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The Aging Spine



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Principles of management of osteometabolic disorders affecting the aging spine

Abstract Osteoporosis is the most common contributing factor of spinal fractures, which characteristically are not generally known to produce spinal cord compression symptoms. Recently, an increasing number of medical reports have implicated osteoporotic fractures as a cause of serious neurological deficit and painful disabling spinal deformities. This has been corroborated by the present authors as well. These complications are only amenable to surgical management, requiring instrumentation. Instrumenting an osteoporotic spine, although a challenging task, can be accomplished if certain guidelines for surgical techniques are respected. Neurological deficits respond equally well to an anterior or posterior decompression, provided this is coupled with multisegmental fixation of the construct. With the steady increase in the elderly population, it is anticipated that the spine surgeon will face serious complications of osteoporotic spines more frequently. With regard to surgery, however, excellent correction of deformities can be achieved, by combining anterior and posterior approaches. Paget's disease of bone (PD) is a non-hormonal osteometabolic disorder and the spine is the second most commonly affected site. About one-third of patients with spinal involvement exhibit symptoms of clinical stenosis. In only 12–24% of patients with PD of the spine is back pain attributed solely to PD, while in the majority of patients, back pain is

either arthritic in nature or a combination of a pagetic process and coexisting arthritis. In this context, one must be certain before attributing low back pain to PD exclusively, and antipagetic medical treatment alone may be ineffective. Neural element dysfunction may be attributed to compressive myelopathy by pagetic bone overgrowth, pagetic intraspinal soft tissue overgrowth, ossification of epidural fat, platybasia, spontaneous bleeding, sarcomatous degeneration and vertebral fracture or subluxation. Neural dysfunction can also result from spinal ischemia when blood is diverted by the so-called "arterial steal syndrome". Because the effectiveness of pharmacologic treatment for pagetic spinal stenosis has been clearly demonstrated, surgical decompression should only be instituted after failure of antipagetic medical treatment. Surgery is indicated as a primary treatment when neural compression is secondary to pathologic fractures, dislocations, spontaneous epidural hematoma, syringomyelia, platybasia, or sarcomatous transformation. Five classes of drugs are available for the treatment of PD. Bisphosphonates are the most popular antipagetic drug and several forms have been investigated.

Keywords Osteoporosis · Fractures · Neurological deficit · Deformity · Paget's disease · Back pain · Spinal stenosis · Myelopathy · Treatment

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Introduction

Osteoporosis and Paget's disease of bone are two metabolic conditions that usually affect the aging population. The former is a very common skeletal disorder, whereas Paget's disease affects about 3% of the population. This paper looks at both conditions. It first addresses principles of surgical management of complications caused by osteoporosis of the spine (minimally invasive surgery for these complications will be addressed in a separate paper in this issue). Secondly, it describes spinal involvement of Paget's disease in bone and outlines the best treatment options.

Osteoporosis

Surgical treatment of osteoporosis is still not widely accepted by orthopedic surgeons, nor well known among the medical community at large. However, recently, it has been gaining support for two main reasons. The first is that more in-depth studies, which are detailed below, have shown that osteoporosis is not an innocent disease characterized by minor complications and disabilities, but a serious health problem that can create devastating complications with substantial morbidity and mortality. The second reason is the advancement of medical knowledge and technology, which allows the use of more sophisticated instrumentation and makes it possible to operate successfully on high-risk patients of advanced age who no longer accept physical conditions limiting their life enjoyment.

The extent of disability and the socioeconomic consequences associated with osteoporosis are well known through widely cited publications [24, 94, 112]. It is not the scope of this paper to review this aspect of osteoporosis. However, it is worth highlighting some pertinent statistics regarding the magnitude and implications of osteoporotic vertebral compression fractures (OVCF) in order to emphasize the need for a more specific treatment. OVCF is the most common fracture that may occur after minimal trauma (e.g. bending, turning, etc), or even in the absence (silent) of any obvious trauma [25].

The estimated incidence of OVCF in European Union Member States is 438,700 clinically diagnosed vertebral fractures (117 per 100,000 person-years) [25], while the US epidemiological databases give an annual rate of 700,000 cases [111].

The average duration of hospitalization ranges from 8 to 30 days [111].

The reported periods of disability for cases of OVCF required for bed rest are 25.8 days for the lumbar region and 12.6 days for the thoracic region. The periods of disability required for limited activity are 158.5 days and 73.6 days respectively. Whereas the figures for hip fracture are 21.6 days for bed rest and 101.5 days for limited activity [37].

Apart from physical impairment incurred by the OVCF [87, 126], these patients also experience a substantial deterioration in quality of life and a cascading of psychoso-

cial disorders, such as sleep disturbance, increased depression, lower self-esteem, increased anxiety, diminished social poles and increased dependency on others [127].

The overall mortality rate also appears to be equivalent to hip fractures. A prospective study of 9575 women, followed over 8 years, demonstrated that patients with OVCF have a 23–34% increased mortality rate when compared to patients without OVCF [69]. This study echoes the findings of Cooper et al. [25], who demonstrated in a retrospective study that the 5-year survival rate in patients with OVCF is significantly lower than the expected normal survival rate (61 vs 76%), and almost comparable to the 5-years survival rate after hip fracture. However, in hip fractures, the excess mortality rate occurs within 6 months of the fracture event, whereas in OVCF survival declines steadily after the fracture [25]. Most common causes of death in patients with OVCF are pulmonary problems caused by chronic obstructive pulmonary disease (COPD) and pneumonia (hazard ratio 2.1) [69]. Lung function (FVC, FEV1) is significantly decreased in patients with thoracic and lumbar fracture. It has been estimated that one OVCF may result in 9% loss of forced vital capacity (FVC) [82, 121, 122].

Eighty-five percent of cases of radiologically diagnosed OVCF are associated with back pain, which in the majority of patients is expected to subside within 2–3 months [34]. However, it has been postulated that in one-third of patients, this pain remains as chronic pain, with varying degrees of physical disability [29]. Several reports also indicate that patients with OVCF are at increased risk for subsequent fractures [68, 84, 114]. Most cases of OVCF are wedge compression fractures (type A1), creating varying degrees of kyphotic deformity of the spine, usually not associated with neurological deficit. These fractures are manageable either conservatively (braces, corsets, analgesics and antiresorptive osteoporotic drugs such as calcitonin and bisphosphonates, or parathyroid hormone, apparently the most effective antiosteoporotic drug) [22, 70, 88], or surgically by means of minimally invasive surgery (vertebroplasty, balloon kyphoplasty). These procedures have been recently introduced in the treatment armamentarium for OVCF as a more effective treatment [42, 83].

According to a study by Parfitt and Duncan, published in 1982 [101], spontaneous crush fractures in osteoporotic patients do not result in spinal cord compression requiring decompressive surgery. However, several reports have since appeared in the literature highlighting the fact that spontaneous osteoporotic fracture with serious spinal cord compression and variable degrees of neurological deficit do occur [6, 8, 26, 27, 63, 71, 72, 75, 77, 90, 97, 98, 118, 119, 125, 132].

There are five main reasons for operating on osteoporotic spines:

1. Acute or subacute osteoporotic fractures that can be corrected or stabilized by minimally invasive surgery (vertebroplasty or balloon kyphoplasty)



Fig. 1 A patient with painful kyphosis. Could this deformity have been prevented?

2. Conditions requiring spinal instrumentation, such as extensive laminectomy, which may destabilize an osteoporotic spine
3. Prevention of severe kyphotic deformity developing from osteoporotic fractures (Fig. 1)
4. Established painful deformities (kyphosis/scoliosis), and
5. Symptomatic neurocompression caused by osteoporotic fractures

Review of a series of 29 cases

A review recently conducted by the present authors of 29 patients treated for serious musculoskeletal spinal and neurological complications from osteoporosis of the spine shows how serious the condition can be and how important it is to maintain surgery as a treatment option. The patients were managed surgically between January 1994 and January 2001 at the University of Texas Medical Branch at Galveston, at the University of Crete, Heraklion, and at the National University of Greece in Athens.

Fifteen patients were treated for severe neurological compromise, ranging from paraplegia to paraparesis (Frankel A: $n=1$, Frankel B,C and D: $n=14$) and 14 for intractable back pain complicating kyphoscoliotic osteoporotic deformities. Acute burst fractures were observed in five patients and were associated with serious neurological complications (Frankel B in four and Frankel A in one). Ten patients suffered from wedge compression fractures, two developed acute onset of symptoms, and in the remaining eight, the neurological deterioration was gradual. (The neurological deficit grading was Frankel B in two, with the rest ranging between C and D.)

Surgical treatment

Anterior decompression was accomplished through an anterior approach in 15 patients (8 for painful deformity and 7 for neurological deficit). Anterior stabilization alone was achieved by means of a Kostuik rod: $n=1$, a Kaneda device: $n=4$, or a plate: $n=1$. Posterior stabilization was performed in three cases, and combination of anterior Kaneda and posterior instrumentation (Varigrip hook) in another six cases. Anterior reconstruction was achieved by means of bone graft in four cases (femoral ring allograft: $n=2$ and ribs: $n=2$), and Harms titanium cages filled with bone graft in 11 cases. A posterior approach alone was used in 11 cases, and consisted of either wide laminectomy and stabilization (eight cases), or indirect reduction and stabilization (three cases). More specifically, instrumentation consisted of multisegmental fixation with either transpedicle screws (bone cement augmentation $n=2$; triangular technique $n=2$) or laminar claws (Varigrip) or a combination of the two.

Three patients who had serious co-morbid diseases were treated with morphine pump. One had a partial paraparesis and the other two intractable painful deformities.

Outcomes

The patient with complete paraplegia never recovered (Fig. 2), whereas patients with Frankel B, C, or D improved by two grades. All patients with serious neurolog-

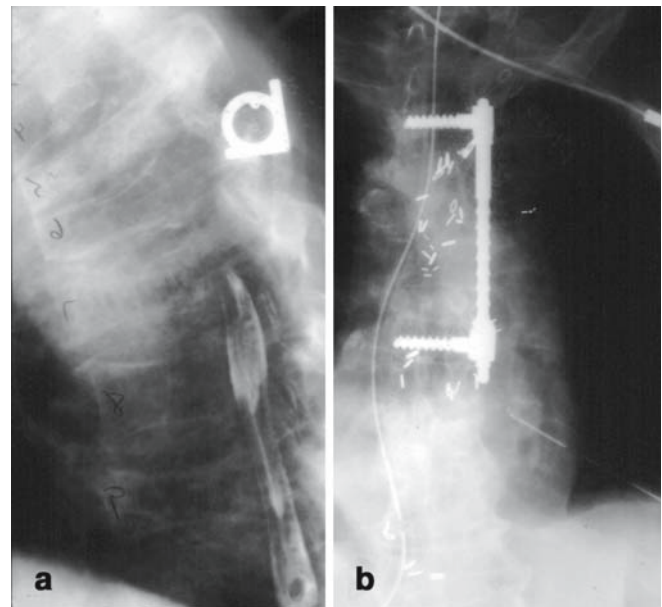


Fig. 2 Osteoporotic pathological fracture of T6, resulting in severe kyphosis and rapid progression of neurological deficit to complete paraplegia (a). The patient failed to recover after anterior decompression and stabilization (b)

Fig. 3 Dislodgment of anterior instrumentation construct in an osteoporotic L1 fracture (a). This resulted from poor application of instrumentation principles in an osteoporotic spine. It was successfully revised using anterior and posterior multisegment fixation constructs (b)

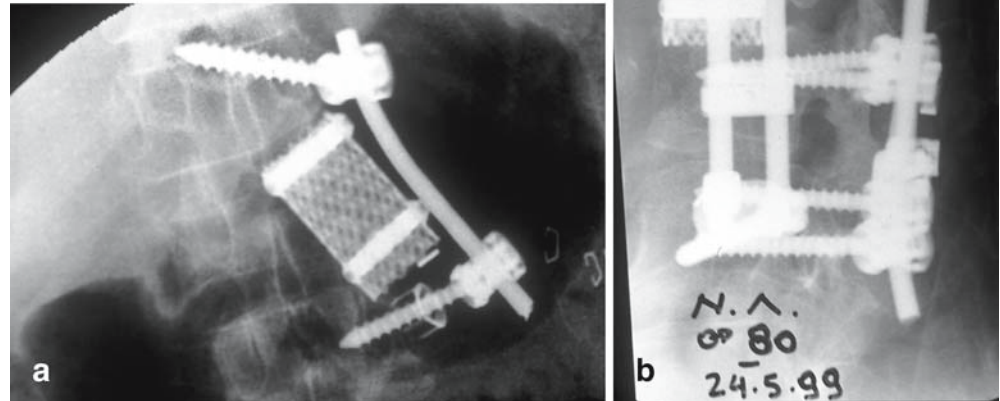


Table 1 Outcomes of surgery for spinal cord neurocompression and painful deformities

Procedure	Serious neurological deficit ^a			Painful deformities (kyphosis/scoliosis)			Combined		
	Total	Improvement	Failure	Total	Success	Failure	Total	Success	Failure
Anterior decompression + graft or cages	7	6/7	1/7	8	5/8	3/8	15	11/15	4/15
Anterior stabilization	3	2/3	1/3 ^b	3	0	3/3 ^c	6	2/6	4/6
Posterior stabilization	–	–	–	3	3/3	0	3	3/3	0
Combined	4	4/4	0	2	2/2	0	6	6/6	0
Posterior decompression, indirect reduction + stabilization	3	3/3	0	–	–	–	3	3/3	0
Posterior decompression + stabilization	4	3/4	1/4	4	2/4	2/4	8	5/8	3/8
Morphine pump	1	0	1/1	2	1/2	1/2	3	1/3	2/3

^a “Serious neurological deficit” indicates Frankel B–D. “Improvement” denotes patients’ neurological status improved by at least two Frankel grades. The patient with morphine pump deteriorated from Frankel D to Frankel B

^b One patient with complete paraplegia never recovered

^c Two patients developed junctional kyphosis. One was successfully corrected by supplementing posterior instrumentation. The other healed in a kyphotic deformity with residual pain. Complete dislodgement of instrumentation occurred in the third patient, who was revised successfully through a combined approach.

ical deficit underwent anterior decompression. Pain improved substantially in all patients, as well as in the patients who underwent revision surgery. Two of the patients in the deformity group who underwent anterior decompression and anterior stabilization developed junctional kyphosis, which was corrected by indirect reduction in hyperextension and stabilization with posterior instrumentation. In one patient, complete dislodgement of a cage and an anterior device occurred soon after surgery, and responded well to revision surgery (Fig. 3). In the pa-

tient with paraparesis, morphine pump was successful as a pain management modality; however, his neurological status deteriorated and the patient died after a few months.

A morphine pump substantially improved the pain in one patient with painful deformity and failed in the other patient (Table 1).

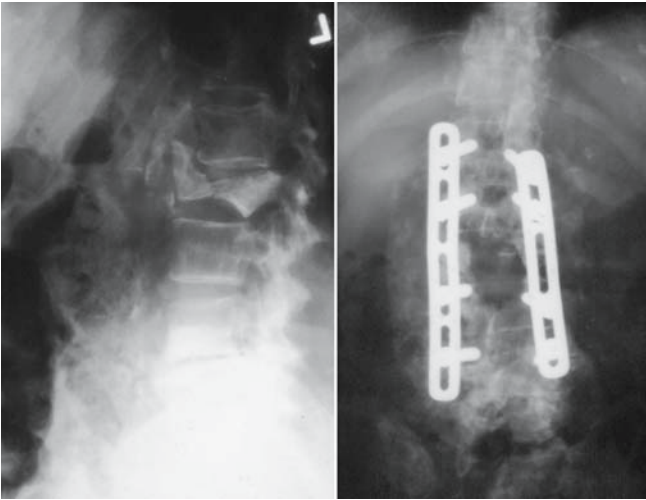


Fig. 4 Acute burst fracture in a patient on chronic use of steroids, who sustained the fracture after a minor trauma (bending over and lifting a heavy object). The onset of severe paraparesis was late, gradual and crippling. Neurological status responded successfully to posterior decompression and stabilization, but the treatment failed to correct the deformity and the patient remained with severe back pain

Discussion

With the increasing size of the elderly population (people at risk), it is expected that the rate of osteoporotic vertebral fracture and resulting neurological complications will rise dramatically.

Acute kyphotic deformity as a result of OVCF is not usually associated with neurological deficit, but may continue to remain as a painful crippling condition requiring major surgical intervention (Fig. 1). The type of OVCF that can cause neurocompression results from either acute crush fracture [77, 98, 102] (Fig. 4) or delayed collapse of an antecedent wedge fracture that leads to retropulsion of a vertebral body fragment and contribution to progressive kyphotic deformity [71, 75, 97].

The reported time period from the original injury to clinical manifestation of neurocompression varies between 1 and 18 months [8, 71, 75]. The cord is compromised either by the severity of the kyphotic deformity or by retropulsion of a posterior wall fragment [8, 63, 71, 75, 97]. The postulated mechanisms of delayed vertebral collapse are attributed to either bone ischemia and necrosis [13, 18, 71, 75], or pseudarthrosis [60]. Apparently, it is a combination of both these factors [71, 75]. Repeated microtraumas have been postulated as the causative factor for pseudarthrosis [75], which produces an unstable kyphotic spine and severe pain [75].

Neurological deficit can range from acute paraplegia (usually after an acute crush fracture) [98, 102] to delayed onset of insidious paralysis that gradually deteriorates to severe paraplegia [69, 73]. The latter phenomenon is usu-

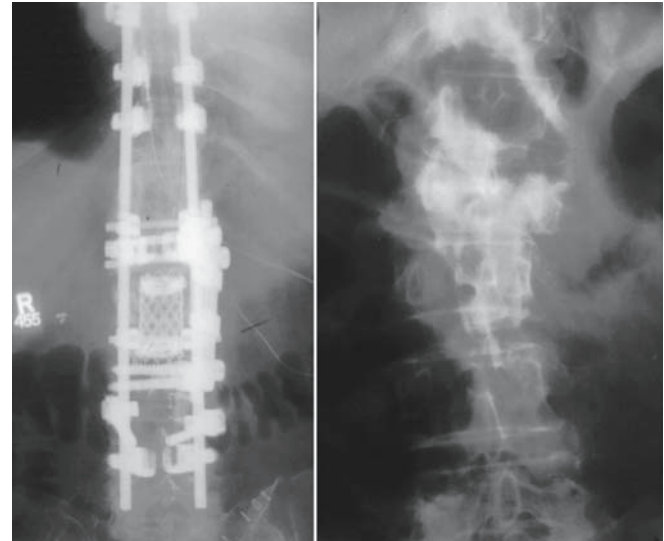


Fig. 5 Correction of a rigid painful post-fracture kyphoscoliotic deformity by means of anterior and posterior instrumentation

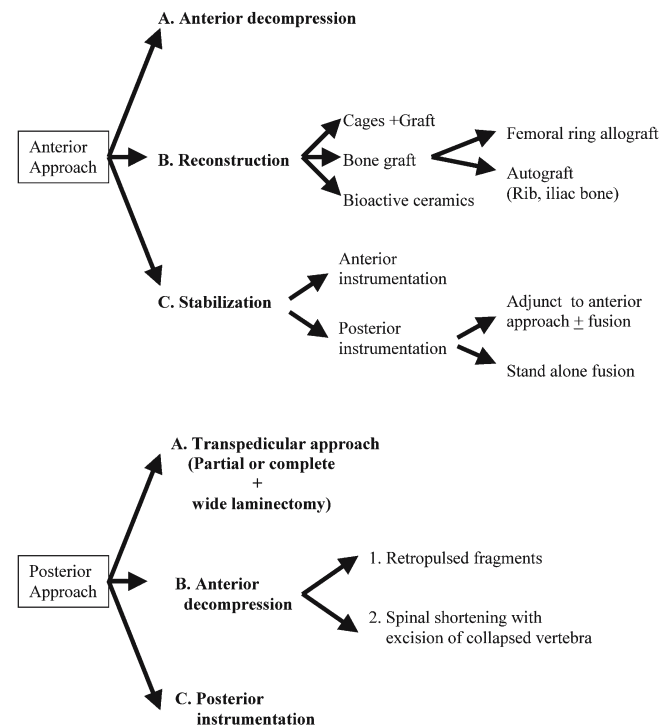


Fig. 6 Principles of surgery of osteoporotic vertebral fracture with neurological deficit or severe painful kyphotic-scoliotic deformity. A,B,C signify sequential steps for each approach

ally associated with delayed vertebral collapse and progressive kyphotic deformity [75]. Within this context, therefore, it is not unreasonable to entertain balloon kyphoplasty, a recently introduced minimally invasive surgery, as a preventative intervention for progressive kyphotic deformity (Fig. 1).

Table 2 Reported cases of severe neurological deficit caused by osteoporotic vertebral fractures

Authors	No. of cases	Neurological status	Type of fracture	Treatment	Results and remarks
Salomon et al. 1988 [119]	1	Spastic paraparesis	Wedge fracture with acute retropulsion	Combined posterior and anterior approach	Complete recovery
Kaplan et al. 1989 [72]	3	Neurological deficit	Burst with retropulsion		Spontaneous Fx, no trauma
Arciero et al. 1989 [6]	2	Paraparesis: acute onset 1, delayed onset 1	Acute burst fracture	Anterior decompression	Nearly complete recovery
Shikata et al. 1990 [125]	7	Delayed paraparesis	5 burst Fx, 5 wedge Fx	Posterior decompression	Substantial improvement
Kaneda et al. 1992 [71]	22	Gradual onset incomplete paralysis	Wedge fracture with delayed bone retropulsion	Anterior decompression	Excellent
Heggeness 1993 [63]	9	Gradual onset of neurological symptoms	Delayed collapse with bone retropulsion		Benign appearing compression Fx may progress to serious situation
Tanaka et al. 1993 [132]	1	Delayed conus medullaris syndrome	L1 burst fracture	Anterior decompression and fusion	Restoration of vesico-rectal function
Korovessis et al. 1994 [77]	7	Delayed cord compression; paraplegia 1	Burst fracture with progression	Anterior or posterior or combined approach	6 recovered, 1 (with paraplegia) died
Cortet et al. 1995 [26]	6	Gradual onset: paraplegia 1, paraparesis 3, leg weakness 2, sphincteric dysfunction 2	Vertebral crush Fx	Surgery: 3 Conservative: 3	1 recovered, 1 improved, 1 unchanged 1 improved, 2 unchanged
Baba 1995 [8]	27	Gradual late paralysis	Delayed collapse with bone retropulsion	Anterior or posterior decompression	Recommend transpedicular posterolateral decompression
Hu 1997 [66]	1	Gradual progression of leg weakness	Progressive loss of vertebral height; retropulsion of fragments; progressive kyphosis	Combined anterior and posterior approach	Recovery
Courtois et al. 1998 [27]	1	Cauda equina syndrome	L2 Fx with osteonecrosis		Imaging failed to diagnose osteonecrosis. Diagnosis made from the biopsy.
Saita et al. 2000 [118]	1	Acute onset with gradual deterioration	Wedge compression	Spondylectomy	Excellent
O'Connor et al. 2002 [98]	1	Acute onset of complete paraplegia	Crush with retropulsion	Conservative	Died
Kim et al. 2003 [75]	14	Gradual onset of severe paraparesis	Wedge fracture with delayed retropulsion	Anterior cord decompression	Excellent
Nguyen et al. 2003 [97]	10	Frankel D: 7, Frankel C: 3; late onset: 9, acute onset: 1	Burst with retropulsion	Surgery	8/10 survived, 6/10 improved, 1/10 deteriorated

Based on our findings and the experience of others, we have shown that posterior instrumentation alone, after wide laminectomy, can improve neurological deficits even in seriously spinal cord-compromised patients in the acute fracture where indirect reduction of kyphotic deformity is feasible. However, for rigid curves (Fig. 5), a combined anterior and posterior approach seems a more appropriate treatment. For an experienced surgeon, anterior decom-

pression and stabilization with or without posterior stabilization can achieve excellent results in terms of neurological decompression and correction of painful deformities [22]. Anterior decompression and stabilization can also be achieved through a posterior or posterolateral trans-laminar approach.

Fig. 6 outlines the techniques of surgical management of OVF when the spinal cord is compromised, and Table 2

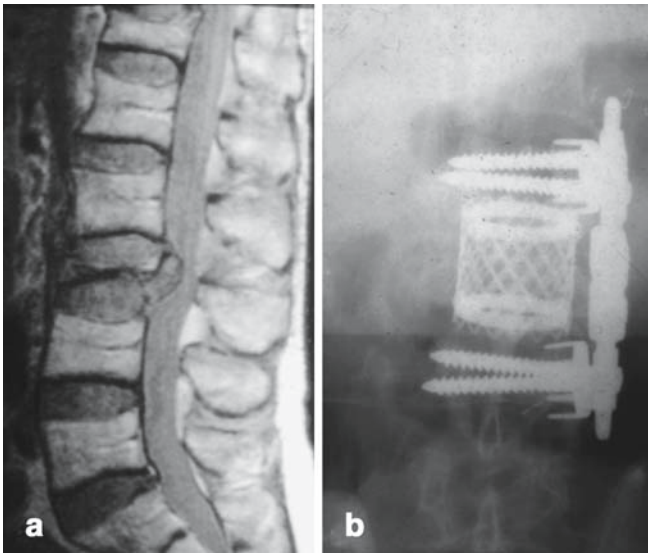


Fig. 7 Paraparesis after spontaneous osteoporotic fracture (a), corrected by anterior decompression and reconstruction (b)

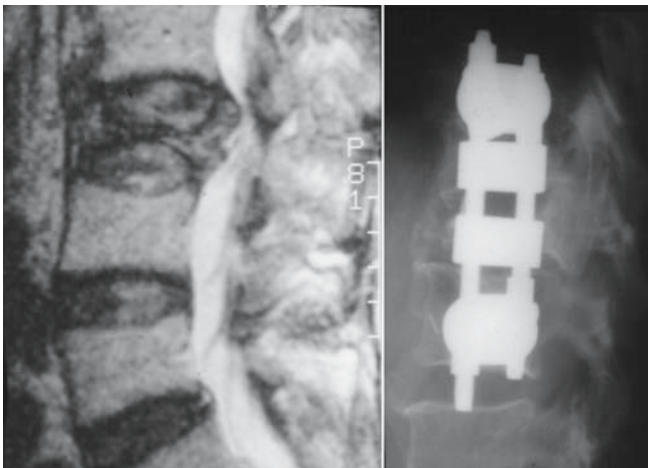


Fig. 8 Pathological osteoporotic fracture with complete restoration of neurological deficit after anterior decompression, iliac bone graft and Kaneda stabilization

summarizes the published reports of serious neurocompression complicating osteoporotic fractures.

Surgical approach

Through an anterior approach, decompression of a retro-pulsed bone fragment can be easily and safely performed. Reconstruction and fusion can be achieved either by femoral ring bone allograft, rib struts, iliac bone, cages filled with bone chips, or bioactive ceramic [71] (we do not use methylmethacrylate as a reconstruction material advocated by others) [6]. Stabilization can be accomplished using a Kaneda device or similar rigid anterior in-

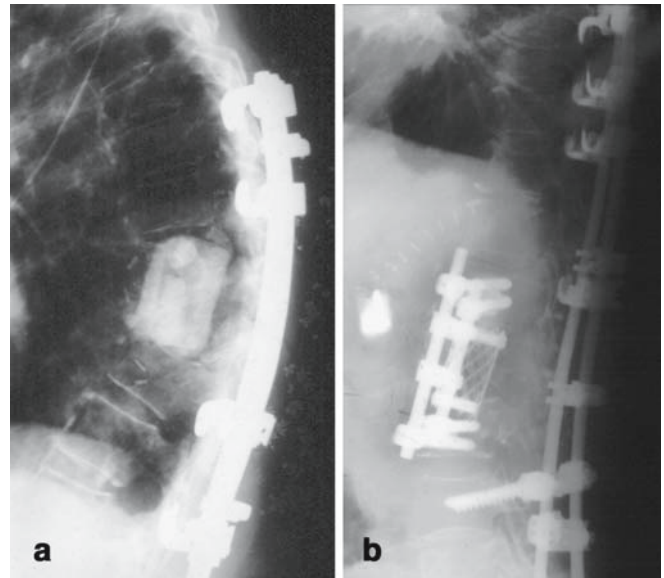


Fig. 9 a Anterior decompression and reconstruction with femoral ring bone graft and posterior stabilization. b Anterior decompression and reconstruction with titanium mesh cage filled with bone chips; stabilization was obtained through a combined anterior and posterior long multisegmental stabilization construct

strumentation (Fig. 7, Fig. 8). Because screw holding grip is incomplete in osteoporotic bone, we advocate that the screw should stabilize the contralateral vertebral body cortex. Stabilization can also be obtained through a posterior approach (Fig. 9). Alternatively the surgeons could elect first to stabilize the spine posteriorly and, in the same sitting, proceed with an anterior decompression [119].

Anterior cord decompression can also be performed through a posterior transpedicle or posterolateral approach. In general, many surgeons who are more familiar with the posterior approach prefer this method, which also avoids the need for sectioning the diaphragm – especially advantageous in elderly patients with serious pulmonary problems [75, 125]. Through this approach, cord decompression can be achieved either by:

- Partial posterior vertebrectomy and bone grafting [75]
- Driving forward the retro-pulsed fragment by gentle direct tapping [125], or
- Performing a vertebrectomy to accomplish shortening and decompression of the spinal cord [118]

The spine is then stabilized through a posterior instrumentation, preferably by using transpedicular screw fixation two to three levels above and below the decompression. The only technical complication reported with this approach is dural tear (14%) [75]. Laminectomy, as a stand-alone procedure, should be rejected, because it does not deal with the anterior cord compression, and further deterioration of neurological deficit from progressive kyphotic deformity has been observed [73].

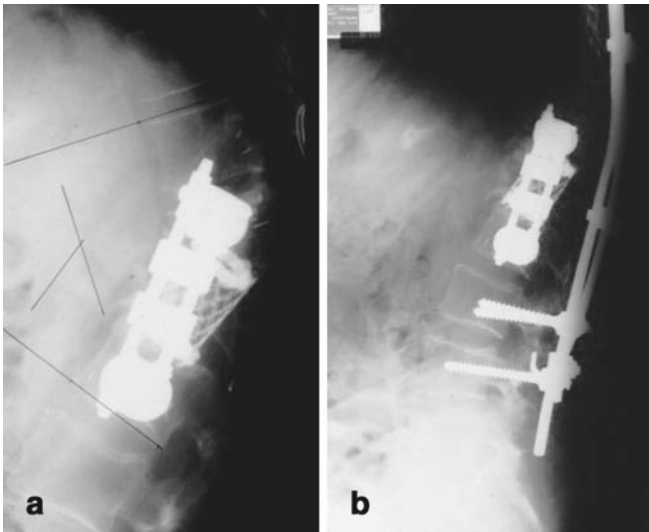


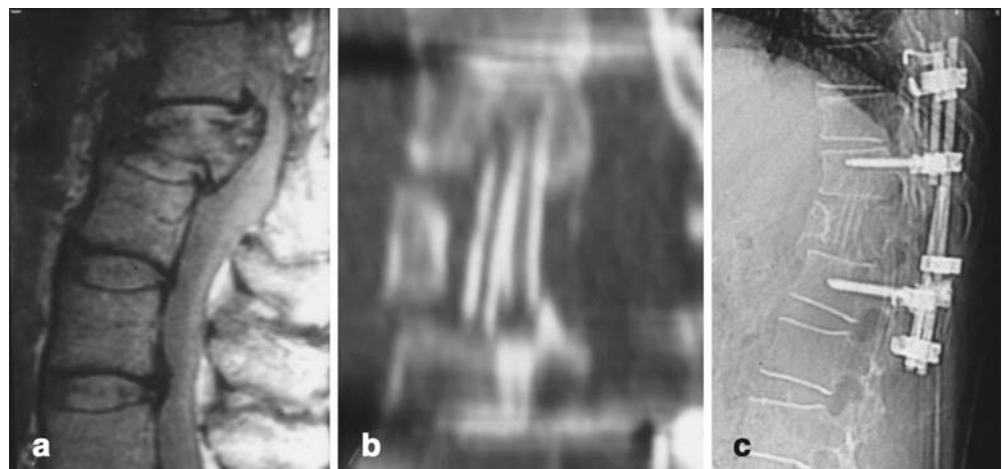
Fig. 10 Junctional kyphosis after anterior instrumentation (a), corrected by posterior instrumentation combining screws and hooks (b)

Options for instrumentation

Hardware loosening or cut-out with dislodgment of instrumentation construct are the most serious technical complications when operating on osteoporotic spines. To avoid this, the surgeon should be aware of certain well-established surgical principles when instrumenting osteoporotic spines, as suggested by Hu [66]:

1. Try to avoid the use of hooks or screws as the sole fixation device.
2. Avoid ending the instrumentation within kyphotic segments [66] (Fig. 10) to prevent junctional kyphotic complications [66, 86].
3. Use multiple sites of fixation to dissipate stresses and therefore decrease stresses at any site [66] (Fig. 9b, Fig. 5). Similarly, the excessive forces on the instrumentations, can be sufficiently dissipated by combin-

Fig. 11 Pathological fracture with severe delayed neurocompression (a), treated by means of anterior decompression and reconstruction with rib strut graft (b). c Posterior stabilization with screws and Varigrip claws



ing anterior and posterior surgical approaches and instrumentation [14].

4. Accept a lesser degree of deformity correction (Fig. 11), in order to avoid hardware pull-out from excessive corrective forces [66].

And, finally, one should keep in mind that fixation may not be feasible!

As an ultimate salvage approach one may consider a morphine pump, as the last attempt to control musculoskeletal pain in moribund patients.

In relation to point (1) above, there are a number of considerations to bear in mind. Laminar hooks are considered to be more resistant to posteriorly directed forces, because laminar bone is more cortical than cancellous and will therefore have been affected by osteoporosis [21]. Hooks in a claw configuration spanning two vertebral levels can augment the holding grip of the construct. Experimental work indicates that transpedicular screw axial pull-out is correlated to the vertebral bone mineral density [21, 58, 99, 131]. Triangulation of pedicle screws apparently resists axially directed screw pull-out [54, 55]. Augmentation of transpedicle screw fixation in osteoporotic patients using polymethylmethacrylate has been accepted as a sound technical principle [22, 85, 96, 131]. A combination of pedicle screw and laminar hooks will provide the greatest resistance to pull-out forces [7, 17, 58, 61, 92] (Fig. 11). Hu thinks that sublaminar wire fixation of spinal rods is a sound surgical principle in osteoporotic spine [66]. Although sublaminar wires pose a potential risk for neurological complications, they are ideal because the multiple sites of wire fixation decrease the stresses generated at points of fixation [66].

Osteoporosis: conclusion

In conclusion, several caveats deserve to be highlighted here. Osteoporotic fracture of the spine is not always an innocent occurrence, as most people are led to believe, but

can give rise to serious and crippling neurological complications and painful deformities as well. Surgery in these cases is apparently the sole alternative approach, and may turn out to be a formidable task. However, the clinician who is armed with knowledge of the best options in surgical treatment can effectively and safely manage the problem, which is anticipated to be seen more frequently in the near future. The aging population should be rewarded with the enjoyment of life without pain and disabilities.

Paget's disease of the spine

The second part of this paper looks at Paget's disease, another osteometabolic disorder that can affect the aging spine. It describes the spinal involvement of Paget's disease in bone and outlines best treatment options.

Etiology

The original disease was described by Sir John Paget [100] in 1877, and despite recent intensive studies, its etiology remains obscure. Paget's disease of bone (PD), a mono-ostotic or polyostotic non-hormonal osteometabolic disorder, is postulated to be caused by a viral infection [10, 49, 127]. This claim is supported by circumstantial evidence garnered from electron microscopic, immunologic, and epidemiologic studies [56].

PD is found more commonly in populations of Anglo-Saxon origin, and is rarely encountered in Asia, Scandinavia, or the Middle East [9]. A survey of PD in South Africa revealed a prevalence of 1.3% among the black population and 2.4% among the white population [44], suggesting that PD may not be uncommon in Africans, as was previously believed [128]. Autopsy and radiographic studies indicate that the overall prevalence of PD is 3–3.7% [23, 104, 123], with a tendency to increase with age. At the age of 90, the expected prevalence is about 10% [123]. A very recent report on radiographic examination of the pelvis [5] revealed an estimated overall prevalence in the US of 1–2%, with near equal distribution between whites and blacks and between sexes.

Genetic factors also play a role in the pathogenesis of PD [62, 65, 129]. A positive family history in patients of siblings was reported in 12.3% of cases, as compared to 2.1% of controls. In another study, the prevalence of PD was found to be approximately seven times higher in relatives of cases than controls.

Viral infection may also help explain the genetic predisposition, by gene mutation, of PD [93]. Circumstantial evidence thus supports the plausible hypothesis that viral infection may trigger the onset of PD as well stimulate inheritable gene mutation. Future research hopefully will cast light on these issues [56].

Histopathology

The histopathology of PD is characterized by two entities: osseous lesions and bone marrow fibrosis. The former is characterized by its so-called mosaic appearance, which is the hallmark of the pagetic lesion. The pagetic cellularity consists of variable sizes of osteoblasts and large osteoclasts with multiple nuclei (up to 100) [106].

Prevalence of back pain and spinal stenosis

The spine is the second most commonly affected site in PD [2, 30, 95], predisposing patients to low back pain and

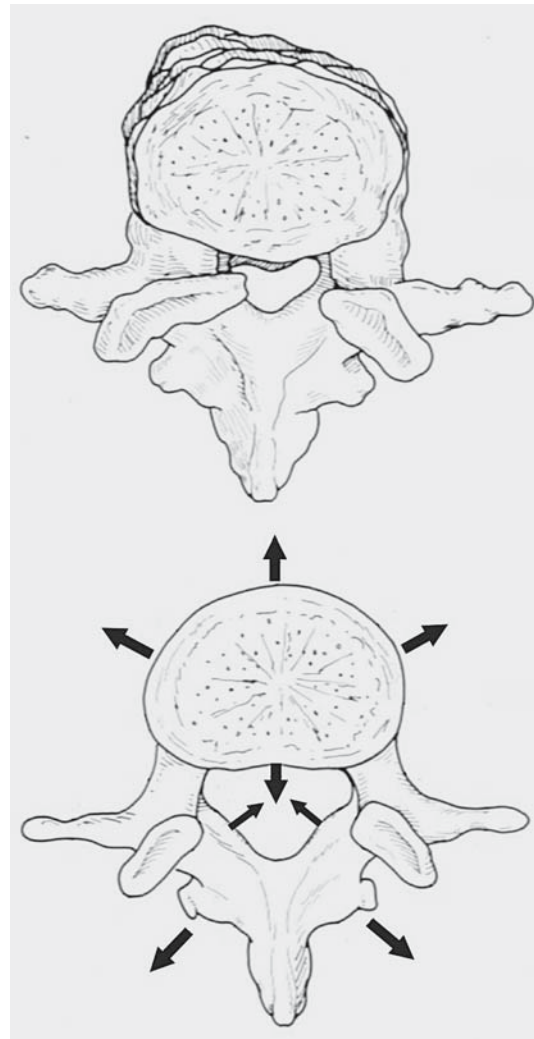


Fig. 12 Bone modeling of vertebra depicted diagrammatically to demonstrate tendency of bone expansion in all directions, leading to hypertrophic facet osteoarthropathy and spinal stenosis. [Reprinted, with permission, from Hadjipavlou A, Lander P (1995) Paget's disease. In: White AH, Schofferman JA (eds) Spinal care. Mosby, St Louis, pp 1720–1737]

Fig. 13 **a** Plain radiography demonstrating pagetic involvement of L4 vertebra with typical expansion in the mixed-blastic phase. **b** Axial computed tomography scan of the third lumbar vertebra, demonstrating circumferential expansion of a mixed-blastic-phase lesion of Paget's disease (PD) causing severe spinal stenosis. [Reprinted, with permission, from Hadjipavlou A, Gaitanis I, Katonis P, Lander P (2001) Paget's disease of the spine and its management. *Eur Spine J* 10:370–384]

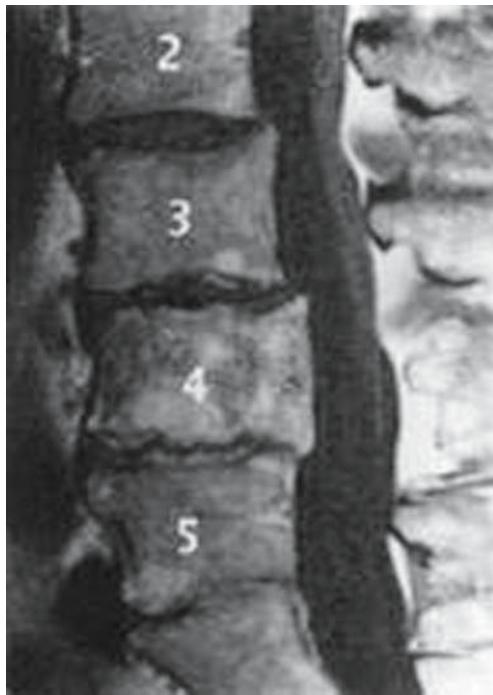
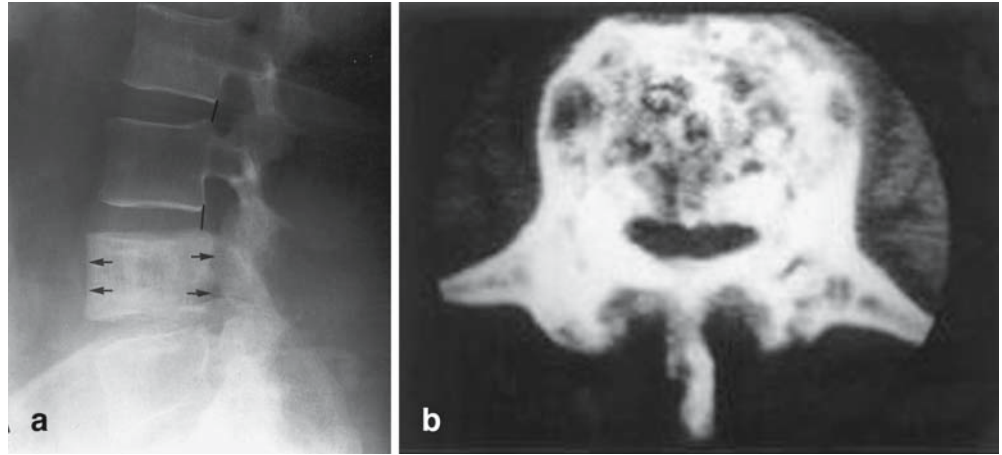


Fig. 14 T1-weighted magnetic resonance image showing posterior expansion of the vertebral body. [Reprinted, with permission, from Hadjipavlou A, Gaitanis I, Katonis P, Lander P (2001) Paget's disease of the spine and its management. *Eur Spine J* 10:370–384]

spinal stenosis [4, 52, 64, 137]. Hartman and Dohn have shown that 15.2% of patients with PD had involvement of the vertebrae, and 26% of these patients had symptoms of spinal stenosis [59]. The reported incidence of back pain in PD ranges from 11% [40] to 34% [2] and as high as 43% [113]. The causal relationship between vertebral PD and back pain has been disputed [2], with low back pain in PD being attributed to coexisting osteoarthritis of the spine in 88% of patients and to PD alone in only 12%. Others consider PD to cause back pain even more rarely

[45]. However, in our population, 33% of patients with PD demonstrated pagetic involvement of the spine; 30% had clinical symptoms of spinal stenosis and 54% of these patients suffered back pain (24% attributed clearly to PD alone, 50% to degenerative changes and 26% to a combination of PD and degenerative changes) [46].

Spinal pain (back pain and neck pain)

PD can be defined as an abnormal disturbance of bone remodeling, giving rise to the four phases of the disease observed radiologically: the osteolytic, mixed, osteoblastic, and osteosclerotic phases [79]. This leads to abnormal modeling, which determines the shape and geometry of the bone [43] (Fig. 12) leading, in turn, to spinal stenosis [79] (Fig. 13, Fig. 14) and facet arthropathy [50, 57].

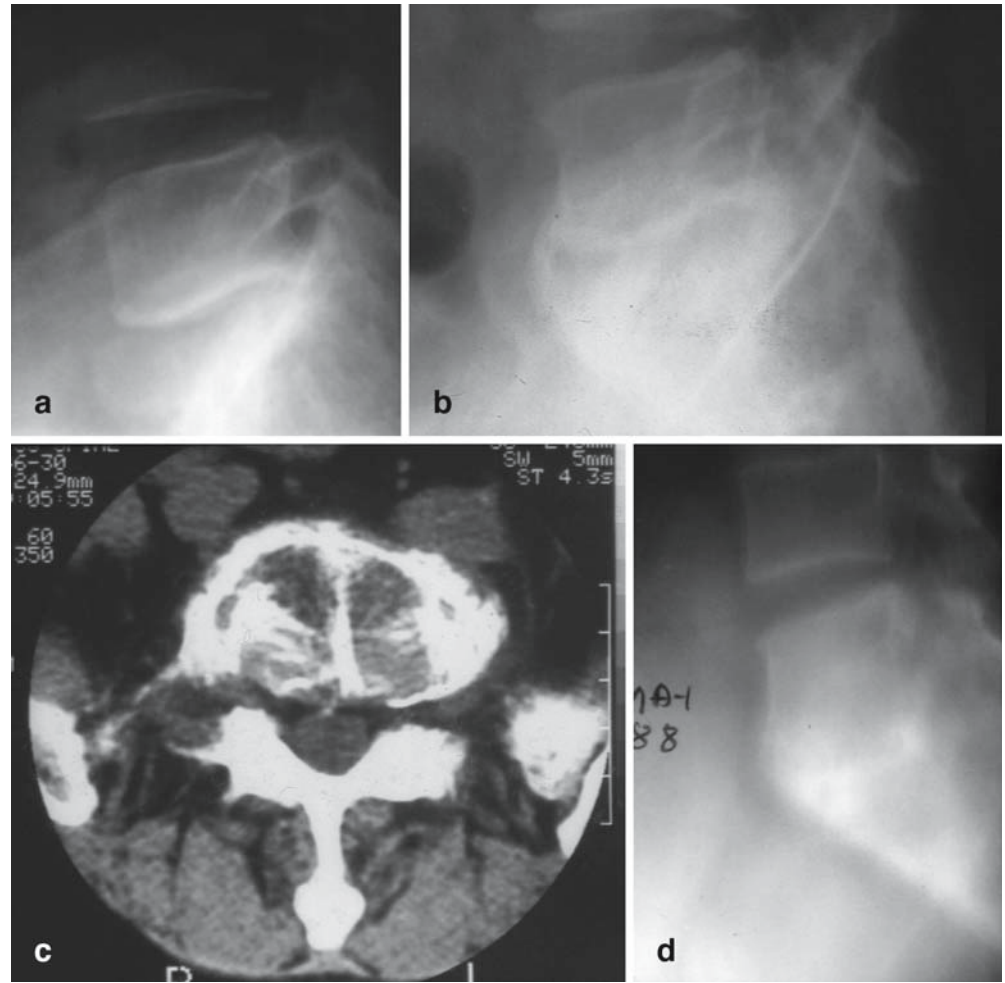
Pagetic facet arthropathy is a major contributing factor to both back pain and spinal stenosis, and the more advanced the facet joint arthropathy, the greater the likelihood that patients will suffer clinical spinal stenosis and/or back pain [46]. However, this does not necessarily preclude that, though present, severe facet arthropathy may remain asymptomatic [46]. Back pain in PD may also be attributed to blood engorgement of the vertebral body caused by vascular and disorganized, hyperactive remodeling processes.

Other factors implicated in spinal pain may include invasion of the vertebral disc space by the pagetic process (Fig. 15) [80], and spinal stenosis [137]. The authors hypothesize that microfractures of pagetic vertebral bodies, especially in the osteolytic or mixed phase, can also lead to back pain [46].

Spinal stenosis

Involvement of the cervical and thoracic spine tends very often to predispose to clinical spinal stenosis with my-

Fig. 15 **a** Lateral radiograph of the lumbosacral junction demonstrating mixed phase Paget's disease of the first sacral segment with moderate narrowing of the L5-S1 disc space. **b** Pagetic bone extension across the disc space with adjacent anterior bridging with sclerotic bone noted 3 years after the initial radiograph. **c** The corresponding axial CT scan of the L5-S1 disc demonstrates pagetic bone within the disc. **d** Lateral tomogram demonstrating the intradiscal bone extension from the adjacent S1 vertebra resulting in complete bony ankylosis 4 years after the initial radiograph. [Reprinted, with permission, from Lander P, Hadjipavlou A (1991) Intradiscal invasion of Paget's disease of the spine. *Spine* 16: 46-51]



elopathy [46]. Ten distinct mechanisms have been implicated in the development of neural element dysfunction in patients affected by PD:

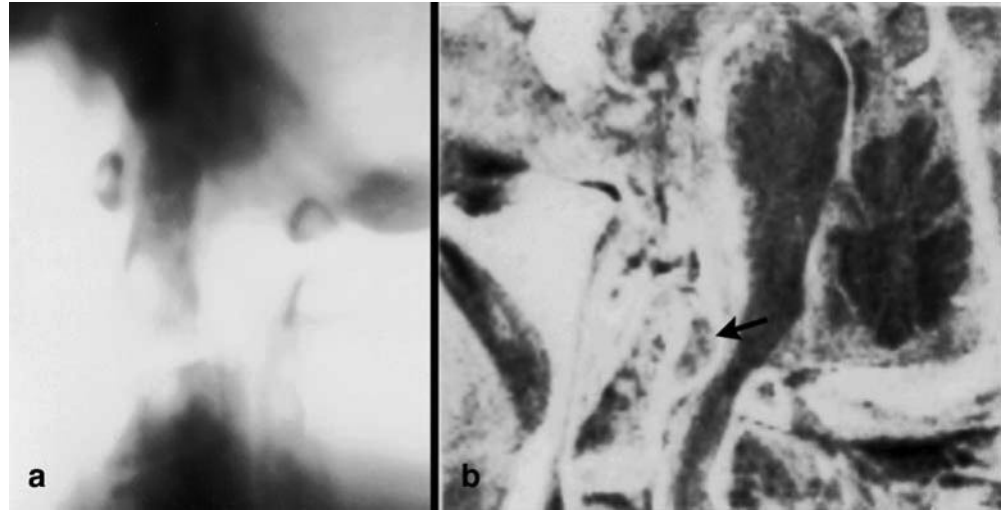
1. Compression of the neural elements by pagetic bone overgrowth [31, 46, 76]
2. Compression by pagetic intraspinal soft tissue [46, 51] (Fig. 16)
3. Ossification of the epidural fat similar to ankylosing spondylitis [20]
4. Neural ischemia produced by blood diversion, causing the so-called "arterial steal phenomenon" [16, 59, 64, 103] (Fig. 17)
5. Interference with blood supply to the cord due to arterial compression by the expanding pagetic bone [123] or other factors not well defined [91]
6. Vertebral fracture or atlantoaxial subluxation [124, 135]
7. Platybasia with impingement on the medulla [28]
8. Spinal cord compression by epidural hematoma from spontaneous bleeding [81, 110]
9. Formation of syringomyelia as a complication of PD of the spine, especially after cranial settling (basilar invagination) [35, 110], and

10. Rarely, neurocompression can be caused by pagetic sarcomatous degeneration [67].

Bone compression by the expanding pagetic vertebrae is by far the most common cause of neural dysfunction [46]; it was first reported by Wyllie in 1923 [136]. However, severe stenosis, as seen on computed tomographic (CT) scan, may remain asymptomatic, suggesting adaptability of the thecal sac and its neural elements to severe spinal stenosis without significant loss of function [124].

The mechanism of neural ischemia is, however, still hypothetical, and supported only by circumstantial evidence. For example, patients with spinal cord symptomatology respond to calcitonin treatment better than patients with spinal nerve root lesions [28]; some patients experience progressive deterioration of neural function without evidence of myelographic block, which is not easily explained by mechanical effect alone [117]; neurologic signs do not always correlate with the site of skeletal involvement; and rapid clinical improvement occurs in some patients with medical antipagetic treatment alone. These observations suggest that neural dysfunction in PD may also result from mechanisms other than simple bone encroach-

Fig. 16 A 63-year-old male patient with pagetic soft tissue expansion originating from the dens and compressing the medulla as seen on: **a** lateral tomogram of dens (bony element), and **b** MRI scan of soft tissue (see arrow). The patient was treated successfully with surgical decompression



ment on the neural element [32, 47, 64, 74, 103, 134, 136], such as deprivation of blood supply to the neural elements by the rapidly remodeling hypervascular pagetic bone, which produces “arterial steal phenomenon”.

Other associated conditions

Malignant transformation

Malignant transformation is the most dreaded complication of PD of bone. Fortunately, this complication is relatively rare, occurring in about 0.7% [52] of cases. In our series of PD patients [52, 53] we have not seen any cases with sarcomatous degeneration in the spine. In Schajowicz et al. [120], of 62 patients with sarcomatous transformation, five of the sarcomas occurred in the spine. Surgical decompression offers little, if any, true relief of pain, with the longest survival reported at just over 5 months [67].

One should be aware of the appearance of “pseudosarcoma” or “pumice bone,” which is a localized extracortical periosteal pagetic bone expansion or a bulky juxtacortical soft tissue mass, giving the erroneous appearance of sarcomatous transformation [62, 78] (Fig. 18).

Rheumatic and arthritic conditions

Forestier’s disease, or disseminated idiopathic hyperostosis (DISH), can frequently affect patients with PD. However, care should be taken not to confuse DISH with Paget’s extraosseous bone formation [15]. The incidence of DISH in PD was reported to range from 14% [48] to 30% [5]. Pagetic tissue may invade the hyperostotic lesions produced by DISH and transform them into pagetic exostosis [46], which may progress to vertebral ankylosis [89].

PD has also been noted to be associated with an increased incidence of gout [40] and pseudogout [105]. These

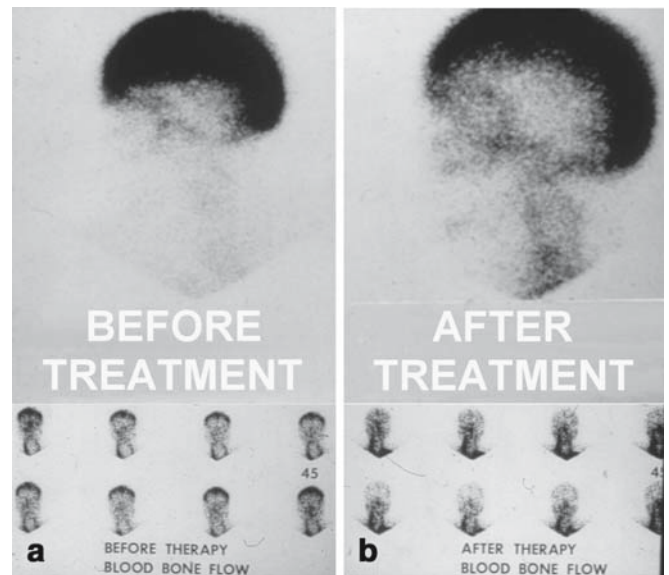


Fig. 17 A 78-year-old male patient presented himself with unsteady gait and confusion. **a** Bone scan (^{99}Tc MDP) revealed increased uptake in the skull, and bone blood flow revealed increased engorgement of the skull. **b** After treatment with i.v. mithramycin, bone scan activity improved somewhat, while bone blood flow was restored to normal. This coincided with improvement of the patients gait and mental status, suggesting that the brain had most likely been deprived of its blood supply (steal syndrome by the skull hypervascularity)

conditions, however, are not clearly implicated in the production of back pain. One has to keep in mind that treatment with sodium etidronate may be responsible for the accumulation of pyrophosphate crystals in the synovial joint, producing pseudogout [41].



Fig. 18 Anteroposterior radiograph of the lumbar spine showing a localized bulky juxtacortical bone expansion of the lateral aspect of L4-L5 vertebrae resulting in bone union. The appearance of the lesion may be misconstrued as sarcomatous degeneration (pseudosarcoma or pumice bone). The cortical margins are well defined in contrast to the usual appearance of sarcomatous transformation, which remains poorly delineated. [Reprinted, with permission, from Hadjipavlou A, Gaitanis I, Katonis P, Lander P (2001) Paget's disease of the spine and its management. *Eur Spine J* 10:370–384]

Treatment

Treatment of back pain

One must be certain before attributing back pain to PD, otherwise the results of antipagetic treatment may not be rewarding [3]. For patients with low back pain and PD, suppressive therapy with EHDP (disodium etidronate) was beneficial to 36% of patients in one report [4]. This suggests that unless a well-defined lesion is related to low back pain, antipagetic therapy is not expected to be effective. If antipagetic medical therapy is ineffective within 3 months, a concomitant nonsteroidal anti-inflammatory drug and other treatment methods (physical therapy, corsets, etc) for back pain should be prescribed, especially when the presenting back pain is mechanical or arthritic in nature [50, 130].

Treatment of spinal stenosis

Because antipagetic medical therapy is rewarding in the treatment of pagetic spinal stenosis syndrome, one should start with antipagetic drug treatment. Calcitonin, mithramycin, sodium etidronate, pamidronate disodium, and clodronate have been reported to either improve or to completely reverse the clinical symptoms of spinal stenosis [1, 16, 36, 107]; however, relapse of spinal stenosis symptomatology after medical antipagetic treatment is not uncommon [32, 33]. Therefore, patients should be closely monitored and cyclical therapy should be continued if necessary until biochemical bone indices normalize.

Severe spinal stenosis of lytic type has been shown to respond successfully to antipagetic treatment with clodronate [36]. It has been suggested that, for pagetic spinal stenosis in the lytic phase of the disease, administration of vitamin D and calcium supplements to improve mineralization of lytic pagetic spinal lesion causing canal block can enhance the effectiveness of bisphosphonate therapy [36].

If the symptoms persist, in spite of bone remodeling markers normalization, surgery is an alternative treatment. Decompression of spinal stenosis should be implemented promptly after failure of antipagetic therapy. In these circumstances, delaying decompression may result in irreversible myelopathy or radiculopathy [80]. On the other hand, the results of surgery have shown variable improvement in 85% of patients [117], with frequent relapses or failures, which may improve with subsequent medical antipagetic therapy [1, 16, 107]. In our series, patients who demonstrated either partial or temporary improvement after laminectomy and were treated with further antipagetic medical treatment exhibited marked improvement of their symptomatology with sustained relief [50]. From our experience and from other reports, spinal surgery for pagetic spinal stenosis may fail to reverse the neurological deficit completely [15], and may be associated with serious complications such as a mortality rate of 11% [117] and dangerously profuse, if not torrential, bleeding [116]. To avoid such catastrophes, we recommend the preoperative assessment of bone vascularity by means of radionuclide bone blood flow in the affected spinal region. We have found this test reliable, simple and reproducible [11]. To decrease potential bleeding during surgery, if there is increased vascularity in the affected region, we strongly recommend a course of medical antipagetic treatment until the bone blood flow normalizes [50]. This may take 2–3 months with calcitonin therapy, or 2–3 weeks with mithramycin treatment [56, 57, 114]. The new generation of IV bisphosphonates can also be used effectively in this situation. In emergency situations, embolization of the region may be indicated. Because of the anticipated massive bleeding during laminectomy, the use of a cell saver is strongly recommended [115].

Surgery for spinal stenosis, when indicated, should be tailored to the pathology responsible for neural compres-

sion. If neural compression is caused by the posterior expansion of vertebral bodies, an anterior approach with corpectomy and fusion is indicated. If neural compression is caused by posterior vertebral elements, then posterior decompression should be the approach of choice [50]. An acute onset of spinal compression seems to bear a graver prognosis than the more gradual development of symptoms; the former tends to respond better to surgical decompression [126]. Surgery is also indicated as a primary treatment when neural compression is secondary to pathological fracture, dislocation, epidural hematoma, syringomyelia, platybasia, or sarcomatous transformation.

Pharmacologic treatment

A pressing issue regarding treatment is whether physicians should treat asymptomatic patients. The progressive nature of PD, the severity of its associated complications, the potential negative impact on patients' quality of life, and the availability of effective and relatively safe new antipagetive drugs have led many experts to recommend treatment for asymptomatic patients who have active disease [50, 93, 133]. According to Meunier et al., in a long-term follow up study of 41 cases of PD, antipagetive therapy that did not normalize biochemical markers in 71% of patients did not prevent new complications in 62% of patients [95], suggesting that antipagetive therapy should continue until normalization of biochemical markers is achieved. However, there are no conclusive data to support the theory that complications are preventable by controlling bone-remodeling with drug therapy [133]. Patients who are asymptomatic and inactive by biochemical and imaging parameters do not require treatment. However, patients who are clinically asymptomatic but demonstrate increased disease activity as shown by biochemical markers, bone scan uptake activity, or increased engorgement by radionuclide investigation should be treated repeatedly until a normalization of these indices is accomplished [95, 130].

Five classes of drugs are available for the treatment of PD: bisphosphonates, calcitonin, mithramycin (plicamycin), gallium nitrate, and ipriflavone. Bisphosphonates appear more effective than calcitonin in suppressing the histological and biochemical activity of PD. Therefore, calcitonin is no longer considered the treatment of choice for this condition. Some of these drugs are still experimental and can be obtained only through clinical trials. A major advantage of the use of bisphosphonates over calcitonin in PD is that biochemical and histological suppression of disease activity may persist for many years after the cessation of treatment [108].

Bisphosphonates. The mechanism of action of bisphosphonates on bone was originally ascribed to their physicochemical effect on hydroxyapatite crystals [38]. They bind strongly to hydroxyapatite crystals and inhibit both their formation and dissolution in vitro. Although such an

effect is characteristic of their overall action, their influence on cells is probably of greater importance. The mechanism of action appears to be complex [39], involving several components:

1. A direct effect on osteoclastic activity
2. A direct effect on osteoclast recruitment
3. An indirect effect on osteoclast recruitment mediated by cells of osteoclastic lineage that are capable of stimulating or inhibiting osteoclastic recruitment (macrophages are osteoclast precursors), and
4. A shorter osteoclast life-span due to apoptosis

Bisphosphonates can be classified into nitrogen and non-nitrogen containing groups; two pharmacologic classes with distinct molecular mechanisms. Several bisphosphonates have been investigated [56, 57], but only the following bisphosphonates have been approved for clinical use: disodium etidronate, clodronate, pamidronate, alendronate, risedronate, neridronate, tiludronate, ibadronate, amino-hydroxybutylene bisphosphonates (ABDP), olpadronate, and zoledronate.

Oral administration of alendronate at a dose of 40 mg per day for 6 months has demonstrated efficacy in normalization of serum alkaline phosphatase [56, 109]. The present authors assessed the effects of an unpublished study of a higher dose (60 mg per day) of oral alendronate (Fosamax, Merck and Co., inc) on PD over a shorter period (3 months) in 28 patients, 18 male and 10 female with a mean age of 68 years. Ten patients had never been treated before, and 18 had previously received drug therapy. The mean period without treatment prior to alendronate was 14 months. Sites of Paget's were visually scored from +1 to +4 for radiological assessment. Quantitative uptake by region of interest (ratio of Paget's to normal bone) was also determined for scintigraphic examination.

As a result of treatment, alkaline phosphatase levels fell from 266.6 to 82.2 IU/l (mean difference 183.8 IU/l, $P=0.000$). Osteocalcin levels fell from 5.1 to 8.7 pmol/l (mean difference 3.6 pmol/l, $P=0.0002$). All patients normalized their alkaline phosphatase levels. Follow-up was carried out on all 28 patients 2 years after the 3-month treatment. All but three were in remission, giving a rate of 89.2%. No side effects were noted in any of the patients treated. The response to therapy was similar between patients who had previously received antipagetive therapy and those who had not. Similarly, there was a marked radiological (Fig. 19) and scintigraphic improvement (Fig. 20).

A major advantage of the bisphosphonates over calcitonin is that biochemical and histological suppression of the disease activity may persist for many years after the cessation of treatment [108].

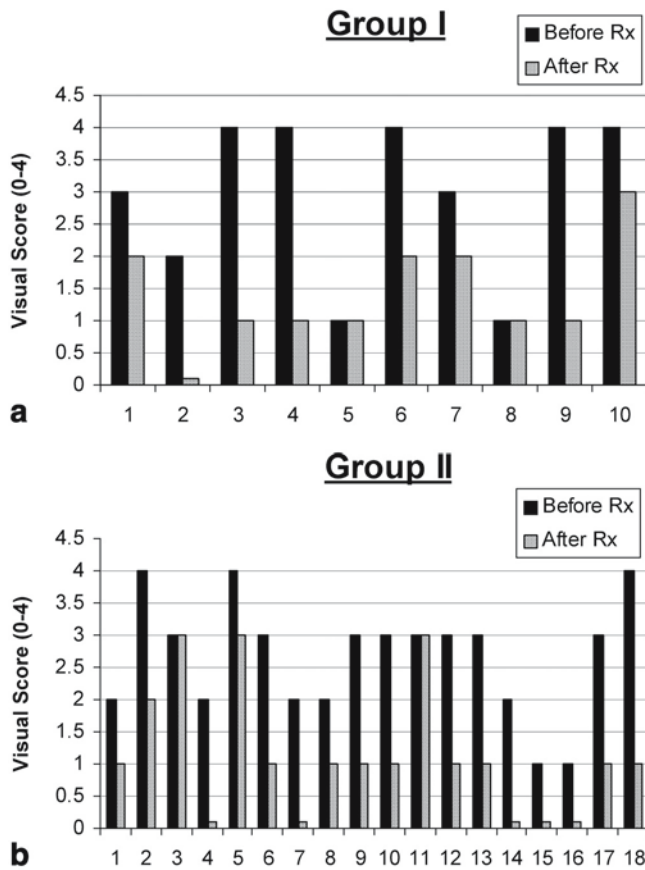


Fig. 19 Radiographic effects of alendronate treatment. Patients in group I had never been treated before alendronate treatment. Group II patients had previously received drug therapy

Laboratory methods for clinical assessment and monitoring antipagetic drug treatment

Imaging resources

The effects of treatment are monitored by the patient's clinical response, imaging modalities, and bone remodeling markers [56, 57].

Radionuclide bone blood flow can be used to monitor vascularity. Therefore, it can be used:

1. To assess a relevant pagetic region for potential profuse bleeding before proceeding with surgery, and
2. To monitor the effectiveness of an emergency intravenous administration of antipagetic agents

Conventional bone scan is recommended before and 6 months after treatment, and 12 months thereafter depending on the behavior of the pagetic lesion. Twenty-four hour retention scan, a more quantitative radionuclide assessment, can be used as an adjunct to bone scan [11]. Quantitative bone scan scintigraphy allows early and objective assessment of PD when evaluating the effects of therapy. Radiographic images should be obtained before treatment and every 1 to 2 years thereafter, to monitor the modeling (bone

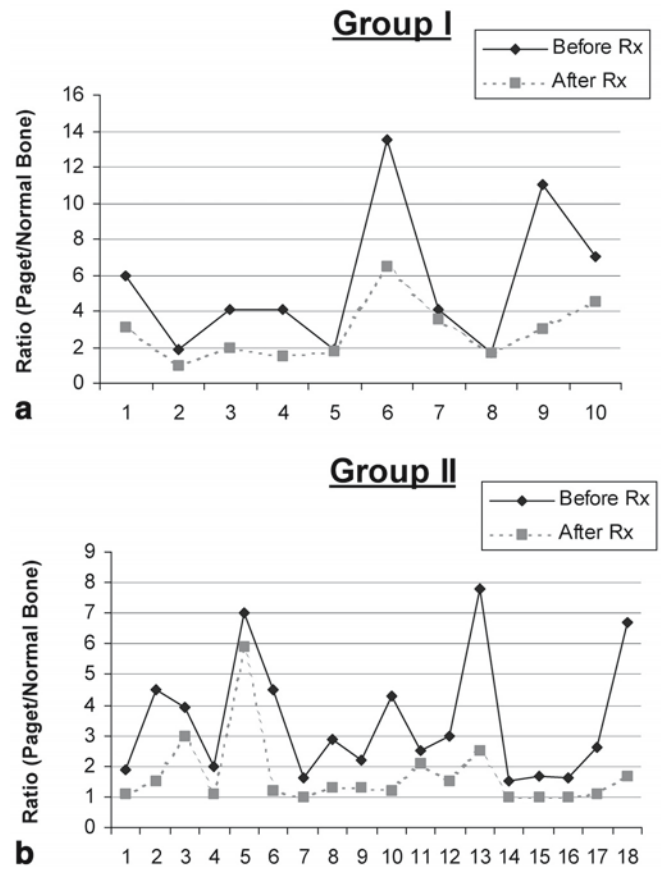


Fig. 20 Scintigraphic evaluation of alendronate treatment. Patients in group I had never been treated before alendronate treatment. Group II patients had previously received drug therapy

expansion) and remodeling changes (phase of the disease activity). Although PD can be diagnosed cost effectively with conventional radiography, magnetic resonance (MR) imaging is well suited for demonstrating specific characteristics of certain complications, including basilar invaginations, spinal stenosis, and secondary neoplasm [12].

Biomechanical bone markers

Recently, the assessment and effectiveness of treatment of patients with Paget's disease have been improved by new emerging biochemical markers for bone remodeling, promptly applied.

Common bone markers used for the evaluation of bone turnover in PD are:

- In serum: total alkaline phosphatase (tAP) and bone alkaline phosphatase (β AP), procollagen type 1 N-terminal polypeptide (PINP), beta-carboxyterminal telopeptide of type 1 collagen (SCTX); osteocalcin and serum bone sialoprotein
- In urine: hydroxyproline (Hyp), amino (NTX) and beta-carboxyterminal (CTX) telopeptides of collagen type I, total pyridinoline (PYD) and deoxypyridinoline (DPD)

Markers of bone resorption representing degradation of type I collagen are: N-telopeptides, C-telopeptides, hydroxyproline and collagen crosslinks-pyridinoline and dextroxyridinoline, and urinary calcium.

Serum tartrated-resistant acid phosphatase is a marker for osteoclastic activity. Bone formation markers include bone-specific alkaline phosphatase and N terminal and C terminal extension peptides of procollagen and osteocalcin.

Resorption markers respond approximately 1–3 months after treatment intervention, whereas markers of formation respond much later, usually after 6–9 months [19].

The serum markers of bone turnover show lower biological variability than urinary markers, and are therefore more sensitive indices of disease activity.

Paget's Disease: conclusions

The natural history of PD affecting the spine is therefore progressive, characterized by bone proliferation, vertebral

expansion, and structural changes, leading to spinal stenosis and facet arthropathy, clinical entities that are not always symptomatic. Pagetic facet arthropathy is a major contributing factor to both back pain and spinal stenosis, and the more advanced the facet joint arthropathy, the greater the likelihood that patients will suffer clinical spinal stenosis and/or back pain. In the majority of cases the clinical picture of pagetic spinal stenosis and facet osteoarthropathy is not expected to differ from that of degenerative spondylosis. A minority of patients (13%), however, exhibits constant spinal pain attributed to the pagetic pathologic remodeling process. Treatment of pagetic spinal stenosis symptoms should start with medical anti-pagetic therapy, with surgery being the alternative choice only if the symptoms persist in spite of normalization of bone remodeling markers.

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