48 h.[33]

However, a number of articles have strongly criticized the NASCIS trial design, analysis and reporting. Coleman *et al.* observed that the NASCIS II and III reports have used specific choices of statistical methods that have strongly shaped the reporting of results. The primary outcome analysis of the trials were negative with modest beneficial effects being proven only through *post hoc* analyses, inappropriately excluding >70% of the patients.[34] After a thorough review of the three NASCIS trials, Hurlbert concluded that evidence of the drug's efficacy and impact is weak and may only represent random events, and the use of high dose methyl prednisolone in the treatment of acute SCI is not proven as a standard of care.[35] A survey published in 2006 revealed that the majority of respondents continue to administer methylprednisolone, but they are motivated predominantly by fear of litigation.[36]

Nonoperative management

Most thoracolumbar fractures are stable injuries amenable to nonoperative management. Simple compression or stable burst fractures without neurologic complications can typically be treated with commercially available thoracolumbar orthoses, or a hyperextension cast that permit early ambulation[37,38] [Figure 6]. There is no consensus on the exact duration of treatment. The advantages of a brace or cast over unprotected ambulation have also not been studied. However, it has been shown that external support has no mechanical stabilizing effect on the lumbar spine.[39] In a systematic review of studies, Giele *et al.* concluded that there is no evidence for the effectiveness of bracing in patients with traumatic thoracolumbar fractures.[40] During nonoperative care, it is common to observe a certain degree of increasing fracture kyphosis in most patients, often closer to the pretreatment sagittal alignment. However kyphosis even up to 30° has not been shown to correlate with pain in several studies.[37,41,42]

Operative management

The advantages of operative treatment of thoracolumbar fractures over the nonoperative approach include avoiding an orthosis in the presence of multiple injuries, skin injuries, and obesity, immediate mobilization and earlier rehabilitation and better restoration of sagittal alignment.[4,43] Surgical decompression of compressing bone fragments over the spinal cord also reliably provides a better environment for restoration of neurologic function. On the other hand, the benefits of surgical treatment must be carefully weighed against the potential surgical morbidity. Conventional open surgical techniques can be associated with morbidity because of approach-related muscle injury, increased infection rates and higher blood loss.

Neurological recovery and surgical decompression

In general, operative treatment is indicated mainly for unstable spinal injuries such as flexion distraction injuries, unstable burst fractures and fracture dislocations. Though operative treatment reduces pain and enables early

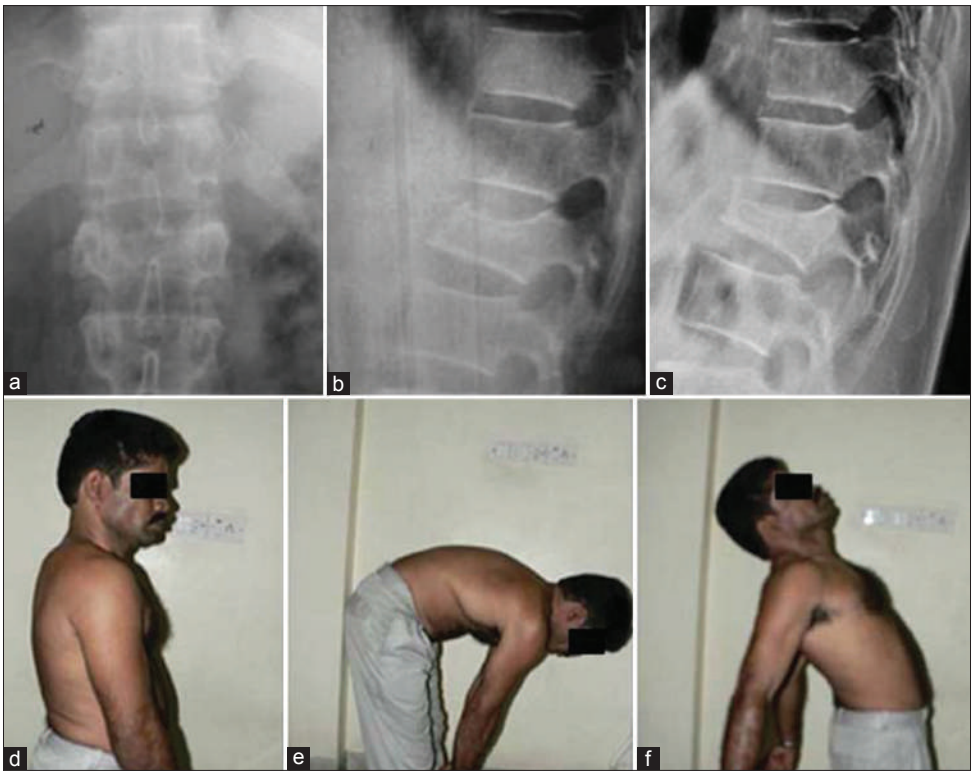

Figure 6: Stable burst fracture of L2 vertebral body treated by conservative care. Lateral radiograph at the end of 1-year shows good fracture healing. Clinical pictures show good functional outcome

mobilization and rehabilitation, there is no difference between operative and nonoperative treatment regarding neurological recovery and long term functional outcomes.[44] Studies in animal models have demonstrated that neurological recovery is enhanced by early decompression.[45] However, this has not been proven in human studies on acute SCI. The severity of neurological injury is determined by the extent of neuronal injury incurred at the time of primary injury. But it is still worthwhile considering early surgical decompression in patients with incomplete SCI in the presence of spinal cord compression. Despite the lack of clear level I or II scientific evidence, the general accepted indications for operative treatment are given in Table 2.

Table 2: Standard indications for surgical treatment in thoracolumbar fractures

Incomplete neurological deficit
Progressive neurological deficit
Spinal cord compression
Fracture dislocation
Kyphosis >30°
Concomitant injuries necessitating early mobilization

Timing of surgery

There is no consensus on how early to operate on a patient with SCI. Vaccaro *et al.* conducted a prospective randomized controlled trial to determine whether neurologic and functional outcome is improved in traumatic cervical spinal cord injured patients with early surgery (<72 h after SCI) compared with those patients who had late surgery (>5 days). They observed no significant neurologic benefit when spinal cord decompression is performed <72 h after injury.[46] However, in a meta-analysis by La Rosa *et al.*, 1687 patients were studied to evaluate the advantages of early decompression in acute SCI.[47] The patients were divided into three treatment groups: Early decompression (<24 h), delayed decompression (>24 h), and conservative treatment. Early decompression resulted in better outcomes statistically when compared with delayed decompression and conservative management. In the presence of progressive incomplete neurological deficit and spinal cord compression, it is prudent to perform urgent surgical stabilization and decompression. Patients with normal neurology and those with complete neurological deficit are optimized for surgery which can be performed at the earliest safe situation for the patient. There is no evidence to perform surgery in the midnight.

Surgical approach

Different surgical approaches and techniques have been described for thoracolumbar fractures including posterior, anterior and combined approaches. However, scientific evidence lacks to support the selection of one surgical technique as advantageous over the other. Factors, such as an anesthetic and surgical burden to the patient, morbidity,

complication rates, costs, and surgeon's expertise should be taken into account in the choice of surgical approach.

Posterior approach

Posterior short segment fixation including the proximal and distal adjacent normal vertebrae is the most commonly performed surgery for the vast majority of thoracolumbar fractures (unstable burst fractures with intact neurology, flexiondistraction injury, Chance fractures). Fracture reduction can be achieved by a combination of postural reduction, and by distraction through ligamentotaxis. Posterior pedicle screw fixation has been shown to be simple, familiar, efficient, reliable, and safe for the reduction and stabilization of most fractures and remains the most popular technique. Disadvantages include instrumentation failure, pseudarthrosis, infection, risks of SCI, inadequate neurological decompression, insufficient correction of kyphosis and the need for late instrumentation removal.[48-50] Depending on the extent of vertebral body comminution, additional anterior reconstruction may be needed to prevent implant failure. McCormack *et al.* retrospectively analyzed 28 patients who had been operated for thoracolumbar injuries with Steffee plates.[24] Three important factors in predicting posterior fixation failure were studied which included the amount of vertebral body comminuted as seen in sagittal CT images, the apposition of fracture fragments as seen in axial CT images and the amount of correction of kyphotic deformity as best measured by comparing pre and postoperative films. Each of these factors was subdivided into three grades of severity and was scored on a point system from 1 to 3, with a higher number indicating increased severity. They observed that anterior vertebral reconstruction is essential in patients with a score ≥7 to prevent implant failure. To avoid anterior surgeries, various authors have described other techniques such as transpedicular intracorporeal bone grafting, vertebroplasty and kyphoplasty, intracorporeal filling with hydroxyapatite or calcium phosphate.[51,52] Other biomechanical measures to improve the strength of the construct include the use of cross-links, supplemental hook fixation at the levels of the screws and the addition of "intermediate" screw into the fractured vertebra.[53,54] Several biomechanical and clinical studies have shown that the addition of intermediate screws significantly increased the strength of a short segment posterior construct thus lowering the rates of loss of kyphosis after correction [Figure 7].[55-57]

High velocity grossly unstable injuries like fracture dislocations usually requires multilevel spinal stabilization. Fixation of two to three segments above and below the injury is recommended for reducing the dislocation and achieving stable fixation. Similarly, unstable fractures of the thoracic spine are subjected to significant shear stresses and hence are treated with multilevel posterior fixation. For select type A and B fractures, Gotzen *et al.* have published their technique of posterior mono-segmental reduction and stabilization.[58] The injuries are usually confined to the upper-end plate alone, and pedicle screw fixation and fusion involves only the fractured and the proximal normal vertebra. In their 2 year followup of 39 patients, no implant failure was noted.

Anterior approach

About 80% of the axial load of an intact spine is supported by the anterior column. When the anterior column is substantially injured, the anterior column support is reduced leaving majority of the stress to be transmitted by the posterior implant and the bony elements. In such situations, restoration of anterior column through a tricortical bone graft or a cage is advised. The other indication for anterior surgery is the presence of spinal cord compression due to retropulsed bone fragments. Spinal canal compromise in patients presenting with neurological deficits that cannot adequately be resolved by a posterior approach requires anterior decompression. The degree of neurological recovery, rate of spinal fusion, sagittal spine alignment, and return to preinjury activities after anterior decompression appears more favorable compared to techniques that do not decompress the spinal canal.[59] Use of anterior vertebral plates and screws, and cages has greatly improved

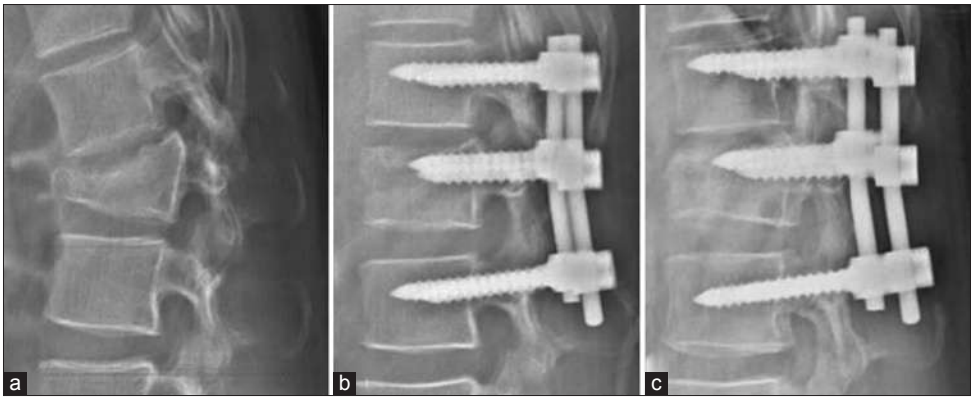

Figure 7: X-ray thoracolumbar spine lateral view showing (a) L1 flexion-distraction injury (b) treatment with posterior short segment fixation and intermediate screws (c) Lateral radiograph performed at the end of 1-year shows good fracture healing

postoperative spinal stability and also reduced donor-site morbidity from major bone graft harvesting techniques. Kaneda *et al.* have reported a study on 150 consecutive patients who had a burst fracture of the thoracolumbar spine with neurological deficits.[60] The patients were managed with a single-stage anterior spinal decompression, strut grafting, and anterior spinal instrumentation. At a mean of 8 years (range: 5-12 years) after the operation, radiographs showed successful fusion of the injured spinal segment in 140 patients (93%). The neurological function improved in 95% of the patients by at least one Frankel grade, while 72% of patients recovered completely.

Relatively few studies compare anterior to posterior approaches for thoracolumbar burst fractures, and most of them show an advantage of the anterior approach. In his series, Gertzbein reported that bladder function significantly improved following anterior compared to posterior procedures.[4] Hitchon *et al.* showed that angular deformity was more successfully corrected and maintained when the anterior approach was used.[61] Sasso *et al.* also showed that although both approaches are associated with a statistically significant initial improvement in sagittal alignment, the posterior approach was associated with increased loss of sagittal correction (8.1°) compared to the anterior approach (1.8°) at followup.[62]

Combined anterior and posterior approach

Select patients with thoracolumbar burst fractures may benefit from combined surgical approaches. Indications for combined approach would include burst fractures with significant kyphosis (>40°), >50% canal compromise and neurological deficit in the presence of spinal cord compression. The advantages of combined surgical approaches are improved sagittal alignment, thorough spinal canal and neural decompression and stabilization of the disrupted PLC. In a series of 20 consecutive patients with a single-level unstable thoracolumbar burst fracture treated by posterior fixation followed by anterior corpectomy and titanium cage implantation, 12 patients with initial neurological deficits recovered an average of 1.5 grades on the ASIA scale.[63] Two years postoperatively, the mean pain score for back pain was 1.6 points and instrumentation failure did not occur. At a mean followup of 6 years, a comparative retrospective study of combined versus posterior-only fixation reported similar clinical outcome and neurological improvement, fusion rate and angle of kyphotic deformity in both groups.[64] However, loss of reduction >5° and instrumentation failure were significantly higher in the posterior-only fixation.

Minimally invasive approach

Open surgical approaches for the treatment of thoracolumbar fractures either by anterior or posterior techniques require extensive exposure and often lead to significant postoperative pain and morbidity. Recently, minimally invasive techniques have been described in thoracolumbar fractures. For posterior stabilization, percutaneous minimally invasive pedicle screw fixation and stabilization can be performed to minimize muscle injury and enable early rehabilitation. The application of posterior minimally invasive techniques reduces the approach-related morbidity like iatrogenic muscle denervation, ischemia, pain and functional impairment.[65-67] It is a useful option in case of poly traumatized patients, obesity, and compromised lung function when conservative treatment is not advisable. Similarly, minimally invasive thoracoscopic vertebral body decompression and cage reconstruction minimizes the morbidity in poly traumatized patients. In an analysis of 65 patients, Kossmann, *et al.* reported no intra or postoperative complications following thoracoscopic anterior decompression and reconstruction.[68] Bühren *et al.* analyzed 38 patients and concluded that, compared to the open method, minimally invasive surgery had the benefit of reducing postoperative pain, shorter hospitalization, leading to early functional recovery and reducing the morbidity of the operative approach.[69]

Complications

Posterior pedicle screw fixation has become the mainstay of spinal instrumentation for fracture stabilization. Despite increasing experience, knowledge and technical advancement, pedicle screw insertion is still associated with a certain degree of complications. The most commonly reported complication is screw malpositioning, with an overall incidence of 0-42%.[70,71] Most of them are asymptomatic without any major sequelae, and serious screw-related complications, such as neurological, visceral, or vascular are very rare. The overall incidence of nerve root or SCI due to screw malpositioning ranges between 0.6% and 11%.[72] A transient self-limiting neurapraxia in the form of numbness is the usual feature and the incidence of permanent neurological deficit is rare. Vascular injuries related to misplacement of screws are potential life- and limb-threatening complications that require early recognition with prompt repair of vascular lesions and screw repositioning.[73] Visceral injuries related to pedicle screw insertions are very rare. The proximity of vertebral bodies to structures like lung and pleura can result in pnemothorax, effusion or an esophageal injury inadvertently. Screws can break when there is a deficient anterior column, progressive kyphosis and pseudoarthrosis. This is mainly attributable to metal fatigue due to excessive strain on the implant.

The abdomen contains many vascular structures including the aorta, inferior vena cava, segmental vessels, and

numerous veins, which are exposed during anterior surgeries and hence at risk for injury. Venous laceration is the most common vascular injury and usually occurs during manipulation and retraction of the great vessels.[74] Vascular injury can also occur while performing the corpectomy, placing the graft, and inserting the screws. Manual compression or primary repair of the tear is generally effective at treating this complication. Visceral injuries and postoperative lymphocele, or chyloretroperitoneum are uncommon events. This is usually evident intraoperatively and requires the expertise of the gastrointestinal surgeon to repair. Injuries to the peritoneum are very common but are easily repaired and do not lead to significant problems.

Conclusion

Despite tremendous improvements in spinal imaging and management techniques in the last two decades, there is still lack of consensus in several areas in the management of thoracolumbar fractures. Principally treatment decisions in these patients require a complete evaluation of the neurological status and identification of the presence of spinal instability. CT scan provides the best information regarding the extent of bony injury and MRI scan shows the extent and severity of cord compression and injury to PLC. The ideal classification that is simple, comprehensive and guides management are still elusive. The most recently described is the AO KF thoracolumbar classification, which appears simple and includes most information regarding the extent of vertebral body injury, neurological injury and patient modifiers. Involvement of all the three columns, progressive neurological deficit, significant kyphosis >30° and canal compromise in the presence of neurological deficit are accepted indications for surgical stabilization. Compression fractures and stable burst fractures can be treated by nonoperative methods. Posterior surgery remains the most preferred technique, and anterior approach is the access of choice when decompression of the spinal cord is the priority. Minimally invasive surgeries are increasingly used to reduce surgical morbidity in the acutely traumatized patient.

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Management of skeletal metastases: An orthopaedic surgeon's guide

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Abstract

Skeletal metastasis is a common cause of severe morbidity, reduction in quality of life (QOL) and often early mortality. Its prevalence is rising due to a higher rate of diagnosis, better systemic treatment, longer lives with the disease and higher disease burden rate. As people with cancer live longer and with rising sensitivity of body imaging and surveillance, the incidence of pathological fracture, metastatic epidural cord compression is rising and constitutes a challenge for the orthopedic surgeon to maintain their QOL. Metastatic disease is no longer a death sentence condemning patients to "terminal care." In the era of multidisciplinary care and effective systemic targeted and nontargeted therapy, patient expectations of QOL, even during palliative end of care period is high. We lay emphasis on proving the diagnosis of metastasis by biopsy and histopathology and discuss imaging modalities to help estimate fracture risk and map disease extent. This article discusses at length the evidence and decision-making process of various modalities to treat skeletal metastasis. The modalities range from radiation including image-guided, stereotactic and whole body radiation, systemic targeted or hormonal therapy, spinal decompression with or without stabilization, extended curettage with stabilization, resection in select cases with megaprosthetic or biological reconstruction, percutaneous procedures using radio frequency ablation, cementoplasties and discusses the role of emerging modalities like high frequency ultrasound-guided ablation, cryotherapy and whole body radionuclide therapy. The focus lies on the role of multidisciplinary care, which considers complex decisions on patient centric prognosis, comorbidities, cost, feasibility and expectations in order to maximize outcomes on QOL issues.

Key words: Bone metastases, pathological fracture, skeletal metastases
MeSH terms: Metastases, fracture, pathological, bone cancer

Introduction

Bone is among the most frequent sites of metastatic disease next only to lung and liver. Approximately, 70% of patients who die of breast or prostate cancer have also had bone metastases.[1] Thyroid, lung, and kidney cancers also have a propensity to involve the skeleton. Approximately, 30-65% of patients with metastatic lung cancers will develop bone metastases,[2] as will approximately 47% of patients with advanced thyroid cancer and 30% of patients with advanced renal carcinoma.[3] It is reported that 9-29% of patients with metastases will have a pathological fracture[4] and 90% of fractures require surgery.[5] With advances in treatment, patients with cancer, especially prostate and breast cancer are living longer and thus there is greater responsibility on the orthopedic surgeon to preserve the quality of life (QOL) by preventing and managing skeletal-related events (SRE). SRE include pain, vertebral fractures, cord compression and pathological fractures of long bones. All these have an impact on mobility and functional independence and therefore greatly impact the QOL.

A lot has changed in the last decade in terms of imaging, detection, medical and surgical management. Management of skeletal metastases is no longer a simple task of fixing a fracture, but involves a multidisciplinary coordination between medical oncologists, radiation oncologists and the surgeon. This article updates the orthopedic surgeon on the current concepts in workup and managing skeletal metastases.

Imaging Modalities in Metastatic Disease

The radiographic appearance of metastatic bone tumors have traditionally been described as osteolytic, osteoblastic, or mixed lytic and sclerotic [Figure 1]. Recently, an

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osteoporotic pattern has been described where the lesions appear as "faded" bone without discrete areas of cortical destruction or increased density in theX-ray.[6] It is estimated that there is at least 25-75% loss of mineral before a lesion is visible on X-ray[7,8] implying that the bone is already significantly weak by the time the lesion is radiologically visible. The extent of bony destruction helps assess the risk of fracture. Lytic lesionsdestroying 50% or more of the diaphyseal cortex can result in a 60-90% reduction in bone strength, significantly increasing the risk of fracture.[9]

Some rough guidelines for prophylactic fixation have been proposed based on the amount of cortical destruction on X-rays. Fidler[10] in 1973 suggested prophylactic fixation of the long bone for more than 50% cortical destruction. In 1982, Harrington,[11] after a review of the literature, added the criteria of lesion length more than 2.5 cm, fracture of adjacent lesser trochanter and persistent pain after radiation. It was far too simplistic not factoring several variables and therefore not accurate. In 1989, Mirels[12] proposed a more refined system [Table 1]. Prophylactic fixation was recommended for a score greater than 9 which predicted a 33% risk a score <7 had a low risk of fracture. Though not categorical or absolute, subsequent studies have validated this system as having high sensitivity but low specificity.[12-14]

More accuracy would involve algorithm based evaluation of computerized tomography (CT) images compared withthe opposite side to assess the bony rigidity. This has been used and reported for children with benign tumors.[15] CT-based finite element modeling has also been used to predict fracture risk in long bones.[16] Magnetic resonance imaging (MRI), Dual energy X-ray absorptiometry (DEXA) and quantitative CT have been tried to evaluate fracture risk in vertebral bodies.[17] Once developed, these would provide a far higher accuracy in estimating fracture risk. Currently, however, none of these can still be used practically in the clinic, and Mirels score remains the standard of care. Despite all the enumerated scoring systems to predict fracture risk, pain at rest and activity remains the single most sensitive symptom to predict fracture risk and increasingly more clinicians rely on this to make judgment calls despite equivocal scores.

Computerized tomography and MRI can evaluate suspicious findings on Technetium-99 (99mTc) bone scans and can provide better spatial resolution and three-dimensional anatomic information about the skeleton as well as softtissue involvement [Figure 2]. CT is excellent at assessing the

Table 1: Mirel's score

Score	Site	Pain	Lesion	Size[b]
1	Upper limb	Mild	Blastic	<1/3
2	Lower limb	Moderate	Mixed	1/3-2/3
3	Peritrochanteric	Functional[a]	Lytic	>2/3

[a]This is pain on functional use like weight bearing in lower limb, [b]Size is amount of cortical circumferential segment involved. Mirel's score – >9=High risk of fracture, <7=Low risk of fracture

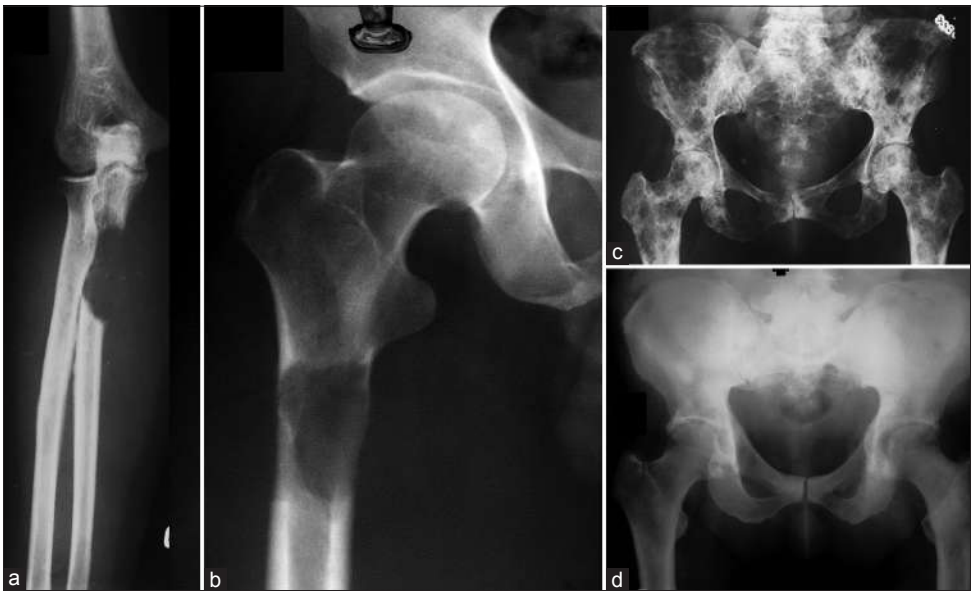

Figure 1: Varied radiological appearance of metastasis-lytic, mixed and blastic. (a) The radiograph of forearm with elbow joint anteroposterior view showing lytic metastasis from lung carcinoma occurring distal to the elbow (Note that metastases below the knee and elbow are rare) (b) The radiograph of hip joint with proximal thigh anteroposterior view showing an impending fracture from a lytic metastasis arising from a colonic primary. Pure lytic lesions are common with renal, lung, thyroid, uterine, adrenal, GI malignancies and melanoma (c) X-ray pelvis with both hip joints anteroposterior view showing extensive lytic and sclerotic metastases to pelvis and both femori from breast cancer. Mixed lesions are known with breast, lung, ovary, cervix, testicular malignancies and lymphoma (d) X-ray pelvis with both hip joints anteroposterior view showing pure sclerotic or blastic metastasis arising from a prostate carcinoma in a 70-year-old male. Pure blastic lesions are common with prostate, bladder cancers, medullary carcinoma thyroid and bronchial carcinoids

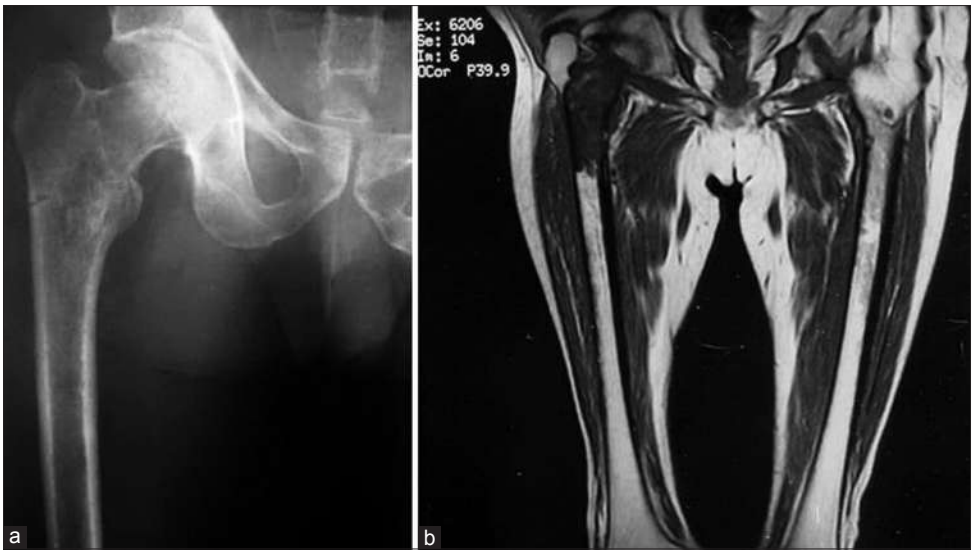

Figure 2: The plain radiograph (a) Underestimates the disease extent identified on magnetic resonance imaging (MRI) images (b) MRI can also identify and delineate soft tissue involvement, joint effusion, skip lesions and other crucial information like relation to neurovascular structures which can critically affect treatment plan

cortical lesions whereas trabecular lesions may be best seen on MRI.[8] MRI is highly sensitive to detect small skeletal metastases not yet detectable on bone scans by revealing abnormal bone marrow; Though MRI is very sensitive, it cannot help differentiate between infection, fracture or inflammation, all of which cause similar marrow signal changes.

Once a lesion is identified as metastatic disease, the clinician needs to know if the lesion is solitary or if there are other sites of disease. 99mTc bone scintigraphy screens the entire skeleton, is very sensitive and has a relative low cost making it the initial imaging modality for detection of bone metastases. It accumulates in areas of increased osteoblastic activity and increased blood flow. Osteoblastic metastases are, therefore, more reliably picked up. Technetium bone scan is false negative for highly aggressive and rapidly growing lytic tumors like myeloma because of minimal reactive bone formation.[18,19] Lytic lesions can appear as "cold" defects but are frequently overlooked.[7] In contrast to plain films, as little as 5-10% change in the ratio of lesion to normal bone is required to detect an abnormality on bone scan. It is estimated that bone scan can detect malignant bone lesions 2-18 months earlier than the radiograph can.[7] This explains why tumors known to have a propensity for skeletal metastases undergo regular screening with bone scan. Bone scan has published sensitivity rates between 62% and 100%, with a specificity of 78-100%.[7] False positives can occur in any area of high bone turnover related to trauma, infection, or arthropathy.[7,20,21] To overcome lack of specificity, correlative imaging with radiographs, CT, or MRI is recommended, especially in the context of equivocal findings (single "hot spot" or few lesions). Lesions like enchondromas, bone islands or healed nonossifying fibromas can appear as hot spots and need differentiation from a metastatic lesion. These are generally obvious on an X-ray. Sometime CT accurately characterizes the lesion. Single-photon emission computed tomography (SPECT) improves the sensitivity and specificity of 99mTc bone scans for detection of small bone metastases,[22,23] by superimposing the hot spot on a CT cut. A focal hot spot with a lytic area is significant for suspected metastases, but MRI still provides better tomographic images. Tuberculosis, particularly in the spine can be a confounding factor in the Asian subcontinent and can coexist with metastatic disease. We recommend a biopsy prior to treatment in any skeletal lesion. The presence of multiple lesions in patients with a known malignancy is more suggestive of metastatic disease, although other nonneoplastic conditions like infection and arthropathy can also have multifocal areas of uptake. Any suspected lesion is further worked up with local X-rays, a focal MRI or CT. MRI is the most accurate when bony destruction is minimal.

Lytic lesions negative on bone scan are better detected by metabolic scans such as fluorodeoxyglucose-positron emission tomography (FDG-PET) because they have a higher than normal glucose metabolism. The poor specificity of the FDG-PET, as well as its lack of anatomic detailing, makes CT and MRI necessary for further characterization. As FDG-PET relies on glucose uptake by the tumor, it can detect early metastases without any bony destruction. It can also help in assessing the response to treatment by showing a corresponding reduction in activity of the tumor. As more knowledge accumulates, its use is increasing for

several malignancies such as lung, breast, and head and neck cancers. Although FDG-PET is superior in detecting osteolytic metastases, it is less sensitive than 99mTc bone scans for detection of osteoblastic metastases.[24,25] It is thus more sensitive than bone scan for myeloma, equivalently sensitive for breast and lung cancers, and less sensitive for prostate cancer. The aggressiveness of the tumor may also influence the sensitivity of detecting bone metastases using FDG-PET.[26] Skeletal PET using F-18 sodium fluoride (NaF-18), a positron-emitting bone-seeking tracer, may improve the utility of PET. The available literature shows that NaF-18 PET is substantially more sensitive and specific than 99mTc bone scan and SPECT[27,28] for detection of metastases, especially for osteolytic lesions, but has a higher cost and involves greater radiation dose.[29] Addition of CT greatly improves the utility of PET by providing better resolution.[28]

Whole body MRI as a tool for systemic surveillance with its zero radiation and excellent anatomic detailing is useful in myeloma for screening the skeleton but unlike PET cannot be used to assess response. PET MRI is a new modality, which also helps decrease radiation and its potential side-effects, while retaining excellent biologic imaging capabilities. Studies are underway to determine its utility and effectiveness in systemic surveillance.

Biopsy and Tumor Markers

A biopsy is a must to prove that the lesion is metastatic. A needle biopsy generally is adequate for most lesions as it provides a diagnosis in over 90% of cases.[30-32] It is important to accurately target the lesion using image guidance (USG/CT/C Arm). A Jamshidi or other trocar cannula based needle is used for entering the bone. For lesions with a soft tissue mass, a tru-cut spring loaded core biopsy needle is adequate and simple to use. Apart from morphology, immunohistochemistry can help give a clue to the possible primary in metastatic disease. Where the primary diagnosis of malignancy has already been made, an FNAC may be used to simply confirm metastatic disease. If the orthopedic surgeon is unfamiliar with the method of doing a needle biopsy or the pathologist is uncomfortable in reporting on the needle biopsy (this often happens in inexperienced centers), it is best to refer the patient to an oncology setup.

Tumor markers are substances that are detected in body fluids (blood/serum/urine) or in tissue (tumor/marrow/bone) that help diagnose, screen, monitor response to therapy and detect a recurrence by minimally or noninvasive methods. Most markers have been proteins that represent a unique genetic signature associated with a particular malignancy. A few commonly used ones are enumerated in the Table 2.

Table 2: Tumor markers

Tumor marker	Disease	Role
Beta 2 microglobulin	Multiple myeloma, chronic lymphocytic leukemia	Prognosis and response evaluation
Beta hCG	Choriocarcinoma and testicular cancer	Evaluation of recurrence and response evaluation
CA 15-3/ CA 27.29	Breast cancer	
CA 19-9	Pancreatic, gall bladder, bile duct cancer	
CA 125	Ovarian cancer	
Calcitonin	Medullary thyroid cancer	
CEA	Colorectal and breast cancer	
Immunoglobulins	Multiple myeloma and waldenstrom macroglobulinemia	
LDH	Germ cell tumors	
PSA	Prostate cancer	
Thyroglobulin	Thyroid cancer	

PSA=Prostate specific antigen, LDH=Lactate dehydrogenase, CEA=Carcinoembryonic antigen, hCG=Human chorionic gonadotropin, CA=Carbohydrate antigen

In spite of full workup like tumor markers, PET-CT and modern immunohistochemistry, the primary may be unknown in about 3-5% of these cases.[33]

Clinical Presentation and Workup

Pathological fracture or impending fracture or painful bony lesion without any known history or treatment for cancer

This is the commonest scenario in which a patient presents to an orthopedic surgeon. Proximal femur and proximal humerus are the most common sites, but any long bone could be affected. Alternatively, the spine may be involved, with or without a vertebral fracture or neurological deficit. The workup is outlined in Figure 3. It is very important not to assume diagnosis of a metastatic lesion just because the patient is elderly as infections and primary sarcomas can have a similar appearance. It is also equally important not to assume that the fracture has resulted from osteoporosis. Either way, one should not be in a hurry to operate as unplanned surgery can lead to inappropriate treatment with permanent, irreversible harm caused to the patient. Assuming metastatic disease and performing intralesional surgery can be a disaster for a primary bone sarcoma [Figure 4]. This is more likely to happen in the proximal femur where chondrosarcomas also present in the elderly and are not always mineralized. Pathological fracture is not an emergency, and a clinician will find it worthwhile to do a complete workup prior to any surgery.

It is important to pay attention to small details like revealing an unexpected unpleasant diagnosis to the patient and their family. Diagnosis of metastasis is often not a "death

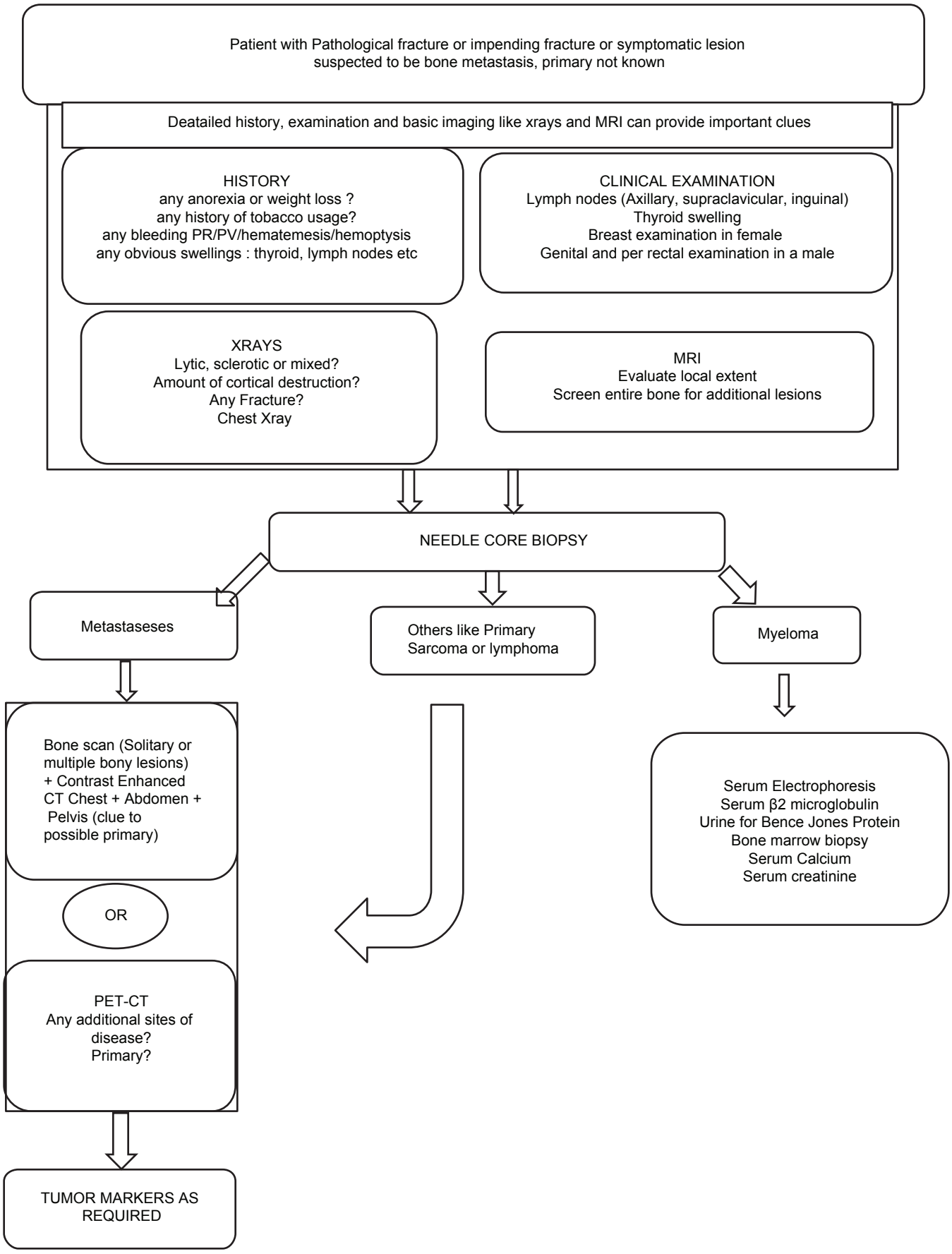

Figure 3: Workup of a patient with a symptomatic bony lesion or impending fracture or pathological fracture from suspected metastases

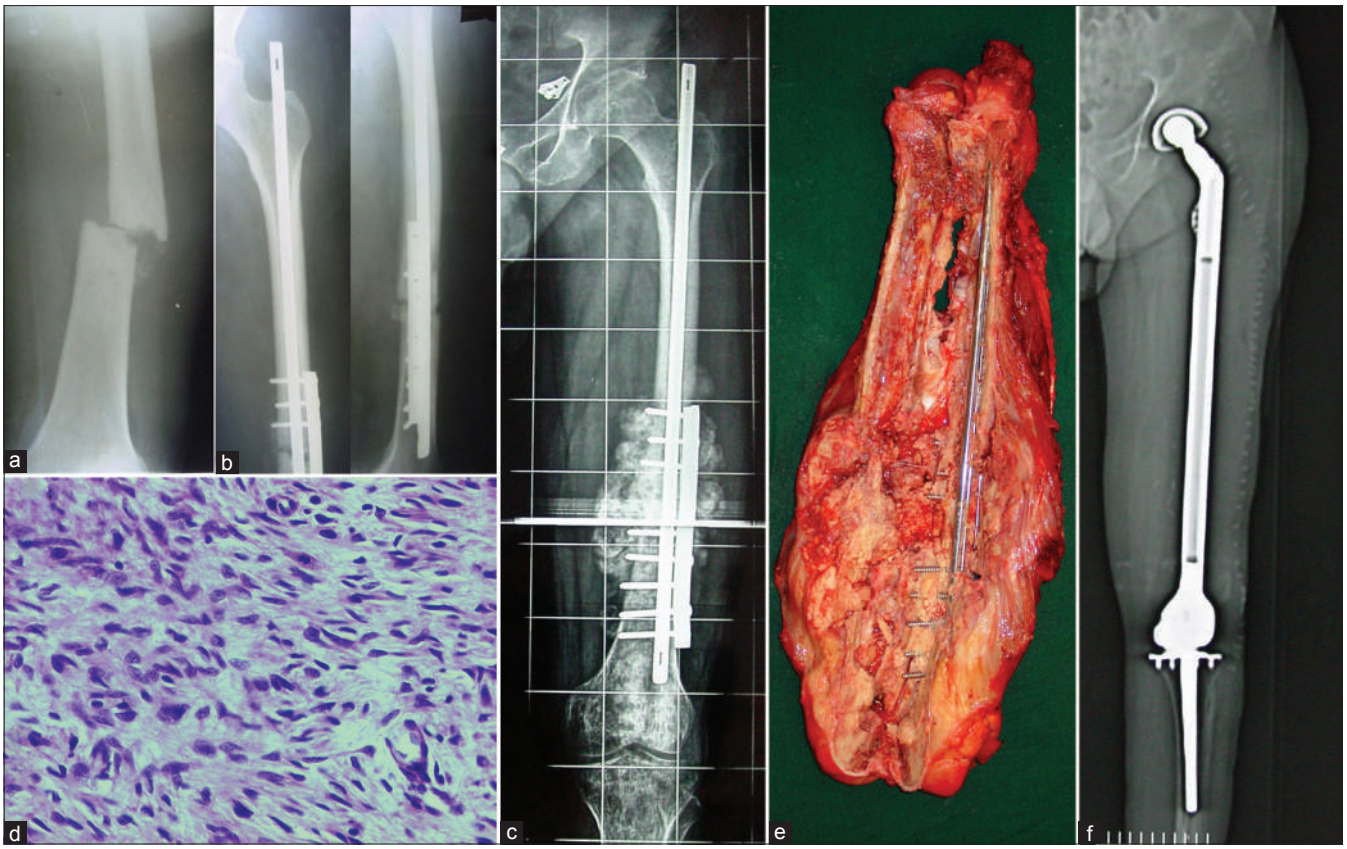

Figure 4: (a) A 50-year-old male with a pathological fracture shaft femur was assumed to have metastasis (b) He underwent immediate fixation with an intramedullary Nail and a derotation plate. No prior biopsy was performed. Figure shows the postoperative X-ray (c) Rapid growth of a bony hard mass at the fracture site a few weeks later prompted a referral. Note the exuberant bone formation (d) Histology proved to be an osteosarcoma (e) Resection involved removing the entire femur. Specimen is bivalved to show the tumor (f) Postoperative X-ray showing the total femur replacement. This would not be necessary were a proper workup done prior to surgery

sentence" and must not prompt resignation and advice for "terminal palliative care." In modern times, patients with metastatic disease can live for several years and early referral to a multidisciplinary oncology team is advised. Once the decision for surgery is made at a multidisciplinary meeting, the surgeon can choose the surgical strategy outlined in the sections below. It is important to estimate a patient's general condition, disease stage and expected survival prior to embarking on any intervention.

Primary is known: The skeletal lesion is picked up on workup or during periodic followup

This presentation is now becoming more frequent as routine surveillance screening with a technetium bone scan or PET-CT often picks up an asymptomatic bony lesion or on followup. Alternatively a bony lesion is detected because of symptoms in a patient known to have a primary cancer. Asymptomatic lesions tend to be smaller, and an opinion is sought by the treating oncologist as to the best line of treatment. A surgeon must not assume that a lesion is metastases even if the primary is known [Figure 5] as infection, benign lesions or primary bone sarcomas (second malignancy) can confound the diagnosis. A needle biopsy can establish the diagnosis. A discussion with the multidisciplinary team which includes at least a medical oncologist and radiation oncologist and preferably also

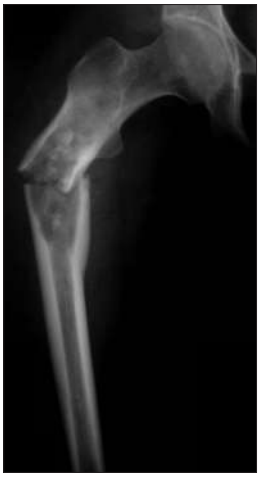

Figure 5: This 54-year-old lady was treated for breast cancer 4 years prior to having this pathological fracture through the proximal femur. It was assumed to be metastasis. A radiologically obvious chondrosarcoma was missed. The treatment and prognosis were radically different, reinforcing the need for histopathological confirmation with a biopsy

an interventional radiologist is required to make the final treatment decision.

Treatment of Skeletal Metastases

The treatment of skeletal metastases is aimed first at maintaining or improving QOL and then at disease control and possible cure. Asymptomatic Metastases detected on workup may require systemic therapy and radiation, primarily aimed at disease control and preventing SRE that include pain, cord compression and fracture. For symptomatic lesions, the treatment is aimed at pain elimination and maintaining ambulation and neurological function. For every lesion, a decision is made by a multidisciplinary team regarding need for analgesia, radiation, systemic medical treatment (chemotherapy, hormonal therapy, targeted therapy or agents to improve bone strength) and need for intervention either minimally invasive (radiofrequency ablation [RFA], cementoplasty, vertebroplasty etc.) or open orthopedic surgery (decompression of spinal cord or vertebral or long bone stabilization). Decision making is best-customized to the individual patient but still based done on evidence-based protocols. With the improvement in systemic treatment, radiation as well as percutaneous interventions, the need for open surgery is much reduced. Logically, the least invasive methods are used upfront reserving the surgical option for the nonresponsive cases in pathological fracture or paraplegia from spinal cord compression.

Bone strengthening (systemic treatment) treatment for prevention of skeletal-related events

The advent of bisphosphonates revolutionized prevention of SRE in both lytic and blastic metastases. By their action on bone turnover they exerted numerous beneficial effects like decreased lysis and associated hypercalcemia, reduced microfractures and insufficiency fractures and associated pain and vertebral fracture induced cord compressions resulting in reduced hospitalizations and improved QOL parameters. These drugs have been useful in pure lytic, blastic and mixed lesions. Zoledronate and pamidronate are time tested pyrophosphate analogues that the work by inhibiting farnesyl pyrophosphataseand causing osteoclast lysis and apoptosis.[34] There is also some evidence suggesting direct antineoplastic activity. Bisphosphonates have been shown to reduce bone-related skeletal events and are widely used for bone metastases in breast cancer, multiple myeloma, lung cancer, and prostate cancer (which also has a level of osteolytic activity).[35,36] The primary side-effects associated with bisphosphonate treatment include anemia, gastrointestinal symptoms (e.g. nausea, vomiting, diarrhea, or constipation), fatigue, fever, weakness, arthralgia, myalgia and less commonly, hypocalcaemia. It is essential to measure serum creatinine before zoledronic acid administration and adjust dosage for renal insufficiency. Since bisphosphonates are known to decrease Vitamin D levels, it is recommended to supplement Vitamin D and calcium before and throughout the duration of bisphosphonate treatment. Osteonecrosis of the jaw (ONJ) is rare, but serious complication of bisphosphonate use most commonly associated with the amino bisphosphonates. A dental evaluation and preemptive dental treatment is recommended to reduce ONJ.[37-39]

Denosumab, a fully human monoclonal antibody to RANKL, is a more potent inhibitor of osteoclastogenesis andbone resorption than bisphosphonates. It has been approved for the treatment of postmenopausal osteoporosis as well as bone metastases from solid tumors and multiple myeloma. It has convenient subcutaneous dosing and is virtually free of immediate adverse events. The incidence of hypocalcemia is a little higher[40] making Vitamin D and calcium supplementation mandatory. The incidence of ONJ is similar but acute reaction like bodyache and flu-like syndrome is much less common than with bisphosphonates.[40] Denosumab was reported superior to zoledronic acid in preventing SRE in a recently concluded randomized trial.[40] It was also easier to administer, it had virtually no short term side-effects and did not need dose adjustments for renal toxicity. The main drawback currently is its high cost. The dosing schedule in all trials has been 120 mg subcutaneously as a monthly dose.

Radiation Therapy

External radiation has a strong role in palliation of pain and local tumor control. Various forms of radiation include external-beam radiation therapy (EBRT) given as multiple fractions or as a single fraction in high dose, stereotactic body radiotherapy and cyber knife radiosurgery. Sophisticated methods of two-dimensionaland three-dimensional conformal radiation therapy (RT), image-guided intensity modulated RT and tomotherapy, have improved precise delivery of radiation and minimized side effects.

The decision for dosage and fraction is determined by location, symptoms, tumor volume and indication for treatment viz. palliation of pain versus medium term tumor control. In most cases for palliative pain relief, equal pain relief is noted by conventional 30 Gy given in 10 fractions versus single dose of 8-10 Gy.[41] Although rate of re-radiation is higher in a single fraction group,[42] it is attractive for its convenience and rapid relief. Evidence shows no difference for response in spinal versus non spinal site and histology of the disease.[41-43] The decision is thus made on life expectancy and patient expectations viz. a patient who has a life expectancy of less than 3 months shall most likely benefit by a single fraction high dose strategy.

The role of hemi-body or whole body radiation is going down with increasing availability of radionuclide therapy that is especially useful in multiple sclerotic bone metastases. Radioiodine is a part of standard treatment for metastases from thyroid cancer. The isotopes for palliative painrelief in use include strontium 89, samarium153 and phosphorous 32. Samarium is the most commonly used isotope in the North American continent. These radionuclides attach to hydroxyapatite and are effective in areas of increased bone turnover. Side effects include debilitating marrow depression which may worsen with repetitive and heavily pre-treated patients. In most cases, adequate repetitive treatment is possible with a tolerable myelosupression. Access and availability in India is yet an unresolved issue. There are no randomized trials evaluating the efficacy of combining bisphosphonates or denosumab with RT. A recent Cochrane review showed equal efficacy of various radionuclides in symptom relief and marrow suppression.[44]

A radiation oncologist's opinion on radio responsiveness of the disease to be treated is a must. E.g., radio resistant painful skeletal metastases from renal cell cancer are unlikely to respond and perhaps are best treated with a surgical modality.

Minimally Invasive Modalities

Upto 30% of patients do not have adequate relief after EBRT. In the modern world, percutaneous modalities like RFA, cryoablation and high intensity focused ultrasound and microwave can relieve the pain and improve bone strength without risk of morbidity from open surgery. RFA is the most common modality used, and multiple studies have shown successful pain relief, decrease in opioid use, and improvement in QOL with minimum complications.[45-47] Most studies have combined cementoplasty (cement injection) after RF ablation particularly for periacetabular lesions. Upto 80% patients have improvement on pain and mobility scores and are able to ambulate independently with low interventional morbidity and complications.[48,49] Cryoablation, with its ability to visualize the ice ball beyond which there is no thermal injury has an advantage over RFA where burn margins are not visible on CT. The postoperative inflammation and pain reported by RF ablated patients seems to be less in cryoablated patients. Although not compared head to head with RF ablation, cryoablation seems to be an attractive modality.[50,51]

High intensity focused ultrasound (HIFU) uses focused ultrasound energy to generate heat. Magnetic resonance guidance is used with HIFU to allow accurate visualization. Published data shows promising results with almost complete pain relief in a high percentage of individuals.[52-56] Lesions less than a cm from the skin surface are unsuitable due to the risk of skin burn. Microwave is another form of thermoablative method under investigation with the advantage of higher ablation volume and faster ablation time.[57-60]

Decision making factors and perioperative considerations

Once a lesion has been completely characterized by full workup including a biopsy, a plan of management is made. Very few conditions like a fracture or impending fracture or neurological deficit warrant early or emergent surgery. Even in emergency, an MRI followed by a biopsy and frozen section can provide a diagnosis in a very short time. If metastasis is strongly suspected as when the primary is known and imaging documents multiple lesions, a frozen section at time of surgery can be used before proceeding to intralesional palliative surgery. This approach is contraindicated in solitary lesions where resection may be considered for metastatic disease and where there is a higher likelihood of the lesion being infection, primary sarcoma or another nonmetastatic lesion. A surgeon must assess whether surgery will provide a QOL. Fixing a painful fracture even in a nonambulatory patient with a limited lifespan is justified if pain relief was not obtained through pharmacological methods or other nonsurgical methods. The most common indications for surgery would be a pathological fracture or an impending fracture. Failure of nonsurgical treatment and pain is also an indication for surgery.

After full staging, a decision is made whether the intention of treatment is curative or palliative. For instance, a patient with operable renal cell cancer and a solitary bone metastasis in femur is selected for R0 resection at both the sites of disease, whereas, same disease with multiple skeletal and spinal metastases is selected for intralesional treatment with palliative intent. The expected lifespan also is an important decision making factor. A longer lifespan favors resection rather than the curettage, for example in hormone-sensitive breast cancer with multiple skeletal metastases and impending fracture of the femoral neck. Longer survival increases the risk of local recurrence with an intralesional surgery and therefore resection may be preferred. It is better to overestimate the survival than underestimate as resurgery in metastatic disease may not be possible or may be risky with advancing disease and deteriorating general condition. The site of disease also matters as disease close to the joint is best resected whencompared to diaphyseal disease. Tumors non-responsive to radiation like renal cell cancer are more likely to require surgery. An unfit patient with poor general condition, coagulopathy or hypercalcemia will also not be a candidate for surgery. Conditions like parkinsonism

that make a patient unreliable for following instructions of limited weight bearing make the surgical option more likely. Finally, the experience and expertise of the surgeon as well as available infrastructure facilities will decide the option of treatment. For example, nonavailability of tumor embolization may go against doing the intralesional surgery in the proximal femur for a large thyroid metastasis.

Once surgery is considered, other factors must be considered that will affect the patient outcome. The patient should have a general condition which allows them to withstand the stress of an operation. Many cancer patients are elderly and have limited physiological reserve due to age or the treatment particularly chemotherapy. It is estimated that 60% of patients may have medical comorbidities.[61] It is important to have a physician and anesthetist evaluate this prior to surgery. Highest mortality related to surgery and anesthesia occurs from cardiac-related events. Patients with renal failure are at particular risk for nonfatal perioperative complications (60%), particularly hyperkalemia, pneumonia, and hypotension.[62] The serum albumin is a quick method to screen the patient's nutritional status. A serum albumin less than 2 g/dL is an indicator of severe nutritional impairment and a risk for wound healing problems.[63] Cancer patients often suffer from an array of electrolyte disturbances related to calcium, magnesium, potassium, sodium and phosphorus which may require correction prior to surgery. The importance and risks with these are commonly underestimated. The risk of hypercalcemia in particular is high and has been estimated to be 5-20%.[64]

Ewer and Ali[65] offer a risk categorization that is geared specifically to oncology patients, which is based on the physical examination, laboratory data, cardiac function, arterial blood gases, and ventilation mechanics. Nonsurgical methods are recommendedfor patients in the high-risk category.

Blood transfusions are frequently needed perioperatively. Oncology patients are often immunocompromised and susceptible to blood-borne pathogens, in particular, cytomegalovirus. Irradiated blood products reduce the risk of this transmissible viral agent. Leukocyte depletion filters reduce the febrile reaction. Intraoperative autologous blood transfusion can reduce the need for banked blood particularly in planned elective surgery. Platelet transfusions and Fresh frozen plasma may be required to correct coagulation disorder. Preoperative tumor embolization upto 24–36 h prior to surgery particularly for very vascular lesions like metastases from kidney and thyroid cancer can reduce the bleeding and need for transfusion.

Deep venous thrombosis is also a perioperative risk both from the malignancy and from immobility in these patients. Adequate prophylaxis or sometimes placement of filters in the inferior vena cava may be required.

Cardiopulmonary dysfunction and hypotension arising from marrow embolism during or following intramedullary instrumentation either for nailing or joint replacement is an underestimated and potentially fatal but avoidable complication.[66] This results from release of showers of vasoactive, inflammatory and thrombogenic substances from the intramedullary canal.[67] The risk of systemic hypotension after manipulation and pressurization of the femoral canal is highly variable and has been reported from 5% to 50%.[68] Choong reported a 20% incidence of hypotension and mortality of 10% or more has been reported after hypotensive episodes.[67,69] Strategies suggested reducing this incidence include pulse lavage to remove tissue and vasoactive products from the intramedullary canal.[70-72] Flexible, small diameter drive shafts to allow the intramedullary contents to escape up the femoral canal,[73] and proximal and distal venting of the canal to reduce build-up of pressure.[74] Additional steps like maintaining normovolemia increased inspired oxygen and decreased volatile agent concentration,[68] and maintaining aortic perfusion pressure with vasopressors like norepinephrine is recommended.[75,76] It is best to perform this surgery electively in the normal daylight working hours when best anesthesia and surgical expertise is available.[67]

If nonsurgical option is chosen, it avoids dangers of open surgery but involves protected weight bearing with crutches or walker and possible use of external orthosis along with radiation. Fracture risk is still present and can happen without warning. Weight bearing can be resumed once lesion has healed radiologically.

Surgery for spinal metastases

Vertebrae are common sites for skeletal involvement, thoracic followed by lumbar and less commonly cervical and sacral segments. Autopsy studies have shown that as many as 70% of patients with cancer have spinal metastases.[77] Spinal metastases with spinal cord compression occur in 5-14% of cancer patients.[77,78] Most metastatic disease is extradural, but rarely intradural or even intramedullary deposits can occur. Surgical techniques today allow more extensive disease to be tackled with lesser morbidity and sometimes even disease control. The main indications for surgery being restoration of neurological function and spinal stability and rarely disease control.

The MRI is able to assess the extent of epidural disease and cord compression. MRI also reveals if the compression is from the soft epidural tumor or from a bony retropulsed fragment.

Round cell tumors like Ewings sarcoma and lymphoma as well as prostate metastases are extremely sensitive to systemic treatment (former to steroids and chemotherapy drugs and latter to androgen deprivation by castration) and can be given a chance at recovery without open surgery [Figure 6]. Tumors located in the junctional regions such as the occipitocervical, cervicothoracic, thoracolumbar, and lumbosacral junctions and in the mobile segments of the spine (C3 through C6 and L2 through L4) are more likely to be associated with instability. Movement-related pain which is absent on recumbency, more than 50% vertebral height collapse, bilateral facet and pedicle involvement or any subluxation or translation points to instability. Severe instability also requires surgery as systemic treatment is unlikely to provide the required stability.[79]

Historically, surgery without fixation was equivalent to EBRT.[80] Patchell *et al*.[81] showed that surgery with EBRT was clearly superior to EBRT alone in maintaining ambulation. 62% of the patients who were nonambulatory at the time of recruitment regained the ability to walk. Literature reveals ambulatory rates ranging from 74% to 100% after surgery, with 57-82% of nonambulatory patients regaining ambulation.[82] Cochrane database review[83] of 2008 reported that surgery prior to radiotherapy gave better recovery of function in selected cases. The authors suggest that radiotherapy alone may suffice for ambulant patients with stable spines but there is evidence of benefit from decompressive surgery in ambulant patients with poor prognostic factors for radiotherapy and in nonambulant patients with a single area of compression, paraplegia <48 h, nonradiosensitive tumours and a predicted survival of more than 3 months. Improvement in pain has been observed in more than 90% of patients who underwent instrumented stabilization.[84] In contrast, Rades *et al*. in a matched pair analysis found no benefit of surgery with RT compared to RT alone, particularly in elderly patients.[85,86] we would recommend a customized approach taking into account several patient and disease-related factors as discussed above.

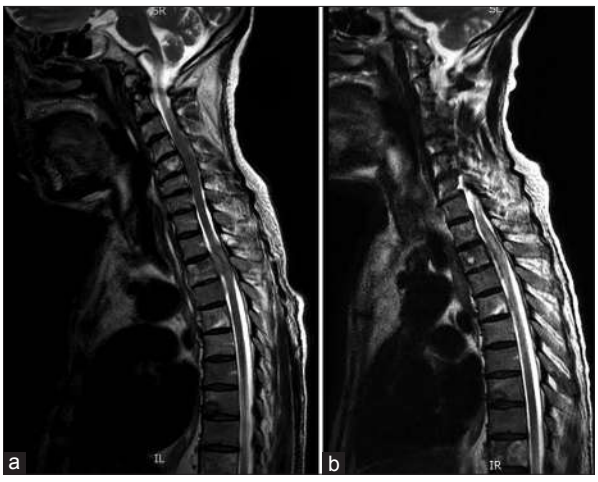

Figure 6: MRI T2W sagittal image showing (a) metastasis with cord compression (prostate) (b) Response to orchidectomy can often be dramatic as shown in the image on the right and may obviate the need for immediate surgery

The amount of surgery ranges from simple decompression to an *enbloc* resection and fixation. Several rating scales have been proposed[87,88] especially to aid selection of patients for more extensive resection. Patients with solitary metastases with favorable histology like breast cancer are more often selected for the *enbloc* resections in view of longer life and therefore need to maintain QOL. Solitary Metastases from lung or Renal cancer which are often radioresistant are also candidates for resection rather than simple decompression and fixation.[89] The approach and the fixation are dictated by the lesion and in this modern era of superspecialization, we recommend that the spine specialists be involved in the surgical care of these patients. As a basic rule, one must do the minimum required to achieve the goal of pain-free ambulation for as long as possible. The anterior or posterior approach depends on the exact site, experience of the surgeon and the procedure to be carried out. The posterior approach is most favored due to the ease, familiarity and ability to decompress as well as stabilize well. Preoperative embolization helps reduce bleeding and transfusion-related morbidity particularly in hypervascular tumors like thyroid and renal cell carcinoma (RCC) metastases. Preoperative embolization also allows better vision and therefore better decompression.

Surgery for metastases of appendicular skeleton

The surgical procedure chosen will have to be customized to the region involved, skill and experience of the surgeon, infrastructure available, costs that patient can bear and expected survival.

Solitary lesions require special mention as they are biologically different and associated with better survival. In selected cases, resection of solitary lesions may improve disease-free survival and even cure.[90-94] If the primary is unknown after the extensive workup, a solitary metastatic lesion should be resected rather than treated with intralesional surgery if morbidity is acceptable.[95]

The usual surgical options vary from internal fixation with a nail or plate with or without cement and endoprosthetic arthroplasty. The exact choice depends on the location, amount of bone loss and responsiveness of lesion to systemic therapy. Non responsive lesions are best resected to minimize the risk and morbidity of a local recurrence [Figure 7]. It may be wise to resect those lesions where patient is expected

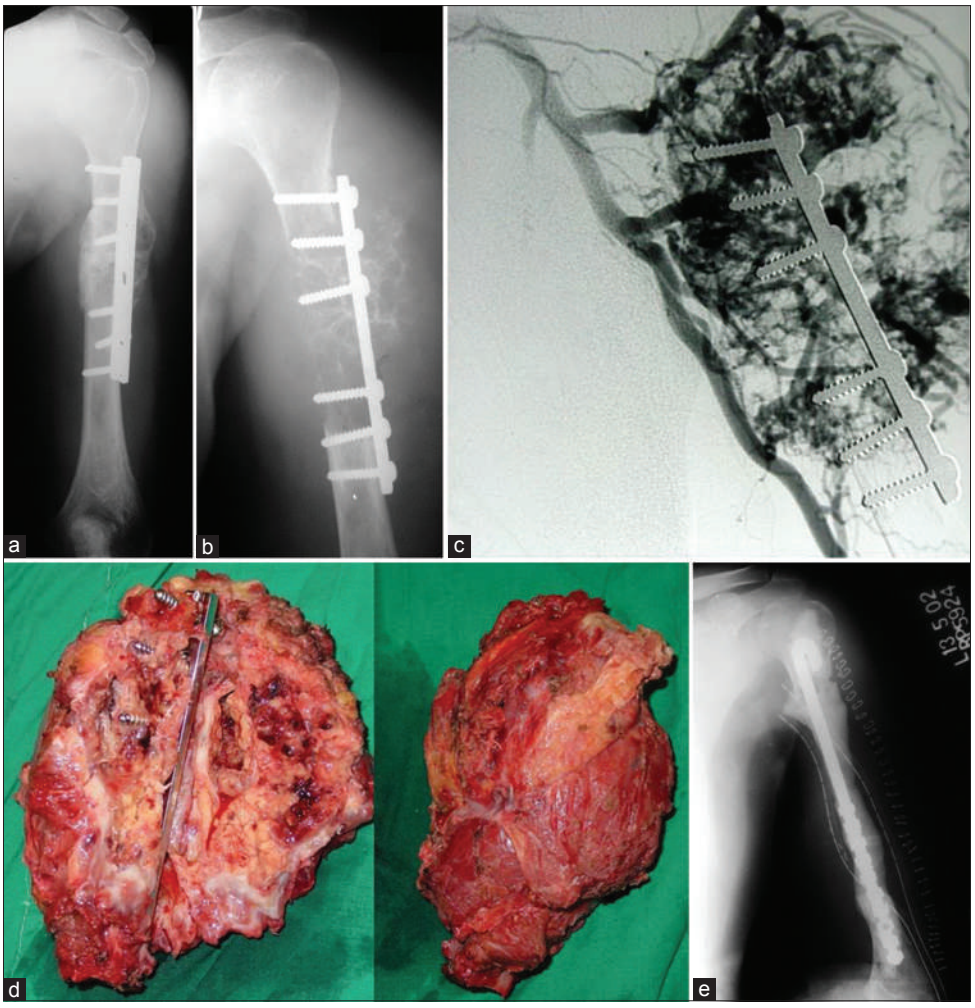

Figure 7: X-ray of the arms with shoulder joint anteroposterior view (a and b) showing local recurrence after previous cementing + fixation in renal cell carcinoma metastasis (c) Angiogram showing the hypervascularity. Preoperative embolisation is a must especially if intralesional surgery is contemplated (d) Resection specimen (e) Postoperative X-ray showing a nail-cement spacer. This is a cost effective construct in the upperlimb and sometimes in the lowerlimb

to have long survival [Figure 8]. Periarticular lesions are often resected and reconstructed with arthroplasty. Diaphyseal lesions can also be resected and reconstructed with a diaphyseal prosthesis [Figure 9] but they are mostly treated with intralesional surgery with or without cement depending on the bone loss. Nails or rods being inside the medullary canal are considered load sharing compared to plates which are external to the bone and considered load bearing. As a general rule, nails are preferred in the lower limbs and plates in the upper limb. Wherever possible, the maximum length of the bone is stabilized inorder to minimize a future fracture at another location. Even when a closed nailing is done for an impending fracture, the lesion should be debulked maximum possible, especially in lesions less responsive to radiation as this reduces the risk and morbidity of local recurrence.[96] Bone cement or polymethyl methacrylate (PMMA) is excellent in filling up areas of bone loss and providing compressive strength to the construct. Bone grafting is, usually, avoided in metastatic lesions as radiation used postoperatively would prevent incorporation. Doses below 3000 rad have been shown not to prevent callus formation.[97] Besides, the goal is to provide immediate mobility for which strength provided by PMMA is ideal. For the same reasons, cemented arthroplasty is preferred over uncemented arthroplasty. With extensive bone loss, resection is preferred. The rate of pathological fracture healing has been reported as 67% for myeloma, 44% for RCC, 37% for breast carcinoma and 0% for lung carcinom.[97] The surgeon is advised to assume that the fracture will not heal, and patient will survive, so that a durable construct is provided. Better to overestimate survival than underestimate. One must keep in mind the fact that a patient operated for metastatic disease may never be fit to undergo another surgery for a complication like implant failure or for local recurrence.

Pelvic and periacetabular defects

Surgery is only required for those lesions that compromise the load transfer from the lower limb to spine. These are

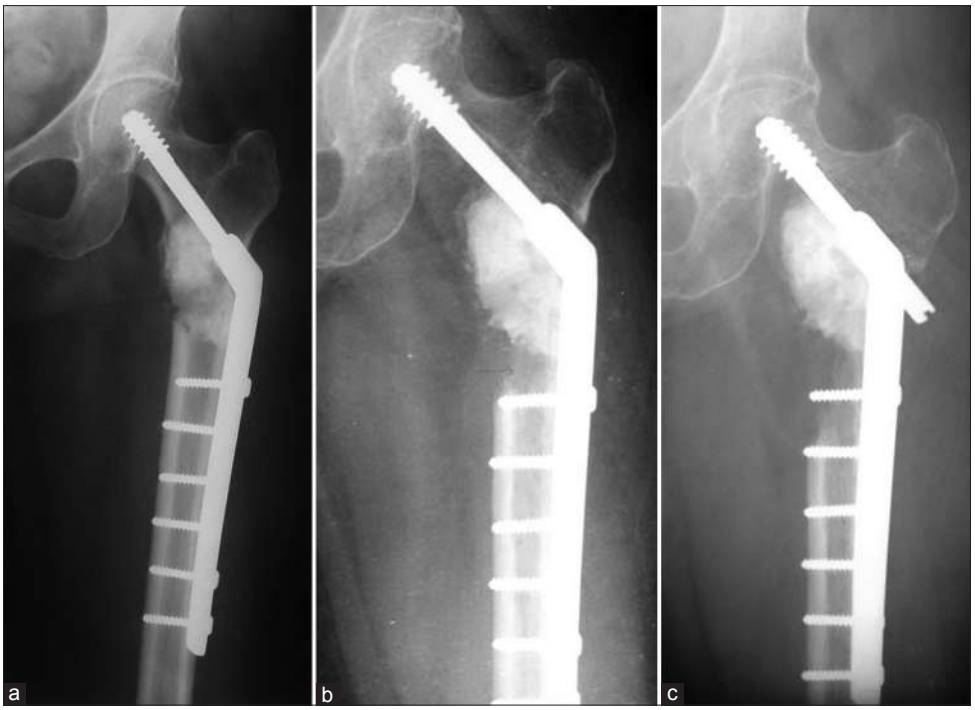

Figure 8: (a) Postoperative X-ray after intralesional curetting and cementing of a metastatic lesion from breast cancer (b) Local recurrence is seen within a year despite postoperative radiotherapy (c) Progressive disease which required resection. In patients with long expected survival, primary resection may obviate need for more surgery in future

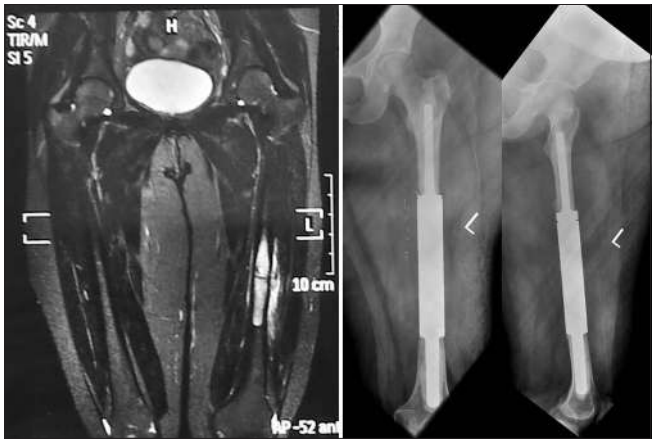

Figure 9: A solitary diaphyseal metastasis from uterine leiomyosarcoma treated with resection and diaphyseal prosthesis. It allowed immediate weight bearing ambulation and preservation of native hip and knee

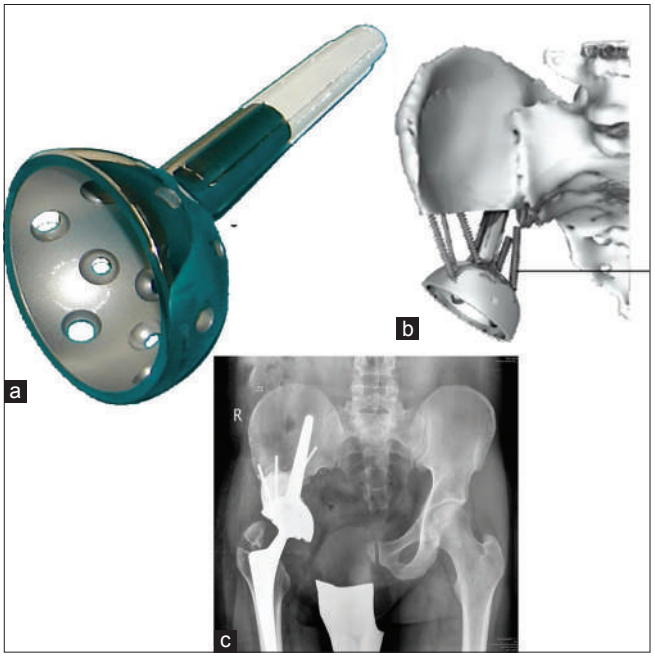

Figure 10: (a) Inverted ice cream cone prosthesis from Stanmore implants worldwide (Stanmore,UK) is useful in reconstructing large periacetabular defects and allows immediate weight bearing (b) The stem is hydroxyapatite coated and anchors in the strong posterior ilium while cement screw struts fashioned allow additional mechanical integrity. It can often be combined with a constrained liner to prevent dislocations (c) Postoperative x-ray showing the implant in place

lesions that affect the superior and medial acetabular walls, as well as the medial column of the pelvis and the posterior ilium in the region of the sacroiliac joint. Posterior Ilium lesions not involving the acetabulum can be treated by intralesional debulking and cement augmentation. Acetabular lesions that are contained (with an intact medial wall) can be reconstructed by a cemented arthroplasty. Uncemented cups run the risk of loosening and migration from failure to osteointegrate from radiation used postoperatively or from osteolysis due to disease progression. Protrusio acetabular cups compensate for deficiencies ofthe medial wall, while cement and pin fixation[5,97-101] (modified Harrington method) can be used effectively to reconstruct large defects in the acetabular

column and dome.[102] Massive bone loss may require resection or reconstruction with an acetabular prosthesis. Stemmed acetabular implants now available (an inverted ice cream cone prosthesis or pedestal cup) allow anchorage of the acetabular shell into the posterior ilium with the stem [Figure 10]. Immediate weight bearing is possible with these implants. Alternatively, a customs acetabular or pelvic prosthesis may be used. As these resections and reconstructions are massive and involve significant blood loss and risk of complications, it is important to have determined preoperatively that the benefits outweigh the risks. Pain relief and immediate weight bearing are the obvious advantages of this reconstruction.[102]

Proximal femur

Lesions of the femoral neck and head are best treated with hip arthroplasty as internal fixation has high failure rate.[100] Hemiarthroplasty is adequate when acetabulum is not involved,[103,104] else an acetabular surfacing is done as well. A routine acetabular replacement would increase the risk of dislocation and is, therefore, reserved for lesions that involve the acetabulum as well. For extensive lesions, proximal femur megaprosthesis is used. A constrained liner can be used in cases judged to be at high risk for dislocation. Cemented stem is preferred as uncemented stems may loosen and fail over a period of time due to nonintegration after radiation or tumor-induced osteolysis. The benefit of a long stem has been that it prevents fracture from another lesion that may appear in the future as entire length of bone can be spanned. However, long stemmed implants increase the chance of embolism from longer canal instrumentation increase.[105,106] The best indication for a longer stem is when a diaphyseal disease is present in addition to the disease in the neck or head. With modern surveillance, should a distal disease appear, it can be tackled on its merit subsequently.

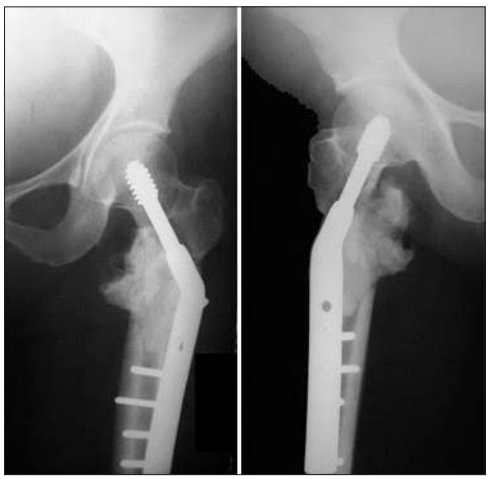

Figure 11: X-ray of hip joint anteroposterior view showing challenge of cementing in intertrochanteric lesions. Calcar has to be built up to allow least chances of failure in a high stress zone

The management of intertrochanteric lesions is more controversial, and opinion is divided between fixation and prosthetic replacement. Most orthopedic surgeons are familiar with the DHS and also the now available gamma nail. If fixation is used it is imperative to confirm that the head and neck offer good purchase as the construct depends on this. The challenge lies in reconstructing the void in the calcar area with cement [Figure 11]. The great advantage is lesser surgery and hip joint preservation. If replacement arthroplasty is chosen, a calcar replacement type or megaprosthesis is chosen.[107] The diseased bone is completely or almost completely excised reducing the risk of local recurrence. Additionally, there is no reliance on that diseased bone for weight bearing. We have generally preferred this option owing to its reliability in restoring ambulation though there is a higher risk of infection, trochanteric fracture or hip dislocation as compared to internal fixation.

The subtrochanteric zone is a high-stress zone with loads reaching 6 times body weight.[108] This poses a great challenge to most internal fixation devices, particularly the nail-plate devices. The implants of choice are, therefore, the intramedullary nail or prosthetic replacement. The nail is preferred for smaller lesions where adequate fixation is possible, and replacement preferred for more bone loss,

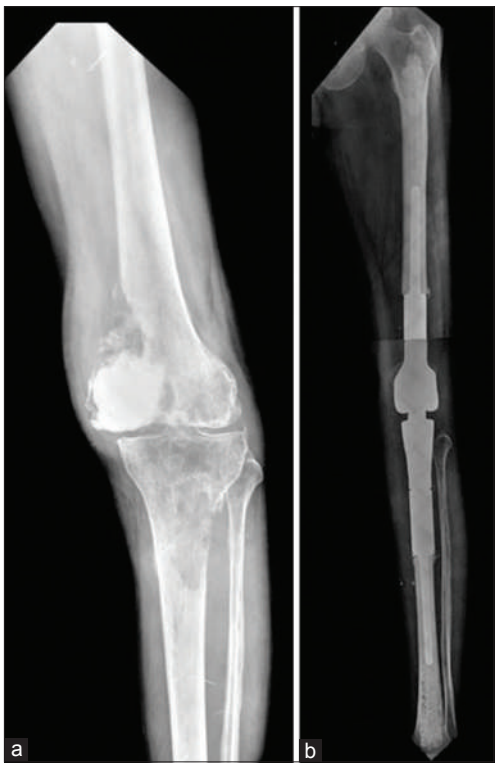

Figure 12: (a) Extensive involvement of distal femur and tibia in a case of renal cell carcinoma resistant to therapy. Intralesional surgery with cement had been done earlier (b) Composite resection of distal femur with proximal tibia over a fixed hinge prosthesis allowing immediate weight bearing

and also if secure purchase in the head and neck is in doubt.

Femoral diaphysis

Lesions of the femoral diaphysis are best treated with an intramedullary nail that not only spans the entire femur but also includes fixation into the femoral neck and head. It is important to ensure that there is no disease in head and neck and that the bone is strong enough for the purchase of interlocking screw failing which failure rates are higher. Calcar replacing or megaprosthetic arthroplasty are preferred in these situations.[107] Titanium nails would be preferred to stainless steel as they can be thinner and stronger allowing lesser instrumentation of the canal and lesser risk of failure. For solitary lesions, resection is done, and reconstruction options available include a diaphyseal replacement prosthesis, a nail-cement spacer or reconstruction with bone (allograft or autograft depending on the length of the defect).

For distal femoral defects, curettage and cementing with or without fixation can be used for smaller defects. Larger defects can be treated with resection and megaprosthetic replacement.

Lesions in Tibia are much less common than in femur and are managed much like in femur. Curettage or resection of proximal tibial lesions depends on the size of the lesion. Sometimes a resection of both distal femur and proximal tibia is required to restore ambulation [Figure 12]. Tibial shaft lesions are treated with the same principles as femoral shaft lesions [Figure 13]. Shows a distal femoral fracture with a tibial lesion in a patient with myeloma treated with a distal femur megaprosthesis and a custom long stem tibial component to bypass the tibial lesion which was curetted and cemented.

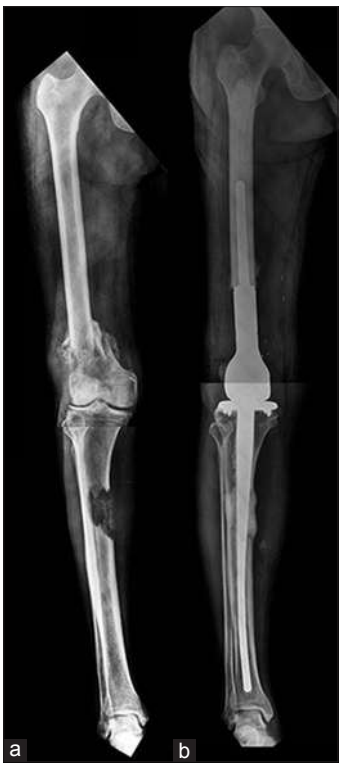

Figure 13: (a) Preoperative X-rays of a 70 year old with recalcitrant but indolent myeloma affecting the distal femur and tibial shaft (b) Reconstruction was done in a single step with a distal femur megaprosthesis with a custom tibial tray with a long stem. The patient, a practicing lawyer was back to work in 4 weeks after surgery

Metastases in the Upper Extremity

In contrast to the lower extremity, the upper extremity being non weight bearing has much less need for endoprosthetic reconstructions. Plate or rod fixation with cement is generally adequate for most lesions with prosthesis being reserved for proximal humerus fractures with massive bone loss. Whether a standard Neers type prosthesis is used or a megaprosthesis is used depends on remaining bone stock. Resections generally require a megaprosthetic type of replacement [Figure 14]. This type of replacement is associated with poor shoulder function, as a normal

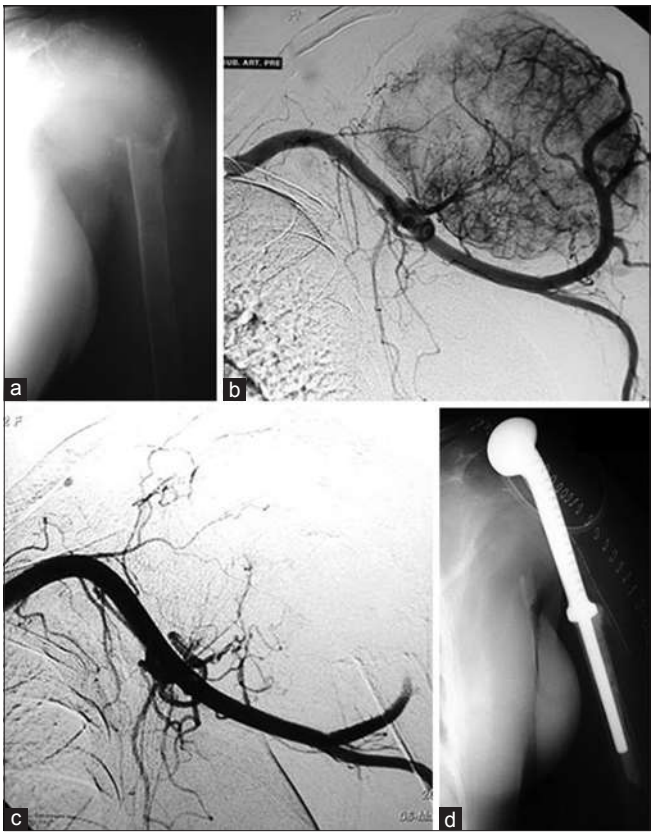

Figure 14: (a) Proximal humeral metastasis from thyroid cancer in a 55-year-old lady (b) Hypervascularity seen on the angiogram (c) preoperative embolization has obliterated hypervascularity (d) Resection was done as thyroid malignancies are associated with relatively long survivals even with extensive bony metastases. Resection greatly minimizes the risk of local recurrence. The embolization makes the surgery easier

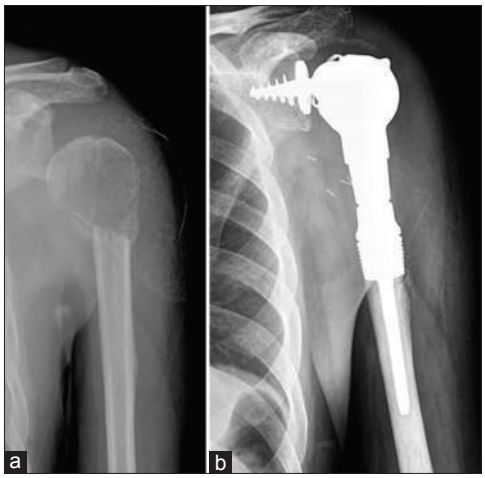

Figure 15: (a) The radiograph depicts a 56-year-old male who presented with a pathological fracture while serving during a game of tennis. Biopsy revealed a metastatic cancer. Positron emission tomography-computerised tomography (PET-CT) showed this to be solitary metastases from renal cell carcinoma (b) Resection and reconstruction with a reverse shoulder type of implant (Stanmore Implants Worldwide, UK) preserving the deltoid muscle and axillary nerve allows better abduction and flexion

attachment sites for the rotator cuff musculature are lost. A reverse type of shoulder prosthesis can be used where glenoid is preserved and where the deltoid muscle and axillary nerve are spared [Figure 15]. A reverse shoulder can provide stability as well as reasonable active flexion and abduction. Both nails and plates can be used depending on the situation as well as surgeon preference. As in the femur, we prefer to fix long to avoid future disease related fractures in the same bone. For scapular lesions, a partial or total scapulectomy is performed generally when resection is chosen. Distal humerus and forearm bone are rarely involved, and resection is required only for large lesions or solitary metastases. Custom implants can sometimes provide good solutions in the forearm [Figure 16].

Conclusions

With the increasing survivals of patients with metastatic disease, a proper workup prior to surgery including a biopsy and early involvement of a multidisciplinary oncology team is recommended. Percutaneous modalities can relieve pain and provide rigidity to bone without the morbidity of open surgery. Surgery should be well planned and properly executed. We emphasize that pathological fractures are not an emergency and proper workup is mandatory before any intervention. The patient's longevity should be over estimated than underestimated, and one must assume that fracture will not heal and plan a construct accordingly. Perioperative steps and intraoperative care can reduce bleeding and embolic events. Resections are done in selected cases particularly for solitary metastases. Wherever possible, an opinion

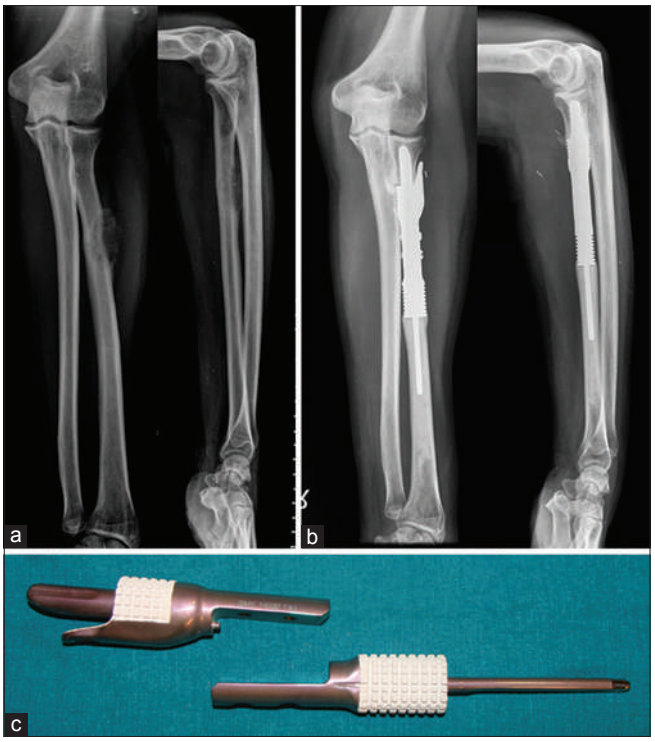

Figure 16: (a) Proximal radius lesion which on biopsy was a metastatic carcinoma. Positron emission tomography-computerised tomography revealed a lung primary with this lesion being a solitary metastasis (b) After chemotherapy, both lesions underwent resection. The radius was reconstructed with a custom intercalary prosthesis (c) Custom prosthesis, proximal and distal segments

from an orthopedic oncologist be sought to ensure that best possible care is being provided. Even if cure is not possible, proper management of metastatic disease can provide QOL for a reasonable amount of time.

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Technical Note

A reduction clamp for an aiming component in associated acetabular fractures

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Abstract

Background: The treatment of acetabular fractures is complex and requires specialized equipment. However, all currently available instruments have some disadvantages. A new reduction clamp that can firmly enable reduction and not hinder subsequent fixation procedures for some special fracture types is needed.

Materials and Methods: In this study, we introduce a new acetabular clamp and its preliminary clinical application in three T-shaped acetabular fractures.

Results: This new clamp can successfully pull the posterior column back to the anterior column and firmly maintain the reduction. This clamp's aiming plate can facilitate the insertion of long lag screws. The clamp is also easy to assemble and use.

Conclusion: This reduction clamp is a useful instrument that can facilitate open reduction and internal fixation of acetabular fractures.

Key words: Acetabular fracture, open reduction, reduction clamp

MeSH terms: Acetabulum, fracture fixation, internal fracture fixation, clamps, surgical

Introduction

Acetabular fracture is usually caused by high energy trauma. If not properly treated, these fractures result in severe disability. Open reduction and internal fixation is the standard treatment for acetabular fractures displaced more than 2 mm.[1] Poor reduction of the acetabular joint surface foretells poor function of the affected hip joint.[1] Until date, the treatment of complex acetabular fractures remains a challenge even to the experienced trauma surgeons.[2-5] Specialized pelvic implants, instruments and facilities are required for optimal treatment of these fractures. Pelvic clamps developed by the Association for Osteosynthesis/Association for the Study of Internal Fixation (AO/ASIF) group and bone hooks are the most commonly used instruments. Each instrument, however, has its own disadvantages and new instruments are required for some special acetabular fractures. We invented a reduction clamp to facilitate the open reduction and internal fixation of associated acetabular fracture types, such as the complete both column fracture, anterior column and posterior hemitransverse fracture and T-shaped fractures. This clamp is mainly used in the anterior or ilioinguinal approach, for reducing the posterior column to the anterior column and for maintaining reduction. In this study, we present the usage and preliminary information on this reduction clamp.

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Materials and Methods

Our reduction clamp comprises a proximal reduction hook, two female screws, an aiming plate to guide drills in the correct direction, a hexagonal socket set and a main pole, the proximal end of which contains threads and its distal end contains a hook and a handle [Figure 1].

A standard ilioinguinal approach was used with the patient in supine position on a radiolucent table and the acetabular fracture was visualized. The internal obturator muscle is elevated from the quadrilateral surface with a retractor, most of the quadrilateral surface is visualized and the edge of the greater sciatic notch could be palpated by fingers. After hematoma and debris are cleaned up, the fracture configuration could be identified and the acetabular fracture can be reduced. For different fracture configurations, different reduction strategies are adopted and several attempts are

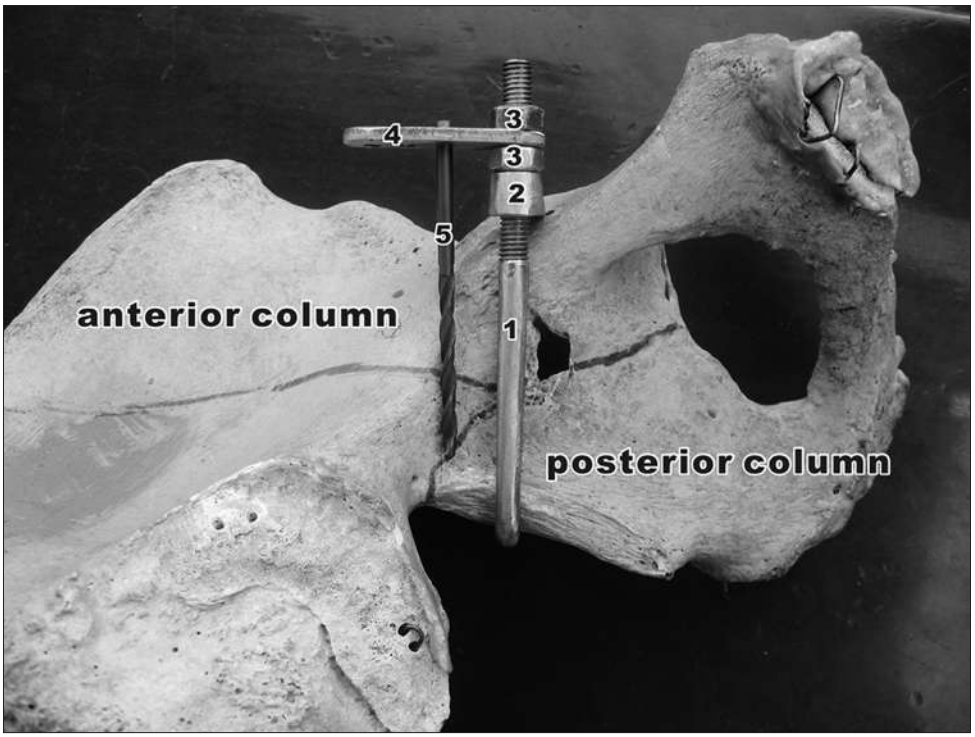

Figure 1: A schematic photograph showing the components of acetabular fracture reduction clamp. 1 main pole, 2 proximal hook, 3 two female screws, 4 an aiming part, 5 the drill

given before the final successful reduction. One of the most commonly adopted strategy is to reduce anterior column to the proximal part of fractured acetabulum and then pull the posterior column onto the anterior column. The detail of this strategy is described as follows. First, the main pole of this instrument was inserted along the quadrilateral surface of the acetabulum. The hook was positioned to catch the greater sciatic notch of the posterior column on the part just below the fracture line. Then, a proximal reduction hook was added along the main pole from its proximal end and was adjusted to hold the anterior column at the arcuate line or iliopubic eminence. A female screw was used and tightened by a hexagonal socket set to close the proximal and distal reduction hooks. Thus, the posterior column was reduced to the anterior column. Any rotation of the fracture fragments was carefully corrected. After the fracture is reduced, the female screw is tightened further to hold the reduction temporally. The aiming plate was added and another female screw was added. A suitable point for inserting a lag screw was selected and the last female screw was tightened by the hexagonal socket set so that the aiming plate was perpendicular to the main pole. A drill was passed through the selected hole in the aiming plate thus, the drill was parallel to the quadrilateral surface to prevent penetration into the acetabular joint. The last female screw was loosened and the aiming plate was rotated aside or taken out after confirming lack of penetration into the joint cavity. A length gauge was used to measure the length of the lag screw and the selected screw was used for fixation. After finishing several long lag screws and some K-wires, the reduction clamp was taken out and a suitable reconstruction plate is selected and adjusted based on the bone shape and surface. After the reconstruction plate was fixed by screws, the reduction and internal fixation was confirmed on C-arm fluoroscopy. The incision closed in layers.

Results

Three T-shaped acetabular fractures were reduced and fixed by this clamp [Figure 2]. The mean operation time was 3.5 h, which is similar to our previous operation time.

Discussion

Associated acetabular fractures are difficult to deal with, even for the experienced trauma surgeon. Reducing and achieving the configuration of the injured acetabular joint is of paramount importance.[6] Open reduction and internal fixation is the standard treatment for displaced ones if no contraindication exists.[7-10] Special tools are needed to facilitate reduction and temporal fixation during the surgical treatment for associated acetabular fractures; these tools, which are currently being used, are still being refined.[11-19] A bone hook is the simplest tool and is used frequently; however, it also possesses obvious disadvantages. First, maintaining consistent pulling of the bone hook requires a strong assistant who will not tire easily. Once the assistant

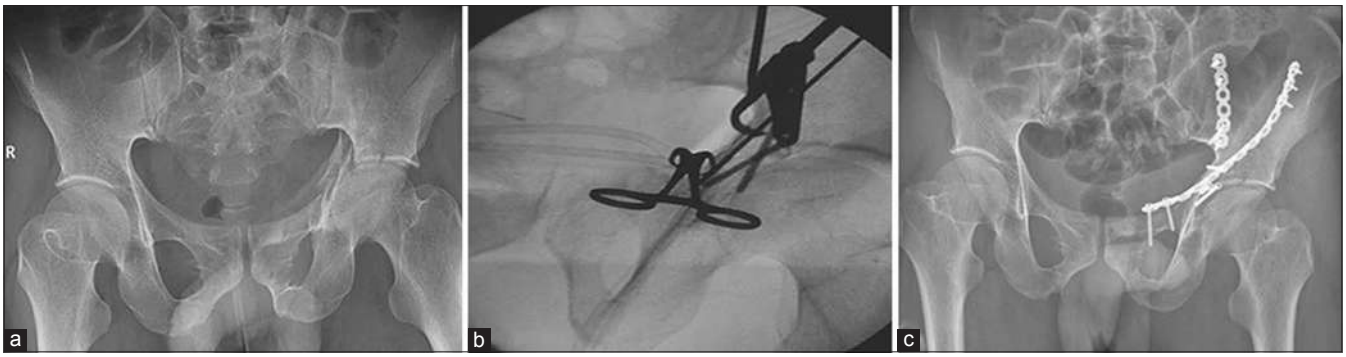

Figure 2: (a) X-ray pelvis with both hip joints anteroposterior view of a man, 46 year-old showing T-shaped acetabular fracture in his left hip. (b) Fluoroscopy image showing the usage of reduction clamp during operation. (c) Postoperative film showing that the fracture is well reduced and fixed with lag screws and reconstructive plates

is fatigued, the reduction of the acetabular fracture will easily be lost during internal fixation. Second, the adjacent neurovascular bundle composed of the sciatic nerve, superior gluteal artery and nerve and obturator artery could be injured if the bone hook accidentally slips off. Pelvic clamps developed by the AO/ASIF group for reduction of fracture fragments are especially helpful.[20] In some occasions, especially in oriental patients with a small body frame work, the bone hook is too large and inconvenient, which may cause some trouble in the process of reduction and plate fixation. Our acetabular reduction clamp, which is smaller than the AO clamp, keeps the reduction firm and persistent. The aiming plate ensures the accuracy of inserting long lag screws to prevent penetration into the hip joint. Our preliminary three cases verify these advantages; however, more number of cases are still needed to demonstrate its advantage. Our reduction clamp may also facilitate the open reduction and internal fixation of other associated acetabular fractures, such as the complete both column fracture, anterior column fracture and posterior hemitransverse fracture.

Conclusion

This acetabular reduction clamp is easy to be use. It can also reduce the posterior column to the anterior column and keep the reduction stable. Moreover, it provides guidance for inserting long lag screws. It facilitates the open reduction and internal fixation of some types of associated acetabular fractures, especially for tiny oriental patients. In comminuted quadrilateral plate fractures or those with acetabular roof/femoral head impaction, this clamp should not be used because compression using the clamp would lead to narrowing or malrotation of the fractured ends and eventual poor results.

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Case Report

Anomalous biceps origin from the rotator cuff

Samik Banerjee, Vipul R Patel[1]

Abstract

Variations in the origin of the long head of biceps tendon (LHBT) have been described in literature; however, its clinical significance remains uncertain. We describe in this report, the history, physical examination and the arthroscopic findings in a patient who had an anomalous origin of the LHBT from the rotator cuff, resulting in restriction of range of motion. This anomalous origin of the long head of biceps tendon causing capsular contracture and restriction of movements leading to secondary internal impingement, has not been extensively reported in the literature. Shoulder arthroscopists should be aware that, although, an uncommon clinical condition, the aberrant congenital origin of the LHBT from the rotator cuff can rarely become pathologic in middle age and lead to shoulder dysfunction. In such cases, release of the anomalous band may be required, along with the treatment of other concomitant intraarticular pathologies in the glenohumeral joint.

Key words: Anomalous, biceps, impingement, rotator cuff
MeSH terms: Shoulder impingement syndrome, rotator cuff, tendons

Introduction

The long head of the biceps tendon (LHBT) is known to originate from the superior glenoid tubercle. After its origin, the LHBT traverses the glenohumeral joint (intraarticular part) and the inter tubercular sulcus (extra articular part) before becoming a musculo-tendinous structure. However, a number of authors have reported substantial variations in its origin.[1-4] Early fetal studies have found that the LHBT and the glenoid labrum develop from a loosely organized layer of cells around the shoulder joint.[5,6] This cellular layer also gives rise to the synovial membrane, joint capsule and the subscapularis muscles. These embryological origins may explain some of the variations in the attachment of the LHBT.[1-4] In a cadaveric study of 105 fresh frozen shoulders of both sexes from 3rd to 9th decade, it was found that in 50% of cases, the LHBT originated from the supraglenoid tubercle and the rest from the superior labrum, with most of the origin reported to develop from the posterior aspect of the labrum.[7]

A number of anatomic variations in the origin of LHBT have been reported in literature, such as supernumerary heads, bifurcated origin from the supraglenoid tubercle and posterior labrum, capsular origin, aberrant intraarticular origin from the rotator cuff, and split tendon from a single origin. However, these variations are seldom observed in clinical practice. Nevertheless, when unexpectedly found, it is often considered to be an isolated entity, which is unrelated to any concomitant shoulder pathology.

The purpose of this report was: (1) to report the rare occurrence of an aberrant thickened fan shaped origin of the LHBT from the under surface of the rotator cuff in a patient who presented with antero lateral shoulder pain and stiffness; and (2) to report that an aberrant origin of the LHBT from the rotator cuff can become pathologically thickened and cord like in middle age from a limited inflammatory process and present in a delayed fashion, potentially causing selective capsular contracture and secondary impingement in the shoulder.

Case Report

A 49-year-old female patient, who had right hand dominance, presented to the shoulder service at our institution with a history of painful restriction of movement of her right shoulder of several years duration. The pain was intermittent, localized to the front and top of her shoulder,

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dull aching in nature, increased to 6/10 in intensity with lifting and decreased to 0/10 with rest and medications. There was no previous history of trauma or injury to her shoulder. She had tried physical therapy without any substantial benefit.

On physical examination, there was no wasting or tenderness around the symptomatic shoulder. Active pain free range of movements of the right shoulder (compared with the left) were 120° (180° on the left shoulder) of forward elevation, 40° (65° on the left shoulder) of external rotation, with the arm in adduction, 45° (90° on the left shoulder) of external rotation with the arm in the abduction and 45° (85° on the left shoulder) of internal rotation with the arm in forward flexion suggestive of predominant anterosuperior and posteriorsuperior capsular contracture. The patient experienced pain on passive elevation beyond 120° and further elevation to 160° was possible. She experienced a painful arc of 40-120°, although further abduction was not restricted in the coronal plane. Tests for acromioclavicluar joint irritability or labral tears were negative. Hawkins and Neer's sign for impingement were however, found to be positive. Rotator-cuff muscle strength was comparable to the opposite side and neurological examination was found to be noncontributory. Plain radiographs of her right shoulder were normal. The Oxford shoulder score at this visit was 26 points.

On repeating the tests for shoulder impingement following a subacromial injection of local anesthetic, the antero lateral shoulder pain was significantly reduced. The pain free range of motion (ROM) improved, but the overall ROM remained unchanged. On the basis of these findings, a clinical diagnosis of subacromial impingement with secondary capsular contracture was made and the subacromial space and the gleno-humeral joint were injected with 40 mg of depot preparation of methyl prednisolone each, after explaining the risks and benefits. She was further advised to undergo regular physical therapy for the next 6 months to specifically address the anterior and posterosuperior capsular contracture. One year later, she still complained of marked shoulder pain, with only marginal improvement in the shoulder stiffness, which prevented her from carrying out activities of daily living. Her Oxford shoulder score was 30 points at her second visit. At this stage, the patient opted for arthroscopic surgical treatment after a thorough discussion of the risks and benefits of continued conservative treatment versus operative intervention.

On examination under general anesthesia, the ROM corroborated with the findings on physical examination. An arthroscopy of the shoulder was planned. The patient was placed in left lateral decubitus with the affected arm in 20° abduction and 15° forward flexion for the arthroscopy. Standard posterior, lateral and anterior portals were established. During the arthroscopic examination the capsule and synovium was found to be healthy without any signs of inflammation. An aberrant fan shaped thickened band from the proximal 1/3rd of the LHBT was seen extending to the under surface of the anterior 1/3rd supraspinatus tendon [Figure 1]. The distal 2/3rd of the intra articular portion of the LHBT was seen to be of normal size and orientation without any evidence of degeneration or deformity. This anomalous band was felt to be a cord-like structure and was seen to be visibly taut and resisting further movement beyond 15-20° external rotation in 40°-55° forward flexion respectively. The aberrant biceps was also seen to be tightening on the abduction of 60-75° and internal rotation beyond 30° respectively. Although accurate evaluation of extremes of glenohumeral motion are difficult during arthroscopy, we did not see any problems in measuring glenohumeral motions at these ranges with the arm out of traction. The biceps pulley was found normal. The glenoid labrum was found to be intact without any evidence of superior labrum, anterior posterior (SLAP) lesion. The main biceps tendon was seen firmly attached to the superior labrum.

The articular cartilage over the glenoid and humeral head, the rotator cuff insertion, the subscapularis tendon, superior gleno-humeral ligament and middle gleno-humeral ligament appeared normal [Figure 2]. The rotator interval did not show any evidence of inflammation or thickening. Bursoscopy revealed a tight subacromial space with moderate prominence of anterolateral acromion. Some fraying of the rotator cuff on the bursal side and scuffing of the coraco acromial ligament was also seen. An arthroscopic anterior acromioplasty with detachment of the coraco acromial ligament from the anterior acromion was performed. Full thickness of the acromion anterior to the acromio clavicular joint was resected with a 5 mm shaver blade. The under surface of the anterior acromion was rendered flat with a shaver through the posterior portal and the lateral edge of acromion was beveled.

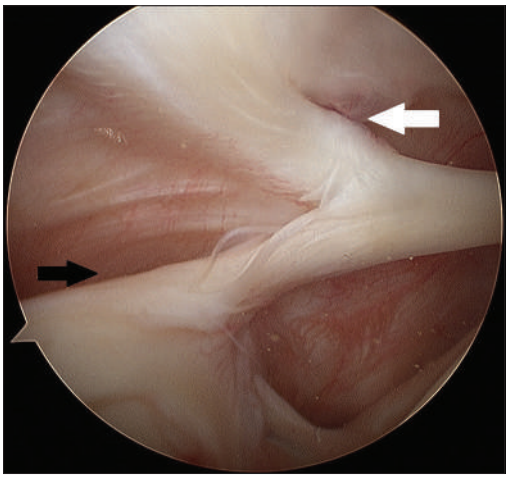

Figure 1: An arthroscopic view: White arrow showing anomalous bifurcated origin of the proximal portion of the long head of biceps tendon from the under surface of the supraspinatus tendon and the black arrow showing its attachment to the superior labrum

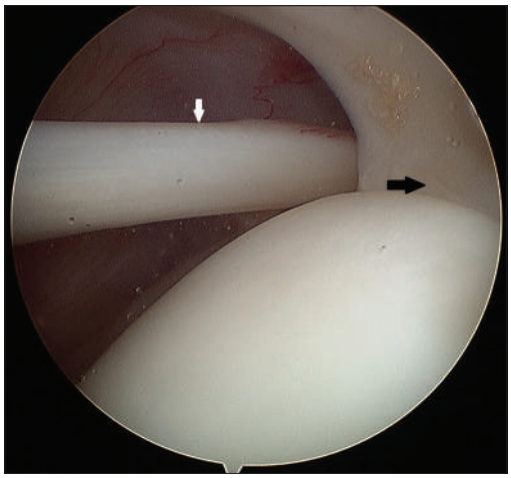

Figure 2: An arthroscopic view: Black arrow showing the intact insertion of the rotator cuff and a white arrow showing the normal appearance of the distal two-third of the long head of biceps tendon

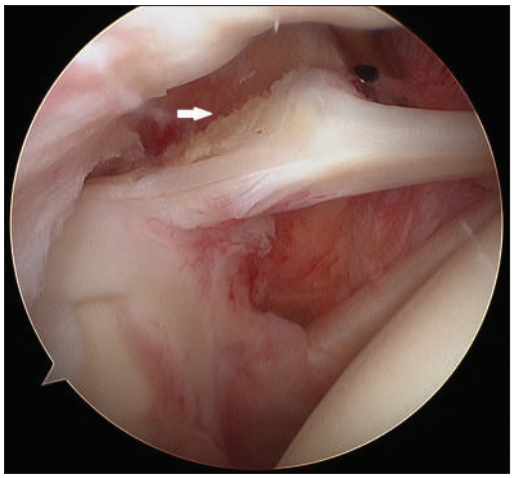

Figure 3: An arthroscopic view: White arrow showing released aberrant origin of the long head of biceps tendon completely from the under surface of the supraspinatus tendon

Attention was then directed to the intraarticular aberrant anatomy. Since the anomalous attachment of the LHBT was found to be contributing to the restriction of external rotation in abduction a decision was taken to proceed with tenolysis of the LHBT prior to release of the rotator interval or capsular release. The aberrant attachment of the LHBT was completely released and freed from the rotator cuff with a radiofrequency wand [Figure 3]. Restoration of free and full rotation and elevation was achieved following the release which was confirmed by removing the arm from the traction and checking the ROM. A formal capsular and rotator interval release was thus, felt unnecessary at this stage.

Postoperatively, the patient was advised to actively mobilize her shoulder as soon as she was comfortable. She was also advised to start a program of active and passive stretching exercises to achieve full elevation, external and internal rotation under the guidance of the physical therapists. There were no postoperative complications. At 12-months followup, her Oxford Shoulder score was 47 points (maximum 48 points, minimum 12 points) and she regained full pain free ROM in all directions with no symptoms or signs of gleno humeral instability.

Discussion

Although multiple variations in origin of LHBTs have been published in embryology and anatomy, they are less often observed in clinical practice with reported incidence up to 7.4% in one study.[8] Moreover, when these variations do occur, their precise role in development of various shoulder pathologies are often debated upon. The purpose of this report was to report a case of anomalous LHBT originating from the rotator cuff, which potentially contributed to the development of capsular contracture and secondary internal impingement.

Some authors, mostly in single case reports, have reported that aberrant origin of the LHBTs may be causally related to a number of conditions such as rotator cuff degeneration, instability, impingement, chronic pain and acromio-clavicular arthritis.[1,4,9,10] Wahl *et al*. in their study of 3 patients with LHBT anomalies, reported that one patient presented with a painful Type 2 SLAP tear associated with a band like fibro synovial thickening extending from the intra articular portion of the LHBT to the under surface of the supraspinatus.[11] The authors believed that the anomalous LHBT may have been causally related to the SLAP lesion, as excision of the fibrotic band led to complete resolution of symptoms, at final followup of 9 months. They classified the anomalous LHBT into 5 types normal (N), incomplete proximal mesenteric (M/p), incomplete distal mesenteric (M/d) and complete mesenteric (M/c) and absent (x). The fan shaped band found in our patient was similar to the incomplete mesenteric type (M/p) of aberrant long head of biceps (LHB). Similarly, Kanatli *et al*., in a series of 50 patients, with LHB anomalies, reported a significantly higher incidence of superior labral and Bankart's lesions in patients with these anatomical variations compared with a population who did have this aberration (32% vs. 13%; $P < 0.001$).[8] The authors reported a 14% (1 out of 7 patients) incidence of superior labral anteriorposterior lesions in patients with a similar proximal capsular aberrant attachment of the LHBT.

However, other authors believe that congenital absence of the LHBTs may be more causally related to the development of shoulder instability and other pathologic conditions, rather than developmental anomalies with no clinical consequences.[12,13] Wittstein *et al*., in their report of 2 patients, found that anomalous origin of LHBT from rotator cables were unrelated to shoulder pathologies and believed that treatment of the primary diagnoses were

sufficient for resolution of symptoms.[12] Similarly, Kim *et al*. in their study have reported a BARC anomaly in a 52-year-old patient presenting with pain and restriction of movement. A bursal side partial thickness tear of the infraspinatus tendon was found during the arthroscopic examination.[13] The cuff tear was repaired without addressing the aberrant LHBT, since it was not believed to be contributing to the symptoms. The patient had regained full-ROM without any symptoms at 23 months followup. However, the authors acknowledged that recognizing insertional abnormalities in the biceps tendon is important since it can be a source of shoulder pain either alone or in combination.

Gramstad *et al*. in a cadaveric study found that the tension in the LHBT was increased significantly with humeral rotations in the coronal and sagittal plane.[14] The results of this study may suggest that abnormal origin of the long head of biceps tendon may potentially lead to restriction of range-of-motion due to alterations in the functional length of the tendon. Although it is difficult to be absolutely certain that adhesive capsulitis didn't give rise to adhesions or a band between the cuff and the long head of biceps tendon in our report, the lack of arthroscopic evidence of capsular, axillary pouch, or rotator interval thickening and restoration of movements after surgical release provides evidence that the mesenteric band was possibly congenital in origin. One possible explanation for delayed presentation of a congenital band of long head of biceps tendon could be that a local adhesive capsulitis-like inflammatory process during middle age, may have led to thickening, reduction in functional length and loss of elasticity of an original, flimsy and nonpathologic elastic band leading to restriction of movement. This may have caused a tenodesis effect leading to selective posterior and superior capsular contracture and secondary internal impingement. Thus, a subacromial decompression with the release of the thickened band was considered to address each pathological entity separately.

Since there are very few cases of anomalous origin of the long head from the rotator cuff reported in literature and still fewer cases, reported clinical symptoms attributed to this anomaly, definite conclusions about its pathologic nature are difficult to construe. Due to the rare nature of these lesions, it is unlikely that a substantial sample size will be generated in future to propose treatment recommendations. Nevertheless, shoulder arthroscopists should be aware of its potential to become abnormally thickened and pathologic causing shoulder dysfunction. It is impossible to concur from an isolated case report that marsupialization remains the sole cause for pain relief, especially when a subacromial decompression was performed simultaneously. However, release of mesenteric attachments may be considered in patients with abnormally thickened aberrant LHBTs who present with clinical symptoms of pain and restriction of pain and movement following failure of conservative methods and surgical treatment of all associated shoulder pathologies.

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Case Report

Nonunion in a distal radius metaphyseal fracture in a child

Role of intact periosteal sleeve in management

Raju Sivashanmugam, Sriram Vijay[1], Balasubramanian Balakumar[2]

Abstract

We present an adolescent with distal radius nonunion following an open fracture and failed surgery which eventually united when the length and stability was restored for eight weeks duration. The intact periosteal sleeve at the nonunion site formed new bone when its tension was restored by gradual differential distraction. This case report highlights the possibility of stimulating bony union in an established atrophic nonunion by distracting the minimally disturbed soft tissue and thick osteogenic periosteal envelope in the paediatric age group.

Key words: Distal radius, nonunion, open fracture, pediatric, periosteum, osteogenic, distraction, atrophic
MeSH terms: Fractures ununited, compound, radius fractures, pediatric

Introduction

Nonunion in pediatric fractures has been reported in diaphyseal regions.[1] In the words of Mercer Rang "nonunion is an adversary almost not known to the child orthopedic surgeon".[2] Nonunion following distal radius metaphyseal fracture is rare. The reported incidence in a series including adults was 0.2% in New York State Worker's Compensation Board.[3] To the best of our knowledge only three such reports are cited in literature in pediatric age group.[4-6] We present a case of posttraumatic manus valgus deformity secondary to persistent nonunion of a distal radius metaphyseal fracture.

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Case Report

A 14 year old boy presented with the complaints of pain, progressive deformity and difficulty in writing using his right hand of 1 year duration. The deformity occurred following a fall from 10 feet height when he sustained an injury of his right forearm. He was initially managed by an osteopath with cleaning, dressing and splint immobilization. No radiographic documentation was carried out at that time. The pain subsided and splint was taken out after 6 weeks. His parents noticed a deformity of the forearm at this time, but did not pursue any further treatment. As the deformity gradually worsened, the child was taken to medical center 4 months after the injury where he was evaluated with radiographs and treated with distal ulnar shortening to correct the forearm deformity [Figure 1]. After 6 weeks of immobilization the child resumed regular activities. He noticed further progression of deformity with pain and difficulty while writing. At this point, he came to our center 1 year after the initial injury. The history was suggestive of punctured wound over the volar aspect on the ulnar side just proximal to the wrist crease, which healed uneventfully with regular dressings. There was no history of persistent infection or wound discharge.

Examination of the right forearm and hand revealed a manus valgus deformity of 45°. A small puckered scar adherent to underlying structures was noted over the ulnar side just proximal to the wrist crease and no sign suggestive of high grade soft-tissue disruption. A surgical scar was seen over the dorsal aspect of the distal ulna. The

ulnar styloid was prominent and extrinsic flexor tightness of 20° (degree) was noted in the fourth and fifth fingers. Wrist dorsiflexion was 5° and palmar flexion was 15° both active and passive. There was a jog of forearm supination and pronation. Shortening of right forearm by 7.5 cm was noted and there was stiffness of the metacarpophalangeal joints and interphalangeal joints. The metacarpophalangeal joints had a jog of passive movement. Active and passive flexion ranging from 20-50° (degree) was noted in the proximal, middle and distal interphalangeal joints.

Erythrocyte sedimentation rate and C-reactive protein were within normal limits. Review of his forearm radiograph carried out before ulnar shortening did not show comminution of radius fracture and there was no ulnar nonunion. The following radiographs revealed a distal radius metaphyseal nonunion with tapered proximal fragment pointing toward the ulna with narrowing of the interosseous space. There was a positive ulnar variance. Due to previous surgery the distal ulna had a nonunion with its epiphysis as well [Figure 2]. Magnetic resonance imaging (MRI) confirmed the diagnosis [Figure 3] and there were no signs of infection in MRI as well. Preoperative computed tomogram revealed the relative position of the fragments [Figure 4].

After discussion with the parents and the boy, a preoperative decision was made to do fixator assisted distraction of the forearm bones as a staged procedure to gain length, to be followed later by bone grafting at the site of nonunion. Under general anesthesia monolateral minirail fixator was applied on both radius and ulna percutaneously under image guidance. The nonunion site was not exposed as per the preoperative planning. The parents were taught to do differential distraction and at a rate of 2 mm/day on the radial side and 1 mm/day on the ulnar side from the next day [Figure 5]. Child was followed up with serial radiographs as an outpatient. At the 4th week of distraction the radius had achieved the required length and the ulnar variance got corrected and he was called back for bone grafting. The patient however did not show up at 4 weeks as instructed for bone grafting, but he visited us back at 8 weeks. The repeat radiographs showed new bone formation along the periosteal sleeve of both radius and ulna.

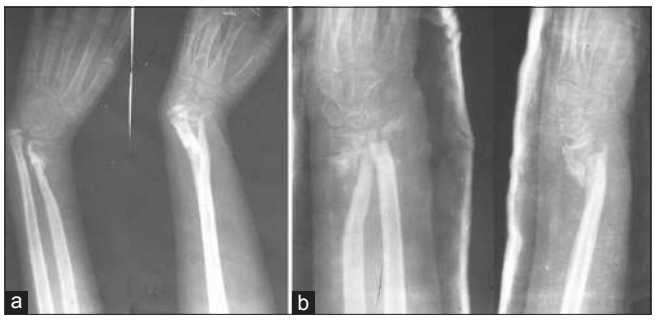

Figure 1: X-ray of forearm with wrist joint anteroposterior and lateral views showing (a) Nonunion distal radius with positive ulnar variance. (b) Post ulnar shortening

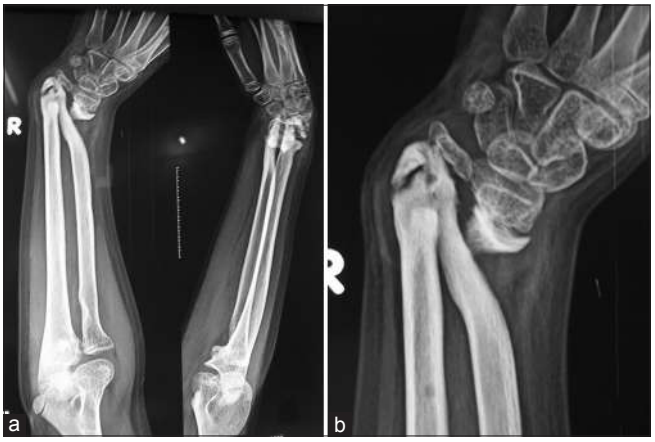

Figure 2: Radiograph of the right forearm anteroposterior and lateral views (a) showing distal radius portraying the nonunion with manus valgus deformity (b) close up view of same x-ray

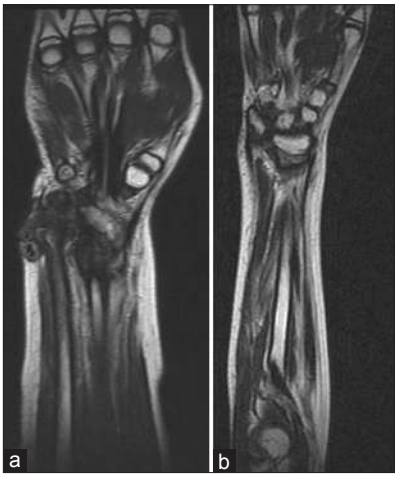

Figure 3: Magnetic resonance imaging (a) Coronal T2 fat suppression images showing the nonunion site at the right distal radius. (b) T1-weighted coronal image showing the distal radius nonunion

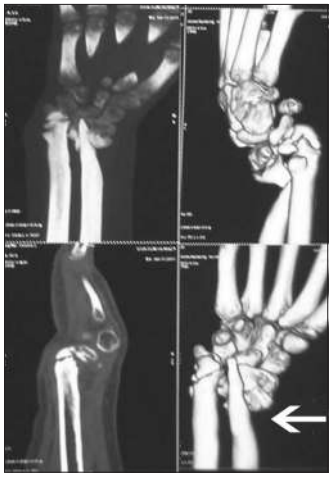

Figure 4: Computed tomogram showing distal radius (arrow) and ulna nonunion

At 8 weeks through a volar approach, the bony projection at the proximal end of union site interposing the interossous space was removed as it was hindering the forearm rotation. An intact periosteal sleeve with the new bone at the nonunion site was found and left disturbed. The union site was reinforced with a Kirschner wire [Figure 6]. Biopsy to rule out infection was not done to avoid violating the periosteum and callus at the nonunion site. The fixator was removed along with the Kirschner wire after 3 weeks and a volar splint was used for another 3 weeks and active range of motion therapy was started [Figure 7]. At 1 year followup the boy is pain free and able to do all activities of daily living including writing without pain and the parents were happy with the cosmesis achieved. The child is not willing for any kind of intervention for extrinsic flexor tightness. The preoperative Disabilities of the Arm Shoulder and Hand (DASH) score was 20 and the postoperative DASH score was 28.7 at 1 year followup. Passive palmar flexion had improved to 45° and dorsiflexion to 30° at the end of treatment. Forearm had a passive pronation of 50° and 80° supination [Figure 8].

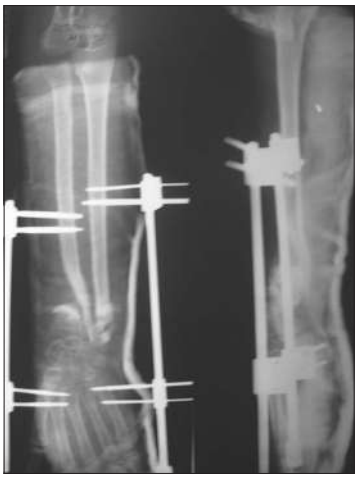

Figure 5: Postoperative radiographs of forearm and wrist anteroposterior and lateral views showing the minirail fixator on the distal radius and ulna and differential distraction in progress

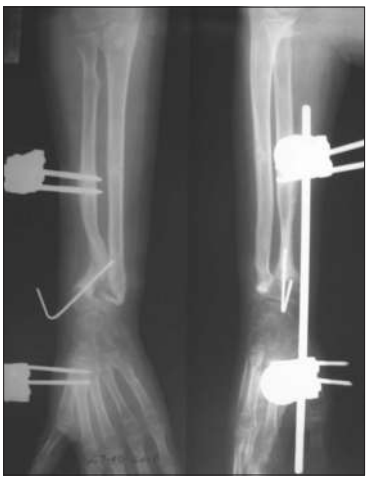

Figure 6: Followup radiographs of forearm and wrist showing spontaneous union at the end of deformity correction in distal radius which was stabilized with Kirshner wire

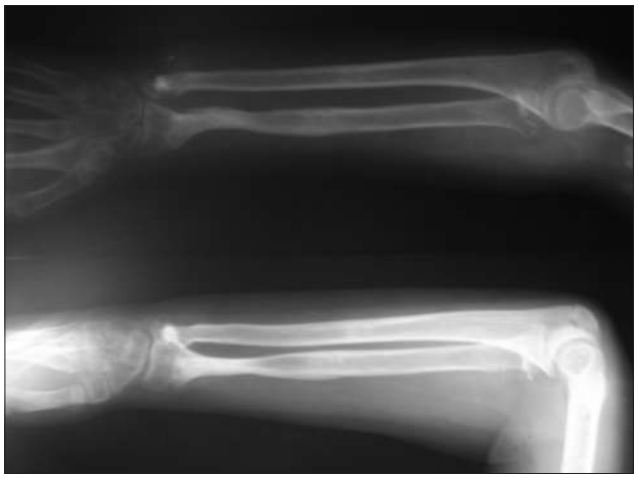

Figure 7: Radiograph at fixator removal depicting union at the fracture site

Discussion

This case report attempts to highlight a rare complication of nonunion in a distal radius metaphyseal fracture in a child and the ability of intact periosteum to reform the bone when length and tension are maintained [Figure 9]. The child had persistent painful nonunion due to various factors such as open injury, inadequate immobilization, and a suspected subacute infection in the initial period.

Kwa *et al*. in the first ever case reported had described a distal radius nonunion following a closed fracture in an otherwise healthy child.[4] This was managed by bone grafting and casting. The factors attributed to nonunion in this report were inadequate immobilization and severe initial displacement. In two other case reports, nonunion in children had been attributed to open surgery[5], soft-tissue or vascular problems.[7]

Open injury, high energy fractures, soft-tissue or vascular problems, open surgery, older age group, presence of infection and inadequate immobilization are contributory to pediatric fracture nonunion.[2,5,8,7,9] Examination of the serial radiographs and MRI of our patient did not reveal evidence of any local pathology including neurofibromatosis or chronic infection.

Sabharwal[6] described bone transport of radius with Ilizarov apparatus in a 12-year-old boy with acquired posttraumatic radial club hand. around 5.1 cm of lengthing was achieved and the docking site was grafted in his case. In our patient after distraction, the stability provided by the fixator and the restoration of length and tension in the periosteum initiated spontaneous regeneration of bone. This was confirmed when we explored for removing the impinging corner of proximal radius and an artist's view of the intraoperative finding is given [Figure 9].

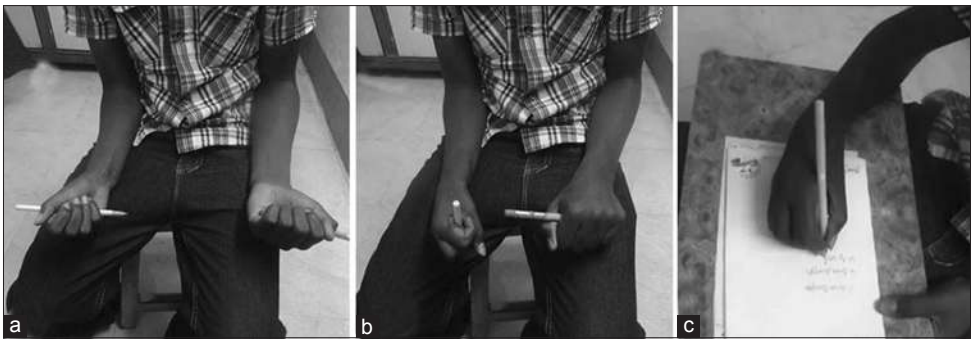

Figure 8: Clinical photograph showing the range of motion and function at one year followup. Active supination and pronation in the right forearm (a and b). The child could grip a pen firmly and write legibly (c)

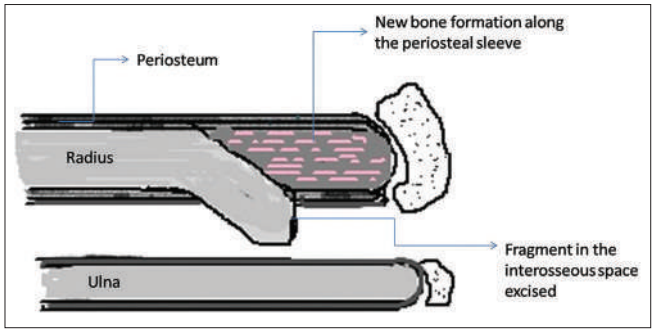

Figure 9: Schematic diagram showing the intraoperative findings

Distraction and compression with Ilizarov circular frames have been used for management of hypertrophic nonunion.[10] Though compression is the current standard of care for atrophic nonunion,[11] this report has demonstrated that distraction of atrophic nonunion can lead to bone formation in pediatric age group provided the periosteal sleeve remains undisturbed. As our initial plan was to gain radial length and correct ulnar variance followed by open bone grafting, we did not use circular frame as osteotomy and compression were not planned, instead a monolateral frame was used.

Wilde *et al*. explained that circumferential periosteal release leads to correction of limb length discrepancy and they found that the periosteum is under tension in a child and it retracts on sectioning[12] and this was reiterated by Warrel and Taylor.[13]

Meticulous closure of periosteum at the donor site of fibula graft and tibial cortical graft has been shown to promote rapid healing of donor site defect.[14,15] Humoral and genetic factors have been described to cause spontaneous regeneration of bone defects in segmental femoral fracture of various lengths in adults when length and stability of the periosteum was maintained.[16]

It becomes clear that the periosteum has great osteogenic potential in children. This can be exploited to bridge bone defects and promote union in conditions where the periosteal sleeve is intact. Our case highlights this phenomenon and also demonstrates that nonunion can occur in the pediatric age group if the basic principles of management are disregarded. We recommend external fixation with distraction as one of the treatment options to treat pediatric atrophic nonunion in selected patients.

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Case Report

External iliac artery thrombus masquerading as sciatic nerve palsy in anterior column fracture of the acetabulum

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Abstract

We report a case of ischemic neuropathy of the sciatic nerve in a patient with an anterior column fracture of the acetabulum operated by ilioinguinal approach. It resulted from occlusion of the blood supply to the sciatic nerve. There were no signs of a vascular insult until ischemic changes ensued on the 6th postoperative day on the lateral part of great toe. The patient underwent crossover femoro-femoral bypass grafting and there was a complete reversal of the ischemic changes at 6 months. The sciatic nerve palsy continued to recover until the end of 1 year; by which time the only deficit was a Grade 4 power in the extensor hallucis longus (EHL) and the extensor digitorum longus (EDL). There was no further recovery at 2 years followup.

Key words: Anterior column fracture of acetabulum, external iliac artery thrombosis, ischemic neuropathy, sciatic nerve palsy
MeSH terms: Acetabulum, thrombosis, sciatic nerve diseases. sciatic neuropathy

Introduction

Earliest descriptions of an arterial thrombosis following acetabular fracture fixation through an ilioinguinal approach were given by Probe and Letournel.[1,2] Formation of collateral circulation prevents the development of clinically evident thrombus and it remains a rare entity[1] Until the present date and to the best of our knowledge, there have been five reports of external iliac artery thrombus arising in the setting of an acetabular fracture in English literature, however none of them presented as a sciatic nerve palsy.[1-5] Though ischemic neuropathy of the sciatic nerve has been reported previously in literature;[6-7] it has never been reported as a complication of acetabular surgery through the anterior approach.

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Case Report

A 61 year old male patient who suffered a seizure and sustained fracture of his right acetabulum and the right proximal humerus was referred to our hospital after 15 days. He was being managed conservatively at some peripheral set up. He was a known case of type II diabetes mellitus, hypertension and epilepsy. Neurovascular assessment was normal. Roentenograms (Anterioposterior pelvis, Judet views) and computed tomography (CT) with reconstructions revealed that he had a fracture of the anterior column of the acetabulum and the quadrilateral plate along with central dislocation of the femoral head [Figure 1a and b]. Haematological investigations revealed a low HDL/LDL ratio.

The fracture site was accessed through an ilioinguinal approach. We used a Schanz screw as a joystick to pull the femoral head laterally to reduce the fracture. Though we did use reduction clamps, we made sure that we do not produce prolonged compression with them. Vessels were retracted on pen-rose drain to facilitate adequate visualization of the fracture site. Anatomical reduction was achieved and the fracture was fixed using a 14 hole reconstruction plate (Synthes; Synthes India Pvt. Ltd., India) spanning from the internal iliac fossa to the superior pubic ramus [Figure 1c]. The artery was palpated during the procedure and prior to closure and had good volume and pulsations.

In the recovery room, the neurovascular status was checked again and was found to be normal. On the

second postoperative day, the patient developed foot drop. Examination revealed weakness in the muscles of the anterior compartment, attributable to the peroneal division of the sciatic nerve. On the 6th postoperative day, he started developing ischemic changes on the lateral part of his great toe [Figure 2]. Vascular surgery consultation was taken and CT angiography for lower extremity was performed, which revealed occlusion in the right external iliac artery [Figure 3a]. The patient was taken up for surgery; intraoperatively a large thrombus occluding the external iliac artery was identified. Cross over femoro-femoral bypass grafting with expanded polytetrafluoroethylene graft (GORE-TEX, WL Gore and Associates Inc., USA) was performed. The patient was put on low molecular weight heparin for 3 days and was switched over to warfarin which was titrated to an international normalized ratio of 2-3 at day 3. Postoperatively, an angiogram was obtained and the graft was found to be patent [Figure 3b].

The patient was given an ankle-foot orthosis and was allowed partial weight bearing with a walker at 6 weeks and full weight bearing at 10 weeks. Nerve conduction velocity and electromyography studies were performed at 1, 3 and 6 months after the onset of the palsy to assess recovery. Six months after the onset of palsy, the ischemic changes reversed completely and muscle strength in the right leg recovered to 4/5 in the peroneus tertius and 3/5 in the tibialis anterior [Figure 4a]. At 1 year the strength of the peronei and the tibialis anterior were 5/5 each and that of Extensor Hallucis Longus and Extensor Digitorum Longus was 4/5 each [Figure 4b]. At 2 years followup, the patient did not show any discernable recovery from that at 1 year.

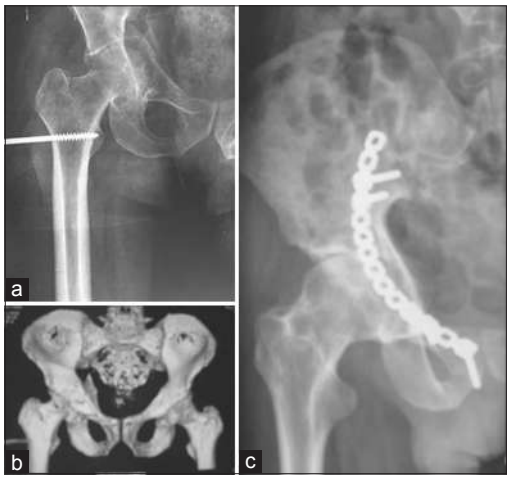

Figure 1: (a) X-rays of (R) hip joint anteroposterior view showing fracture of anterior column of acetabulum with fracture of the quadrilateral plate. (b) Computed tomography scans of the same patient (c) Postoperative X-rays of patient showing well fixed fracture

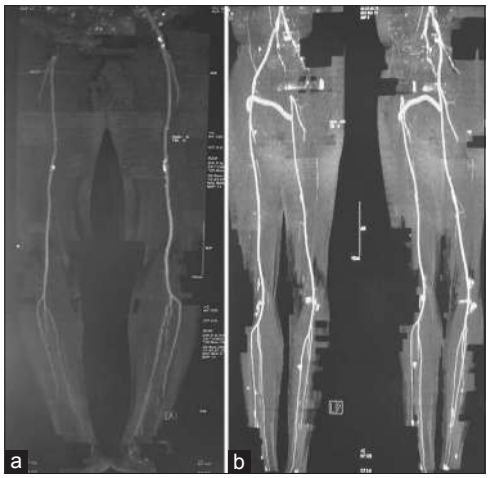

Figure 3: (a) Computed tomography angiogram of lower extremity showing a large thrombus occluding the right external iliac artery (b) Postoperative computed tomography angiogram showing patency of the graft

Discussion

Mechanism of injury in most acetabular fractures is either a strong impact by femoral head onto the acetabulum or

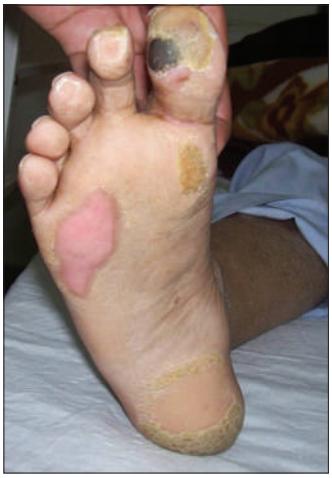

Figure 2: Clinical photographs showing ischemic changes on the lateral and plantar aspect of great toe

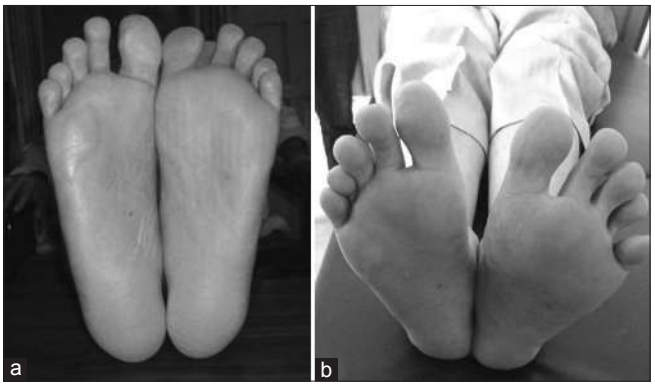

Figure 4: (a) Clinical photographs 6 months after onset of palsy showing healing of necrotic patch (b) Clinical photographs after 2 years of surgery showing necrotic patches healed completely

a direct lateral blow to the ilium. With such an impact the external iliac and proximal femoral arterial segments are subjected to traction. The medially coursing internal iliac and the inferior epigastric vessels can undergo tethering, resulting in intimal lesions and plaque rupture, which may give rise to thrombotic complications.[8] With ilioinguinal approach these vascular structures are at further risk of thrombogenesis due to their inadvertent handling during the surgical procedure.[1] The risk amplifies when this approach is used in patients who are high risk for thrombogenesis.

In the present case, the patient was a diabetic, epileptic, hypertensive and atherosclerotic male who was managed in traction for 15 days prior to undergoing surgery. He was on antiepileptic medication (phenytoin), which is known to cause osteoporosis.[9] His lab investigations revealed hyperlipidemia and postoperative CT angiography showed sclerotic changes in many vessels. It is therefore conceivable that when he sustained an epileptic seizure, he suffered a traumatic intimal lesion and/or rupture of an atherosclerotic plaque, leading to activation of the coagulation cascade. The development of sciatic nerve palsy is attributable to dislodgement of an embolus from the thrombus which settled in vasa nervorum of the sciatic nerve.[10] Concomitant small vessel vascular disease further predisposed the patient to the development of sciatic neuropathy. The development of ischemic changes on the lateral aspect of the great toe is attributed to occlusion by thrombus of an already compromised blood supply.

Although sudden onset sciatic nerve palsy is most commonly caused by trauma or iatrogenic injuries[11,12] the possibility of a vascular insult as a cause of the neuropathy should not be ignored. In our case, the peroneal division of the sciatic nerve was affected which resulted in weakness of muscles of the anterior compartment of the leg and the patient developed foot drop. The same has been reported in literature by various authors.[13,14] Comparison of cross section of both the divisions shows that the peroneal division has fewer and thicker nerve bundles than the tibial division, where the nerve bundles are greater in number and thinner, thus the vasa nervorum have to supply larger fibers in peroneal division as compared to the tibial division. Any ischemic insult to the vasa nervorum thus manifests itself more easily in the peroneal division.[13-15]

Conclusion

Although rare, the possibility of a vascular disorder should be considered in a case of abrupt onset sciatic neuropathy, especially in patients who are at high risk, even though there may not be classical manifestations of a vascular insult. We urge caution in using the ilioinguinal approach in this subset of patients and recommend to use an alternative approach such as Stoppa's approach,[15] which allows adequate exposure of the anterior column and avoid dissection around the vessels or there inadvertent handling.

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