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Review article

PAGET’S DISEASE OF THE BONE AND ITS MANAGEMENT

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Paget’s disease of bone (PD) is a monostotic or polyostotic non-hormonal osteometabolic disorder. Over a century after the original disease was described by Sir John Paget in 1877, and despite recent intensive studies and widespread interest, its aetiology remains obscure. This review describes the pathomechanism of the structural changes which occur in bone affected with PD, induced by the different dynamic patterns of activity of the disease, and outlines the current methods of treatment.

Aetiology

The tendency for sarcomatous transformation, the variability of the appearance of the osteoblasts as regards size, shape and staining, the peculiarity of the osteoclasts with differences in size and up to 100 nuclei, as seen also in giant-cell tumours, and control of the disease by antimitotic agents such as plicamycin, also known as mithramycin, suggest that PD may be a benign neoplasm of the mesenchymal osteoprogenitor cell, as was suggested by Rasmussen and Bordier in 1973. It has been postulated that it may be the result of a viral infection. Electron microscopy of osteoclasts has shown the presence of viral intranuclear inclusion structures resembling those of an RNA-type virus related to measles or subacute sclerosing panencephalitis. Immunological studies have indicated the presence of specific viral antigens in osteoclasts and cells grown from Paget’s bone. A characteristic feature of paramyxoviruses is their ability to persist at very low levels, and to invade the host immune system. Factors which can be activated by the ROS virus, for example, IL-6, C-fos and Bcl-2, are all strongly elevated in PD suggesting that it may be a viral infection.

It has been noted that PD is associated with the ownership of birds, dogs, cats or cattle. Investigations have shown that canine distemper, a paramyxovirus closely related to measles, can contaminate human osteoclast cells, which may contribute to the development of PD. Other studies, however, have found no risk factors associated with dogs or cats.

Prevalence, distribution and genetic factors

PD is found more commonly in people of Anglo-Saxon origin and is rarely encountered in China, Japan, Iran, India, Scandinavia, Africa or the Middle East. A survey in Johannesburg, South Africa, revealed a prevalence of 1.3% among the black population and 2.4% among the white, but a recent report on radiological examination of the pelvis showed an estimated overall prevalence in the USA of 1% to 2% with nearly equal distribution between whites and blacks and between sexes. Post-mortem and radiological studies indicate that the overall prevalence of PD is 3% to 3.7%, increasing with age. By the age of 90 years, the expected prevalence is about 10%.

Genetic factors play a role in the pathogenesis of PD, which is inherited as an autosomal dominant trait with high penetrance. It may be seen in more than one member of a family with a prevalence of approximately seven times more in relatives or patients than in control subjects. Studies in families with PD have shown linkage to a region of chromosome 18q near the polymorphic locus D18S42, most likely as a result of gene mutation. Genetic heterogeneity is almost certainly present; data from some families with PD suggest the presence of at least one additional locus, which remains to be identified.

Histopathology

Histopathological examination shows changes in the structure of bone and fibrosis of the marrow. The bone has a so-called mosaic appearance, the hallmark of a Pagetic lesion, and a peculiar cellularity consisting of variable sizes of osteoblast and large osteoclasts with up to 100 nuclei. Bone-marrow fibrosis is not associated with anaemia.
Pathomechanics of bone deformity

There is a disturbance of bone remodelling. Frost has defined remodelling as a constant bone renewal or turnover without changes in the size and shape of bone. In PD, changes in this process give rise to the four phases of the disease observed radiologically: the osteolytic, mixed and osteoblastic phases, and the inactive osteosclerotic phase characterised by normal or decreased activity as seen on bone scanning. The process of modelling determines the shape and geometry of the bone and in PD may lead to expansion or contraction by centrifugal or centripetal drift of cortical bone. Bone expansion with a wide cortex is due to apposition of bone on the periosteal and endosteal envelopes. An increase in the external diameter with a thin cortex is caused by periosteal apposition with concomitant absorption in the endosteal envelope, leading to enlargement of the marrow cavity. Bone contraction, or centripetal cortical bone drift, is produced by apposition on the endosteal and absorption on the periosteal surface (Figs 1 and 2).

Complications include pathological fractures, delayed union, progressive skeletal deformities, chronic bone pain, neurological compromise of the peripheral and central nervous systems with facial or ocular nerve compression and spinal stenosis etc, Pagetic arthritis, malignant transformation, loss of hearing, Peyronie’s disease and high-output heart failure.

Pathological fractures

Pathological fractures are a frequent complication and may be the presenting feature, with a reported incidence of between 10% and 30%. Fractures of the long bones occur in all phases of remodelling, but are more common in the mixed and osteoblastic stages. Those in the osteolytic phase usually occur at the junction of normal bone density and the radiolucent front. Union tends to be delayed in the osteoblastic and sclerotic phases, whereas fractures in the osteolytic stage usually heal in the expected time. The incidence of nonunion also increases in patients being treated with disodium etidronate which should not be used in the presence of fractures.

Predisposing factors to complete fractures are partial stress fractures, stress rises at bone-plate interfaces and prolonged therapy with etidronate. Partial or incomplete stress fractures arise mostly on the tension side of long bones where they partially involve the cortex, either from the endosteal or the periosteal surface, and occur mostly in the blastic and sclerotic phases. Circumstantial evidence suggests that sclerotic bone is brittle and therefore may predispose to fracture.

Pain and local tenderness at the site of a partial stress fracture suggest impending progression to a complete lesion. Treatment then depends on the stage of remodelling. In the mixed phase, walking on crutches with or without bracing may suffice. In the osteoblastic or sclerotic phases, especially with associated deformity, prophylactic realignment osteotomy and intramedullary stabilisation are the appropriate treatment which avoid stress rises associated with fixation by a plate. The mean time for union of femoral fractures treated by an intramedullary nail is approximately 32 weeks.

Fractures which occur in the presence of pronounced bony deformity are best treated surgically, allowing correction of the malformation, a major factor contributing to fracture, and improvement of the alignment of the adjacent joint. Patients treated by electrical stimulation and bone grafting usually show exuberant formation of callus and therefore this procedure is recommended for fractures occurring in the blastic or sclerotic phase.

Rheumatic and arthritic conditions

Forestier’s disease, or disseminated idiopathic hyperostosis (DISH), may affect patients with PD, and should not be confused with focal Pagetic bone formation. The incidence of DISH in PD has been reported to range from 14%...
to 30%. Pagetic tissue may invade the hyperostotic lesions produced by DISH and transform them into Pagetic exostoses which may then progress to vertebral ankylosis. Other rheumatic and arthritic conditions such as psoriatic or ankylosing spondylitis may coexist and be responsible for the clinical presentation. PD has also been noted to be associated with an increased incidence of gout and pseudogout. Treatment with sodium etidronate may be responsible for the accumulation of crystals of pyrophosphate in the synovial joint, producing pseudogout.

Osteoarthritic change in PD has been considered to be either a non-specific arthropathy, a coincidental finding, or a specific entity. Several distinct pathological processes contribute to the degeneration and destruction of articular cartilage. Erosion of the subchondral bone may lead to collapse of the articular cartilage which can also be eroded by accelerated endochondral ossification of the subchondral bone or by the invasion of aggressive Pagetic change. Bone expansion and bone deformity may also produce incongruity of the articular cartilage, contributing to arthritic change.

Pain which originates in an arthritic Paget joint may be attributed to the occurrence of microfractures or to increased vascularity of the bone. Normalisation of blood flow in the bone with anti-Pagetic therapy may influence pain relief. Such treatment may also produce improvement in the appearance of bone scans and in the level of activity markers of bone remodelling, but if pain persists, conservative therapy has then failed.

In the presence of bone deformity with joint malalignment, and a relatively good preservation of the articular cartilage, osteotomy can correct the deformity and restore joint mechanics. The osteotomy can be stabilised successfully by either intramedullary nailing or Ilizarov external fixation. Total joint arthroplasty is indicated for patients with advanced destruction of cartilage.

When osteoarthritis of the hip is associated with varus deformity of the femur, this can be managed by single or multiple osteotomies, followed by implantation of a long-stemmed, fully-coated, porous ingrowth hip system. Another option is to use a two-stage procedure in which the varus deformity is first treated by a conventional osteotomy and fixation with an intramedullary nail followed by removal of the nail and a total joint replacement.

The survivorship to revision for total hip arthroplasty has been reported to be 98% at ten years and 91% at 15 years for the acetabular component, and 93% at ten years and 89% at 15 years for the femoral stem. The only increased risks identified were nonunion of the trochanteric osteotomy (13%) and the occurrence of heterotopic ossification in 29% of cases. The results for cemented arthroplasty appear to have been slightly worse than those for uncemented components but the long-term results for the latter remain to be established. Patients with a sclerotic acetabulum may be at risk of perioperative fracture when an underreaming technique is used.

Malignant transformation

This is relatively rare, occurring in about 0.7% to 0.9% of patients with PD, although a higher incidence of between

**Radiographs**

a) of the distal forearm showing contraction of the ulna produced by endosteal apposition and periosteal absorption, b) of the femur demonstrating a thick cortex as a result of endosteal and periosteal apposition and c) of the proximal forearm showing a localised bone expansion with a thin cortex of the radius as a result of endosteal absorption and periosteal apposition. The ulna shows a drift by the same modelling defect.
5% and 5.5% has been reported.33,60 Since the condition was first noted by Sir John Paget in 1889,61 numerous reviews have described malignant transformation and defined its clinical and radiological presentation.62-68

The tumours noted to arise from Pagetic bone have been, in decreasing order of frequency, osteosarcoma (22% to 90%),58,59,64,65,68,69 fibrous histiocytoma (7% to 26%),58,63,69 fibrosarcoma (3% to 25%),59,62,64,66,69 chondrosarcoma (1% to 5%),62-64 giant-cell sarcoma (3% to 10%),62,66 unspecified malignant neoplasm (9%),66 lymphosarcoma (12%),58 and rarely haemangiosarcoma and lymphoma.71 Pagetic sarcomatous transformation constitutes between 3.3% and 14% of all osteogenic sarcomata of bone.63,72

An acute onset of pain or an increase in the intensity of chronic pain is usually the presenting complaint.62,67,71 Confusion as to the radiological appearance of the primary Pagetic lesion and malignant transformation may overlap, leading to a delay in diagnosis.73,74 Swelling or associated soft-tissue masses are present in 48% to 75% of cases58,62 but swelling in Paget’s disease is not always due to malignant transformation. Benign focal modelling lesions can result in a localised periosteal expansion, a so-called ‘pum-ice-stone’ appearance.27 This lesion is characterised radiographically by a smooth uninterrupted margin. In contradistinction, the margins of a localised sarcomatous lesion are irregular and interrupted. Similar juxtacortical soft-tissue formation called ‘pseudosarcoma’ may mimic a juxtacortical sarcoma.75

CT67 and MRI can delineate the cortical penetration and associated soft-tissue mass invariably seen with a sarcomatous lesion. Biopsy is necessary to establish a definite diagnosis. The differential radiological appearance of malignant transformation must be distinguished from pseudosarcomatous osteolysis secondary to medication,76 cystic degeneration of Pagetic lesions causing pseudoneoplastic lesions with central necrosis,74 and active PD with variable abnormalities of remodelling.27,62

Some reviews have identified the pelvis as the most common site of sarcomatous transformation,63,65,69 whereas others58,67 have found an equal incidence in the humerus, femur and skull. Most lesions in the appendicular skeleton are found in the metaphyseal-diaphyseal region.58,62 There is no consensus in the literature regarding the most common phase of remodelling at which sarcomatous transformation occurs, but a high frequency of osteolysis has been described at the site of the sarcoma.58,62-65,67

Pathological fractures may present as the initial clinical manifestation with a reported incidence ranging from 10% to 50%.58,62,64-68 Sarcomatous transformation of Pagetic bone at the site of a previous fracture has been observed58,64-67 and fractures have even been implicated as a possible causative factor.65-67

The prognosis for sarcomatous transformation in PD is dismal. In spite of regimes of management incorporating amputation, chemotherapy, and radiation, the five-year survival rates range from 0% to 15% (0%,58,65 2%,64 5%,62,63 8%,59,68 15%72,77), but in most series reported most patients have died from their malignant neoplasms within a few months.69 The poorer outcome of these patients compared with those with de novo sarcomatous lesions has been attributed to the increasing vascularity of the Pagetic bone allowing unimpeded haematogenous spread of the tumour,59 especially in older patients who may have less resistance to malignant neoplasm. Lymphoma-lymphosarcoma associated with PD has a better prognosis.58,66,71,78

Giant-cell tumours complicating PD have a very good prognosis and have been described as responding very well to steroid therapy.79

**Spinal involvement**

The spine is the second most commonly affected site in PD.24,34 predisposing patients to low back pain and spinal stenosis.80,81 Hartman and Dohn82 have shown that 15.2% of patients with PD had involvement of the vertebrae, and 26% of these patients had symptoms of spinal stenosis. The reported incidence of back pain in PD ranges from 11%28 to 34%34 and 43%.83 The causal relationship between vertebral PD and back pain has been disputed because of the high incidence of coexisting osteoarthritis.34,84 In one study,39 of 33% of patients who demonstrated Pagetic involvement of the spine, 30% had clinical symptoms of

![Diagram showing bone modelling of the vertebra](https://example.com/diagram.png)
Spinal stenosis. About one-third of patients with spinal involvement have symptoms of clinical spinal stenosis. Involvement of the cervical and thoracic spine may predispose to myelopathy. Different factors have been implicated in producing dysfunction of the neural elements. The most common is neurocompression by overgrowth of bone due to abnormal modelling (Figs 3 and 4). This Pagetic spinal stenosis is characterised by exuberant bone formation and is reminiscent of exaggerated degenerative spondylotic disease. However, severe spinal stenosis may remain asymptomatic, suggesting adaptability of the thecal sac and its neural elements without significant loss of function. Other distinct factors contributing to neural dysfunction are ischaemia produced by blood diversion, causing the so-called 'arterial steal phenomenon', or neurocompression by Pagetic intraspinal soft tissue or ossification of the epidural fat similar to ankylosing spondylitis and interference with the blood supply to the cord due to arterial compression by the expanding bone or other factors. Platybasia or cranial settling (basilar invagination) may cause either impingement of the medulla or the formation of syringomyelia. Rarely, neurocompression can be produced by an epidural haematoma from spontaneous bleeding or Pagetic sarcomatous degeneration. Spinal pain. Pagetic facet arthropathy is a major contributing factor to both back pain and spinal stenosis, and the more advanced the arthropathy, the greater is the likelihood that patients will suffer clinical spinal stenosis and/or back pain. However, severe facet arthropathy may remain asymptomatic. Back pain may also be attributed to engorgement of the vertebral body caused by vascular processes and by disorganised hyperactive remodelling. Other factors implicated in spinal pain may include invasion of the vertebral disc space by the Pagetic process which results in vertebral ankylosis.

Treatment

Treatment of back pain. Care must be taken before attributing back pain to PD, otherwise the results of anti-Pagetic treatment may be disappointing. Suppressive therapy with disodium etidronate is beneficial in about one-third of cases in patients with back pain and PD of the spine. This suggests that unless a well-defined focus of PD is related to low back pain, anti-Pagetic therapy is not expected to be rewarding. If such therapy is ineffective within three months, a concomitant non-steroidal anti-inflammatory drug and other methods of treatment for back pain should be prescribed, especially when the pain is mechanical or arthritic in nature.

Treatment of spinal stenosis. Treatment of the symptoms of spinal stenosis in Paget's disease should begin with medical therapy. Calcitonin, mithramycin, sodium etidronate, pamidronate disodium, and clodronate have been reported to either improve or completely reverse the clinical symptoms, but subsequent relapse is not uncommon. Patients should be closely monitored and cyclical therapy should be continued if necessary until the biochemical bone indices are normal. If symptoms still persist operation should be considered.

Decompression of spinal stenosis should be implemented promptly after failure of anti-Pagetic therapy. Delay in decompression may result in irreversible myelopathy or radiculopathy. The results of surgery have shown variable improvement in 85% of patients with frequent relapses which may improve with subsequent medical treatment. Surgery may fail to reverse the neurological deficit completely and may be associated with serious complications such as dangerously profuse, if not massive, bleeding and a mortality rate of 11%. Preoperative assessment of bone vascularity by means of radionucleide studies of bone blood flow in the affected spinal region is a reliable, simple and reproducible test. In order to decrease potential bleeding during surgery, when there is an increased vascularity in the affected region, a course of medical treatment should be given until the blood flow in the bone is normal. This may take two to three
months with treatment with calcitonin or two to three weeks with mithramycin. The new generation of intravenous bisphosphonates can also be used effectively in this situation. In an emergency embolisation of the region may be indicated. Because of the expected torrential bleeding during laminectomy, the use of a cell saver is also suggested.

Surgery for spinal stenosis, when indicated, should be tailored to the abnormality responsible for neural compression. If this is caused by the posterior vertebral elements posterior decompression should be undertaken. If compression is caused by the posterior expansion of the vertebral body, especially when the cervical or thoracic spine is involved, an anterior approach with corpectomy and fusion should be carried out. An acute onset of spinal compression has a more grave prognosis than the gradual development of symptoms. Surgery is also indicated as a primary treatment when neural compression is secondary to pathological fracture, dislocation, epidural haematoma, syringomyelia, platybasia, or sarcomatous transformation.

Pharmacological treatment. The progressive nature of Paget’s disease, the severity of its associated complications, the potential negative impact on quality of life and the availability of effective and relatively safe new drugs have led many experts to recommend treatment for asymptomatic patients who have active disease. However, there is no conclusive evidence to suggest that complications can be prevented by controlling bone remodelling by drug therapy. Patients who are clinically asymptomatic, but show increased activity of the disease as indicated by abnormal biochemical markers, bone-scan activity or increased engorgement on radionucleide investigation, should be treated repeatedly until these indices return to normal values. Patients who are asymptomatic and inactive when assessed by biochemical investigation and imaging do not require treatment.

Five classes of drugs are available: bisphosphonates, calcitonin, mithramycin (plicamycin), gallium nitrate and ipriflavone. Some of these are still under development and can be obtained only for use in clinical trials. A major advantage of the bisphosphonates over calcitonin is that biochemical and histological suppression of the disease may persist for many years after the cessation of treatment.

Bisphosphonates. The mechanism of action of bisphosphonates on bone can be ascribed to their physicochemical effect on hydroxyapatite crystals and to their influence on bone cells, which is probably of greater importance. Interference with the growth of calcium phosphate crystals inhibits normal calcification. The bisphosphonates also inhibit bone resorption at the cellular level, and eventually bone formation also decreases, probably because of the coupling effect between formation and resorption. The mechanism of action appears to be complex, involving several functions including a direct effect on osteoclastic activity, a direct effect on recruitment of osteoclasts, an indirect effect on the latter mediated by cells of osteoclastic lineage which are capable of stimulating or inhibiting osteoclastic recruitment and shortening of the life-span of osteoclasts because of apoptosis.

Bisphosphonates can be grouped into two pharmacological classes with distinct molecular mechanisms of action. Nitrogen-containing bisphosphonates are the most potent and act by inhibiting the mevalonate pathway in osteoclasts, thereby preventing prenylation of small GTPase-signalling proteins required for osteoclast function. Bisphosphonates which lack nitrogen in their chemical structure do not inhibit prenylation of protein and have a different mode of action which may involve the formation of cytotoxic metabolites in osteoclasts or the inhibition of protein tyrosine phosphatase.

Other cellular effects of bisphosphonates have been described such as an increase in the production of alkaline phosphatase, an increase or decrease in the synthesis of proteoglycans, inhibition of the synthesis of prostaglandins which are powerful bone-resorbers and a decrease in the production of lactic acid, which plays an important role in crystal dissolution. They can also directly induce apoptosis and disruption of actin rings in osteoclasts. In general, these effects are not uniform but vary from bisphosphonate to bisphosphonate.

The quality of the newly-formed bone is lamellar in appearance without significant defects in mineralisation. Giving large amounts of bisphosphonates such as disodium etidronate, however, can inhibit mineralisation by a physiological inhibition of crystal growth and result in osteomalacia.

Bisphosphonates appear to be more effective than calcitonin in suppressing the histological and biochemical activity in Paget’s disease. Calcitonin is no longer considered to be the treatment of choice for this condition. Several bisphosphonates have been investigated, but only those shown in Table I have been approved for clinical use. Other anti-Pagetic drugs are shown in Table II.

Methods for clinical assessment and monitoring of anti-Pagetic drug treatment

 Imaging. The effects of treatment are monitored by the clinical response, imaging modalities and bone-remodelling markers.

Determination of radionucleide blood flow can be used to assess a relevant Pagetic region for potential profuse bleeding before proceeding with surgery, and to monitor the effectiveness of emergency intravenous administration of anti-Pagetic agents. A conventional bone scan is recommended before and six months after treatment, and every 12 months thereafter depending on the behaviour of the Pagetic lesion. A 24-hour retention scan, a more quantitative radionucleide assessment, can be used as an adjunct to a bone scan. Quantitative scintigraphy allows early and objective assessment of PD when evaluating the effects of treatment.

Radiographs should be obtained before treatment and every one to two years thereafter to monitor changes in
modelling and remodelling. MRI is suitable for demonstrating specific characteristics of certain complications, including basilar invagination, spinal stenosis and secondary neoplasms.

**Biochemical bone markers.** Recently, the assessment and effectiveness of treatment of patients with Paget's disease have been greatly enhanced by evaluating biochemical markers for bone remodelling.

Common markers in the serum used for the evaluation of bone turnover in PD are the total alkaline phosphatase (tAP), bone alkaline phosphatase (BAP), tartrated-resistant acid phosphatase, procollagen type-I N-terminal propeptide (PINP), β-carboxyterminal telopeptide of type-I collagen (SCTX), osteocalcin and serum bone sialoprotein.

Biochemical markers for clinical assessment in the urine are hydroxyproline (Hyp), amino (NTX) and β-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 deoxypyridinoline. The urinary calcium is an indicator of bone resorption. The serum tartrated-resistant acid phosphatase is a marker for osteoclastic activity. Markers of bone formation include bone-specific alkaline phosphatase and N-terminal and C-terminal extension peptides of procollagen. Osteocalcin, produced by osteoblasts or released during degradation of bone matrix by osteoclasts, may

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Administration*</th>
<th>Side-effects</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Bisphosphonates approved for clinical use</td>
<td></td>
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<tr>
<td>Disodium etidronate (EHDP)</td>
<td>5 mg/kg per day for 6 months, or 10 mg/kg per day for 3 months, or 20 mg/kg per day for 1 month. Repeat every 6 months until normalization of bone-remodelling markers</td>
<td>PO, IV also available</td>
<td>Osteomalacia, pathological fractures</td>
<td>May become ineffective after 6 months of treatment</td>
</tr>
<tr>
<td>Chlordronate (Cl2MBP)</td>
<td>800 to 1600 mg per day for 6 months, 300 mg daily for 5 consecutive days</td>
<td>PO, IV</td>
<td>Association with leukaemia observed</td>
<td>Very potent bisphosphonate without mineralisation defect</td>
</tr>
<tr>
<td>Pamidronate (ADP)</td>
<td>1200 mg per day for 5 consecutive days, 15 to 25 mg daily for 5 to 7 days or 60 mg in 0.9 saline over 2 hours, oral 180 mg per day course over 3 days</td>
<td>PO, IV, IV</td>
<td>Transient febrile reactions with myalgias, transient hypocalcaemia, neutropenia, and lymphopenia, mild thrombophlebitis, uveitis, scleritis. Appendicular bone loss (secondary hyperparathyroidism) close monitoring is required for prolonged remission</td>
<td>For severe forms of PD, or refractory to other medications. Effective in healing lytic lesions. Further studies are needed to determine optimal dose, the length of treatment and whether oral and IV therapies when combined, would allow for prolonged remission</td>
</tr>
<tr>
<td>Alendronate (Aminobisphosphonate)</td>
<td>40 mg per day for 3 to 6 months, 10 mg daily for 5 days</td>
<td>PO, IV</td>
<td>Gastrointestinal (25%, oesophagitis, oesophageal ulcer or erosions)</td>
<td>Potent aminobisphosphonate. Effective in healing lytic lesions. Does not impair mineralisation</td>
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<tr>
<td>Risedronate (Pyridinylbisphosphonate)</td>
<td>30 mg per day for 2 to 3 months or less</td>
<td>PO</td>
<td>Gastrointestinal</td>
<td>Highly effective in osteolytic lesion after 6 months of treatment</td>
</tr>
<tr>
<td>Neridronate (Aminohexane biphosphonate) (AHBP)</td>
<td>400 mg per day for 1 to 3 months, 15 to 20 mg daily for 5 days or 200 mg in a single dose</td>
<td>PO, IV, IV</td>
<td>Not significant</td>
<td>Long-lasting remission, successful when other bisphosphonates fails</td>
</tr>
<tr>
<td>Ibadronate (Aminohydroxybutylidene bisphosphonate) (ABDP)</td>
<td>2 mg per day</td>
<td>IV</td>
<td>Fever, hypocalcaemia, hypophosphataemia, gastrointestinal intolerance, flu-like symptoms</td>
<td>Long suppression, rapid action, no significant side-effects</td>
</tr>
<tr>
<td>Tiludronate (Chloro-4-phenylthiothiophosphonate)</td>
<td>200 to 400 mg per day for 6 months</td>
<td>PO</td>
<td>Hypophosphataemia, gastrointestinal intolerance, flu-like symptoms</td>
<td>Very potent third-generation bisphosphonate with rapid action</td>
</tr>
<tr>
<td>Aminohydroxybutylidene bisphosphonate (ABDP)</td>
<td>5 mg per day for 4 to 5 days</td>
<td>IV</td>
<td>Fever, neutropenia, lymphopenia</td>
<td>New bisphosphonate with profound inhibition of bone resorption</td>
</tr>
<tr>
<td>Olgapronate (3-Dimethylamino-1-dydroxypropylidene bisphosphonate)</td>
<td>200 mg per day for 12 days</td>
<td>PO</td>
<td>One of the latest bisphosphonates. Potency is similar to alendronate, but more soluble in the digestive system</td>
<td></td>
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<tr>
<td>Zoledronate (Dimethylamino-1 -dhydroxypropylidene bisphosphonate)</td>
<td>400 mcg (single dose), 200 mg/day for 10 days</td>
<td>IV, PO</td>
<td>New, very potent and promising bisphosphonate but merits further study to determine optimal dose and safety. Long-lasting effect</td>
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* PO, orally; IV, intravenous
indicate either formation when resorption and formation are coupled or turnover when they are uncoupled. Therefore this is not a practical bone marker.

Markers of bone resorption respond approximately one to three months after treatment begins, whereas those of bone formation respond much later, usually at six to nine months. The serum markers of bone turnover show lower biological variability than urinary markers and are therefore more sensitive indices of the activity of the disease. Bone alkaline phosphatase and PINP seem to reflect Pagetic activity best. The total alkaline phosphatase can also be considered to be a sensitive and inexpensive marker for therapeutic monitoring of Paget's disease. However, more specific markers may improve the usefulness of the biochemical assessment in certain situations. Urinary N-telopeptide (NTX) has emerged as a sensitive marker for bone resorption in the management of Pagetic patients. Serum levels of pyridinium cross-links correlate well with its urinary excretion (a sensitive index of bone resorption), in patients with PD. Therefore the determination of serum levels of pyridinium cross-links avoids the usual problems related to the collection of urinary specimens. Urinary excretion of β-isomers of type-I collagen (CTX) reflects lamellar bone turnover which is impaired in PD, whereas α-CTX is an index of the woven bone structure present in active PD. An abnormal α/β-CTX ratio, which becomes normal after therapy, probably indicates the formation of lamellar structures in the newly-formed bone.

Patients should be followed by measuring bone markers every three to six months depending on the activity of the Pagetic lesions and the drug used. Treatment should be recommended when remodelling indices rise above the upper limits of normal or by 25% above the previous lowest point.

Other texts. The haematological profile, the level of serum electrolytes, and tests of kidney and liver function are helpful in assessing the side-effect of the drugs, or the overall medical condition in elderly patients. They may help to detect potential side-effects especially when drugs such as mithramycin or the latest generation of bisphosphonates are being given.

References


