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Paget's Disease of the spine and its management

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Abstract A review of the literature was conducted to study the pathomechanics by which Paget's Disease of bone (PD) alters the spinal structures that result in distinct spinal pathologic entities such as pagetic spinal arthritis, spinal stenosis, and other pathologies, and to assess the best treatment options and available drugs. The spine is the second most commonly affected site with PD.

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. 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. Since, in the majority of cases with pagetic spinal involvement, there are also coexisting osteoarthritic changes, anti-pagetic medical treatment alone may be disappointing. Therefore, one must be careful before attributing low back pain to PD alone. Five classes of drugs are available for the treatment of PD: bisphosphonates, calcitonins, mithramycin (plicamycin), gallium nitrate, and ipriflavone. Bisphosphonates are the most popular, and several forms have been investigated, but only the following forms have been approved for clinical use: disodium etidronate, clodronate, aledronate, risedronate, neridronate, pamidronate, tiludronate, ibadronate, aminohydroxylbutylidene bisphosphonate, olpadronate, and zoledronate. Several of these forms are still under investigation.

Keywords Paget's Disease · Back pain · Spinal stenosis · Myelopathy · Complications · Medical treatment · Surgery · Review

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Introduction

Previous studies have shown that the spine is the second most common site of involvement by Paget's disease of the bone [4, 33]. This peculiar metabolic disorder of bone triggers abnormal bone remodeling and modeling processes that can predispose the spine to stenosis and facet joint arthritic changes.

This study has three main objectives: a; to review in perspective the mechanism of structural changes that occur in the spine when it is affected by pagetic disease, b; to propose a unified theory of the different dynamic patterns of Paget's disease to the spine, and finally c; to suggest, on evidence based medicine, the best available treatment options.

Etiology

Paget's Disease of bone (PD) is a mono-ostotic or polyostotic nonhormonal osteometabolic disorder. Over a century after the original disease was described by Sir John Paget [117] in 1877, and despite recent intensive studies and widespread interest, its etiology still remains obscure.

The proclivity to sarcomatous transformation, the variability of osteoblasts (size, shape, and staining), the peculiarity of osteoclasts (size and number of nuclei, up to 100, seen also in giant-cell tumors), and control of the disease by antimitotic agents such as plicamycin (also known as mithramycin) suggest that the disease may be a benign neoplasm of the mesenchymal osteoprogenitor cell, as was hypothesized by Rasmussen and Bordier in 1973 [125].

It has been postulated that the disease may be caused by a viral infection [15, 71, 149]. Electron microscopy of osteoclasts reveals viral intranuclear inclusion structures resembling those of an RNA-type virus related to measles or subacute sclerosing panencephalitis. Immunologic studies show the presence of specific viral antigens in osteoclasts and cells grown from Paget's bone [107]. There is considerable evidence in support of a viral etiology for PD [102]. A characteristic feature of paramyxoviruses is their ability to persist at very low levels and invade the host immune system. Factors that can be activated by virally induced ROS (e.g., IL-6, C-fos and Bcl-2) are all elevated in PD, strongly suggesting viral infection.

Some reports have indicated that PD is a zoonosis, because it is associated with ownership of birds, dogs, cats, or cattle [85, 95]. These studies have suggested that canine distemper, a paramyxovirus closely related to measles, can contaminate human osteoclast cells, contributing to the development of PD [79, 116]. However, other studies [133, 152] found no risk factors associated with animals. In addition, it should be noted that all of the claims mentioned above are only supported by circumstantial evidence garnered from electron microscopic, immunologic, and epidemiologic studies.

Prevalence, distribution, and genetic factors

PD is found more commonly in populations of Anglo Saxon origin. PD is rarely encountered in China, Japan, Iran, India, Scandinavia, Africa, or the Middle East [13]; however, Singer [150] mentioned that 10% of the patients in the Los Angeles area are of African descent. A survey of PD in Johannesburg, South Africa, revealed a prevalence of 1.3% among the black population and 2.4% among the white population [62]. These findings suggest that PD may not be as uncommon in Africans as was previously believed. Autopsy reports indicated that the overall prevalence of PD is 3–3.7% [30, 144], with a tendency to increase with age. At the age of 90, the expected prevalence is about 10% [144]. Radiographic studies revealed a prevalence of 3.5% [96, 122]. A very recent report on radiographic examination of the pelvis [7] revealed an estimated overall prevalence in the United States of 1–2%, with near equal distribution between whites and blacks and between sexes.

Genetic factors play a role in the pathogenesis of PD, which is inherited as an autosomal dominant trait with high penetrance [75, 78]. PD often occurs in more than one member of a family [153]. A positive family history in siblings of patients was reported in 12.3% of cases as compared to 2.1% of controls. The prevalence of PD was approximately seven times higher in relatives of cases than controls.

Studies in families with PD have shown linkage to a region of chromosome 18q near the polymorphic locus D 18S42, most likely due to gene mutation [29, 75, 90]. Genetic heterogeneity is almost certainly present [75, 111]; data from some families with PD suggest the presence of at least one additional locus, which remains to be identified [75]. Viral infection may also help explain the genetic predisposition, by gene mutation, of PD [91, 102]. Circumstantial evidence thus supports the plausible hypothesis that viral infection may trigger the onset of PD as well stimulating inheritable gene mutation. Future research hopefully will cast light on these issues.

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 – the hallmark of pagetic lesion. The pagetic cellularity consists of variable sizes of osteoblasts and large osteoclasts with multiple nuclei (up to 100) [125]. Bone marrow fibrosis is not associated with anemia, because bone marrow hemopoietic activity can expand to the appendicular skeleton [33]. Uncommonly, extramedullary hemopoiesis occurs in the thoracic cavity [132]. These phenomena compensate for the extensive bone marrow fibrosis.

Prevalence of back pain and spinal stenosis

The spine is the second most commonly affected site in PD [4, 33, 82, 105], predisposing patients to low back pain and spinal stenosis [6, 72, 76, 170]. Hartman and Dohn [74] 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% [49] to 34% [4], and 43% [137]. The causal relationship between vertebral PD and back pain has been disputed by Altman et al. [7], who attributes the low back pain in PD to coexisting osteoarthritis of the spine in 88% of patients and to PD alone in only 12%. Others [63] consider PD to cause back pain even more rarely. However, in our population [66], 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 [66] (24% attributed clearly to PD alone, 50% to degenerative changes, and 26% to a combination of PD and degenerative changes).

Pathomechanics of facet joint arthropathy, spinal stenosis, and pain

PD can be defined as an abnormal disturbance of bone remodeling, which in turn leads to abnormal modeling. Frost [51] has defined remodeling as a constant bone re-

Fig. 1 Diagram of cross-sections of a long bone to demonstrate possible patterns of modeling in the periosteal and endosteal envelopes. The arrowheads show the direction of cortical drift due to bone apposition or absorption. Patterns A, B, and C all represent bone expansion: A shows apposition within the periosteal envelope, with the endosteum unchanged; B shows apposition within the periosteal envelope and absorption in the endosteal envelope resulting in a thin cortex; C shows apposition in both periosteal and endosteal envelopes, resulting in a thin cortex. D represents bone contraction; periosteal absorption with endosteal apposition causes a centripetal cortical drift. (Reprinted from Lander and Hadjipavlou [81], with permission)

newal or turnover without changes in the size and shape of bone. Disturbance of the bone remodeling process, as seen in PD, changes the bone texture and gives rise to the four phases of the disease observed radiologically: the osteolytic, mixed, and osteoblastic phases, and the inactive osteosclerotic phase, characterized by normal or decreased bone scan activity [89]. Bone modeling is a process that determines the shape and geometry of the bone [60] (Fig. 1). In PD, disturbed modeling contributes to bone expansion that leads to spinal stenosis [90] (Fig. 2).

More specifically, pagetic spinal stenosis can be caused by posterior expansion of the vertebral body alone (least common) (Fig. 3), by the expansion of the neural arch and the overgrowth of the facet joints, or by a combination of these [66, 162, 170] (Fig. 4).

Facet arthropathy can be produced by abnormal pagetic remodeling and modeling changes, causing the joint to become hypertrophic and incongruous, with destruction of articular cartilage, as may occur in other pagetic joints [64, 103].

Spinal stenosis

About one-third of patients with spinal involvement exhibited symptoms of clinical spinal stenosis [66]. Clinical spinal stenosis can be characterized as lateral or central stenosis. Lateral spinal stenosis manifests itself as constant or intermittent leg pain of variable intensity with specific radicular distribution associated with paraesthesias. This pain is exacerbated by walking, may improve with rest, and may be associated with motor weakness, reflex, and sensory changes. Central stenosis, on the other hand, is characterized by bizarre symptomatology, especially leg weakness and cramps with variable amounts of pain that is provoked by walking and improves with rest. Objective clinical signs are usually absent. A combination of central and lateral stenosis may also be present. Central stenosis with myelopathy is associated with upper motor neuron manifestations.

Fig. 2 Bone modeling of vertebra depicted diagrammatically to demonstrate tendency of bone expansion in all directions, leading to hypertrophic facet osteoarthropathy and spinal stenosis. (Reprinted from Hadjipavlou and Lander [67], with permission)

Fig. 3 T1-weighted magnetic resonance image showing posterior expansion of the vertebral body

Fig. 4 Axial computed tomography scan of the third lumbar vertebra, demonstrating circumferential expansion of a mixed-phase lesion of Paget's Disease causing severe spinal stenosis

Several authors have mentioned that neural involvement is more commonly associated with PD of the thoracic spine [74, 87, 145] or the cervical spine [101], rather than the lumbar spine. This is attributed to the large size of the spinal cord in the thoracic and cervical regions relative to the capacity of the vertebral canal; therefore, the

same proliferation of bone in all vertebrae would result in compression of the cervical and thoracic thecal sacs sooner than it would in the lumbar spine [145]. Involvement of the cervical and thoracic spine tends very often to predispose to clinical spinal stenosis with myelopathy [66]. Ten distinct mechanisms have been implicated as producing neural element dysfunction in the spines of patients affected by PD:

1. Compression of the neural elements by pagetic bone overgrowth [37, 66, 87]
2. Compression by pagetic intraspinal soft tissue [66, 72]
3. Ossification of the epidural fat similar to ankylosing spondylitis [28]
4. Neural ischemia produced by blood diversion, causing the so-called "arterial steal phenomenon" [26, 74, 76, 121]
5. Interference with blood supply to the cord due to arterial compression by the expanding pagetic bone [145] or other factors not well defined [99]
6. Vertebral fracture or atlantoaxial subluxation [145, 167]
7. Platybasia with impingement on the medulla [32]
8. Spinal cord compression by epidural hematoma from spontaneous bleeding [92, 132, 134]
9. Formation of syringomyelia as a complication of PD of the spine, especially after cranial settling (basilar invagination) [43, 59], and
10. Rarely, neurocompression can be caused by pagetic sarcomatous degeneration [81, 143]

Bone compression by the expanding pagetic vertebrae is by far the most common cause of neural dysfunction [66]; it was first reported by Wyllie in 1923 [169]. 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 [145].

The mechanism of neural ischemia is, however, still theoretical 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 [32]; some patients experience progressive deterioration of neural function without evidence of myelographic block, which is not easily explained by mechanical effect alone [142]; 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 encroachment on the neural element [40, 68, 76, 83, 121, 162, 169], such as deprivation of blood supply to the neural elements by the rapidly remodeling hypervascular pagetic bone producing "arterial steal phenomenon."

Spinal pain (back and neck pain)

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 [66]. However, this does not necessarily preclude the possibility that, though present, severe facet arthropathy may become asymptomatic [66]. Back pain in PD may also be attributed to blood engorgement of the vertebral body caused by vascular and disorganized, hyperactive remodeling processes [90]. Other factors implicated in spinal pain may include invasion of the vertebral disc space by the pagetic process [90], and spinal stenosis [170]. We hypothesize that microfractures of the pagetic vertebral bodies, especially in the osteolytic or mixed phase, can also lead to back pain [66].

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% [73] of cases. In our series of PD patients [67, 73], we have not seen any cases with sarcomatous degeneration in the spine. In Schajowicz and co-workers' series [143], of 62 patients with sarcomatous transformation, five malignancies occurred in the spine. These observations suggest that the incidence of malignant transformation in the spine is even more rare, and represents 7% of all sarcomatous degeneration in PD [143]. The association between PD and osteosarcoma seems to be the result of a single gene or two tightly linked genes on chromosome 18q [29, 112]. A more recent study reported that both pagetic and sporadic osteosarcoma tumors showed loss of constitutional heterozygosity (LoH) for all or part of the distal portion of chromosome 18q. Clinical presentation of Paget's sarcomatous transformation is characterized by severe and persistent pain with rapid deterioration and eventual neurocompression and death [81]. Surgical decompression offers little, if any, true relief of pain, with the longest survival reported at just over 5 months [81]. Less common is the appearance of "pseudosarcoma" or "pumice bone", which is a localized extracortical periosteal bone expansion or a bulky juxtacortical soft tissue mass giving the appearance of sarcomatous transformation [75, 88] (Fig. 5).

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

Fig. 5 Anteroposterior radiograph of the lumbar spine showing a localized bulky juxtacortical bone expansion of the lateral aspect of L4-L5 vertebrae and resulting in bone union. The appearance of the lesion can 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

extraosseous bone formation [23]. The incidence of DISH in PD was reported to range from 14% [69] to 30% [6]. Pagetic tissue may invade the hyperostotic lesions produced by DISH and transform them into pagetic exostoses [66], which may progress to vertebral ankylosis [98]. Other rheumatic and arthritic conditions such as psoriatic or ankylosing spondylitis may coexist and may be responsible for the clinical presentation [4, 49]. PD has also been noted to be associated with an increased incidence of gout [49] and pseudogout [123]. These conditions, however, are not clearly implicated in the production of back pain [66]. 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 [55].

Treatment

Treatment of back pain

One must be careful before attributing back pain to PD, otherwise the results of antipagetic treatment may be dis-

appointing [5]. For patients with low back pain and PD, suppressive therapy with EHDP (disodium etidronate) was beneficial to 36% of patients in one report [6]. This suggests that unless a well-defined lesion is related to low back pain, antipagetic therapy is not expected to be beneficial. If antipagetic medical therapy is ineffective within 3 months, a concomitant nonsteroidal anti-inflammatory drug and other treatment methods for back pain should be prescribed, especially when the presenting back pain is mechanical or arthritic in nature [70, 156].

Treatment of spinal stenosis

Treatment of pagetic spinal stenosis symptoms should start with medical antipagetic therapy. Calcitonin, mithramycin, sodium etidronate, pamidronate disodium, and clodronate have been reported to either improve or to completely reverse the clinical symptoms of spinal stenosis [3, 26, 44, 126, 164]; however, relapse of spinal stenosis symptomatology after medical antipagetic treatment is not uncommon [40, 41]. Therefore, patients should be closely monitored and cyclical therapy should be continued if necessary until biochemical bone indices normalize. Antipagetic medical therapy is rewarding when treating pagetic spinal stenosis syndrome. Severe spinal stenosis of lytic type has been shown to respond successfully to antipagetic treatment with clodronate [44]. 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 the pagetic spinal canal block can enhance the effectiveness of bisphosphonate therapy [44]. 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 [90]. If the symptoms persist, in spite of the normalization of bone remodeling markers, surgery is an alternative treatment. On the other hand, the results of surgery have shown variable improvement in 85% of patients [142], with frequent relapses or failures, some improving with subsequent medical antipagetic therapy [3, 26, 126]. In our series [70], 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. From our experience and from other reports, spinal surgery for pagetic spinal stenosis may fail to reverse the neurological deficit completely [23] and may be associated with serious complications such as a mortality rate of 11% [142] and dangerously profuse, if not massive, bleeding [141]. Therefore, we advocate 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 [19]. In order to decrease potential bleeding during surgery

[70], if there is increased vascularity in the affected region, we strongly recommend a course of medical antipagetic treatment until the bone blood flow normalizes. In our experience, this may take 2–3 months with calcitonin therapy, or 2–3 weeks with mithramycin treatment [140]. 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 expected torrential bleeding during laminectomy, the use of a cell saver is strongly recommended [140].

Surgery for spinal stenosis, when indicated should be tailored to the pathology responsible for neural compression. 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 [70]. 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 [147]. 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 antipagetic drugs have led many experts to recommend treatment for asymptomatic patients who have active disease [70, 102, 160]. According to Meunier and Vignot [104], in a long-term follow-up study of 41 cases of PD, antipagetic therapy that did not normalize biochemical markers in 71% of patients did not prevent new complications in 62% of patients. However, there are no conclusive data to support the proposition that complications can be prevented by controlling bone remodeling with drug therapy [160]. 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 there is a normalization of these indices [104, 156].

Five classes of drugs are available for the treatment of PD: bisphosphonates, calcitonin, mithramycin (plicamycin), gallium nitrate, and ipriflavone. 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 histo-

logical suppression of disease activity may persist for many years after the cessation of treatment [127].

Bisphosphonates

Bisphosphonates are chemically stable analogs of inorganic pyrophosphate. These compounds are characterized by two carbon-phosphorus (P-C-P) bonds that, in the past, were erroneously called "disphosphonates" [47].

According to Fleisch [47], the mechanism of action of bisphosphonates on bone was originally ascribed to their physicochemical effect on hydroxyapatite crystals. This action consists of the inhibition of normal calcification by interfering with calcium phosphate crystal growth. 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 bisphosphonates inhibit bone resorption at a cellular level, and, after a certain time, bone formation decreases as well, probably because of the well-known coupling effect between bone formation and resorption. The mechanism of action appears to be complex [48], 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 grouped into two pharmacologic classes with distinct molecular mechanisms of action. Nitrogen-containing bisphosphonates are the most potent class and act by inhibiting the mevalonate pathway in osteoclasts, thereby preventing prenylation of small GTPase signaling proteins required for osteoclast function. Bisphosphonates that lack a nitrogen in their chemical structure do not inhibit protein prenylation and have a different mode of action that may involve the formation of cytotoxic metabolites in osteoclasts or the inhibition of protein tyrosine phosphatase [136].

Dichloromethylene bisphosphonate or clodronate (Cl_2MBP) and 1-hydroxymethylene-1,1-bisphosphoric acid (HEBP) inhibit prostaglandin synthesis in bone cells; prostaglandins are powerful bone resorbers. Numerous 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, and decrease in lactic acid production, which plays an important role in crystal dissolution. In addition to its direct inhibition of osteoclastic bone resorption, etidronate can directly induce apoptosis and disruption of actin rings in osteoclasts [77].

Intravenous administration of 4-amino-1-hydroxybutylidene-1,1-bisphosphonate (AHButBP), or 3-amino-1-hydroxypropylidene-1,1-bisphosphonate (AHPBP, APD), or 6-amino-1-hydroxyhexylidene-1,1-bisphosphonate (AHHexBP) induces an acute phase response (APR) which, irrespective of the underlying disease, manifests as a fall in the number of circulating lymphocytes and serum zinc concentrations, and a rise in C-reactive protein (CRP); febrile reaction occurs in 39% of patients [86]. This APR occurs within 28–30 h of intravenous administration of bisphosphonates and disappears 2–3 days later, despite continuous treatment. Bisphosphonates seem to interact with macrophage-like cells resident in the skeleton and stimulate interleukin-1 release, which is responsible for the appearance of APR. At the same time, these cells are rendered insensitive to further stimulation for several months [1].

The quality of newly formed bone is lamellar in appearance, without significant mineralization defects. Large amounts of bisphosphonates, however, can also inhibit mineralization through a physicochemical inhibition of crystal growth [48]. A sufficient dose of etidronate inhibits bone mineralization and may result in osteomalacia. Cl_2MBP displays relatively little inhibiting activity on bone mineralization.

From these reports, 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. Several bisphosphonates have been investigated, but only the following bisphosphonates have been approved for clinical use: disodium etidronate, clodronate, pamidronate, aledronate, risedronate, neridronate, tiludronate, ibadronate, aminohydroxybutylene bisphosphonate (ABDP), olpadronate, and zoledronate. Nitrogen-containing bisphosphonates are: risedronate, zoledronate, ibadronate, aledronate, and pamidronate. Non nitrogen-containing bisphosphonates are: clodronate, etidronate, and tiludronate.

Disodium etidronate (EHDP). The usual dose of disodium etidronate (EHDP) for PD is 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. Etidronate is effective in most patients. The drug should be taken on an empty stomach, at least 2 h before eating; dairy products should be avoided for 5–6 h to improve absorption.

Treatment with disodium etidronate should aim at reducing the serum levels of alkaline phosphatase by 40–50% at 3 months, with subsequent adjustment of dosage [45]; and it should be repeated cyclically every 6 months until normalization of bone remodeling markers is observed. If EHDP is ineffective after 6 months of treatment, or if it becomes resistant after a few treatments, other agents such as Cl_2MBP , APD, or calcitonin are recommended. Higher doses or more prolonged therapy may result in osteomalacia and pathologic fractures [60, 69,

151]. Combination treatment of 1 α -hydroxyvitamin D3 with disodium etidronate used to prevent the mineralization defect caused by the bisphosphonate was not successful in the treatment of PD [124].

Clodronate. Clodronate, or dichloromethylene bisphosphonate, is a very potent bisphosphonate. The recommended dose is 800–1600 mg per day orally for 6 months [35, 61], with a prolonged remission expected to last about 1–2 years after withdrawal of the drug [16, 25, 35]. The recommended IV dose that can substantially suppress disease activity is 300 mg daily for 5 consecutive days (1500 mg total) [84]. Clodronate action on the skeleton consists of the inhibition of bone resorption without mineralization defect [35, 131]. The inhibitory effect of bone resorption is mediated mainly through a cytotoxic effect on osteoclasts [131]. The clinical response seems to be better than that achieved with EHDP or calcitonin [35]. A study comparing oral clodronate (Cl₂MBP) 600 mg daily and etidronate 5–10 mg/kg per day for 6 months shows that the proportion of patients responding to etidronate was less than the clodronate group, which had a more sustained response [61].

Clodronate has also been shown to reverse progression of pagetic deformity [16]. Unfortunately, leukemia has been associated with treatment in three patients with clodronate treatment and this observation has halted its release for clinical practice except for clinical investigation [61].

Pamidronate. Pamidronate (3-amino-1-hydroxypropylidene-1,1 bisphosphonate, ADP) is available in intravenous and oral forms. Because of its profound effects on mineral and bone metabolism, close monitoring is required during intravenous treatment with ADP [42]. IV administration is given at a dose ranging from 15 to 25 mg for 5–7 consecutive days, a single dose of 60 mg in 0.9% saline infusion over 2 h [159, 163], or a dose of 180 mg per course, usually given over 3 days [163]. The suppression period of bone turnover after IV administration of this bisphosphonate has not been established with certainty. Estimates range from 2 to 12 months [38, 158, 159, 163]. The oral form given at a high dose of 1200 mg per day over 5 consecutive days induces a rapid decline of biochemical indices.

ADP is a very effective drug, usually given for severe forms of PD, or if the disease becomes refractory to other medications. Pamidronate binds with hydroxyapatite crystals in the bone matrix, inhibiting osteoclastic activity by preventing attachment of osteoclast precursor cells to bone. This drug has a prolonged biochemical response and can reverse the alkaline phosphatase activity to normal or nearly normal values in severely symptomatic patients. As opposed to EHDP-treated patients, who demonstrated significant deterioration in bone texture in 50% of the lytic lesions [38], ADP is effective in healing lytic lesions [38, 96]. The clinical and biological effects of

pamidronate may wane as the number of courses increases [161]. Although APD is a useful means to rapidly suppress the bone turnover, further studies are needed to determine optimal dosage, the length of treatment, and whether oral and IV therapies when combined would allow for prolonged remission [163, 164].

Transient febrile reactions, which are sometimes accompanied by myalgias, and lymphopenia commonly occur after the first infusion. Other reported adverse events include transient hypocalcemia [22], and neutropenia, mild thrombophlebitis, and rarely ocular complication (uveitis, scleritis) [31]. Bone loss of the appendicular skeleton after intravenous treatment has recently been described [157] and has been attributed to secondary hyperparathyroidism. This effect can be prevented by the administration of calcium and calcitriol. Otherwise, no major side effect has been reported [22, 42, 97].

Aledronate. Aledronate is a potent amino-bisphosphonate, and one of the most popular antipagetic drugs. The drug is safe and well tolerated at a daily oral dose of 40 mg for 3–6 months [86, 94, 130, 154], or intravenously at a dose of 10 mg daily for 5 consecutive days [114]. Aledronate has been rigorously demonstrated to heal lytic bone lesions [130] and normalize alkaline phosphatase levels by 6 months in the majority of patients. This drug is capable of producing long-term biochemical remissions. Aledronate at the cellular level does not interfere with osteoclast recruitment or attachment; however, there is interference with active osteoclastic resorption, as evidenced by their lack of ruffle borders.

Histomorphometric assessment failed to demonstrate any evidence of impaired mineralization [86, 130].

Gastrointestinal [86] side effects occur in 25% of patients. According to the pharmaceutical company Merk & Co. Inc. (White House Station, N.J., USA), which produces the drug, adverse esophageal effects, such as esophagitis, esophageal ulcers, and esophageal erosions, occasionally with bleeding and rarely followed by esophageal stricture, have been reported in patients receiving treatment with aledronate. These risk factors appear to be greater in patients who lie down after taking aledronate and in those who fail to swallow it with a full glass of water.

Risedronate. Risedronate is a pyridinyl bisphosphonate that can be administered orally in lower dosages than other antiresorptive bisphosphonates. The recommended dose is 30 mg per day for 2–3 months or less [10, 21, 80, 155]. A 2–3 month treatment can reduce the associated pagetic pain [80, 106] and significantly reduce or normalize the bone markers of disease activity with long-lasting remission. Risedronate can also provide additional remission in subjects who exhibited an incomplete response to previous etidronate treatment [155]. This drug is highly effective in osteolytic lesions after 6 months of treatment

[21]. In general, risedronate is well tolerated and has a good safety profile.

Neridronate. Neridronate (aminohexane bisphosphonate, AHBP) is another bisphosphonate that has been tried successfully in PD. The oral dose is 400 mg daily for 1–3 months, and the IV dose is 15–50 mg daily for 5 days or 200 mg in one single dose or in two separate doses on consecutive days. This drug provides a long suppression of biomechanical indices in the majority of patients (up to 18 months), with normalization of alkaline phosphatase in more than 60% of patients. AHBP has also been used successfully in patients in whom resistance to treatment developed after disodium etidronate [11, 36] or clodronate treatment [46]. Neridronate has neither adverse effects on mineralization nor significant side effects.

Tiludronate. Tiludronate (4-chlorophenylthiomethylene bisphosphonate) is a potent oral bisphosphonate that has been extensively evaluated in the treatment of PD of bone [138]. The drug can be taken orally at a dose of 200–400 mg daily for 6 months. The average drop in alkaline phosphatase activity at 6 months after the onset of treatment is reported at $42 \pm 4\%$ ($p < 0.01$) for the 200 mg and $48 \pm 9\%$ ($p < 0.01$) for the 400 mg dose [128]. An oral dose of 400 mg for 3 months is more effective and as well tolerated as etidronate at 400 mg per day.

Tiludronate disrupts the preformed actin rings and suppresses bone-resorbing activity by inhibiting protein tyrosine phosphatases in osteoclasts [109]. Tiludronate has a relatively rapid action, with marked clinical improvement observed as early as the 1st month of treatment. Tiludronate is a safe drug [129] with sustained antipagetic effects that can last more than 18 months [50]. This drug can normalize bone turnover without impairing mineralization [138]; no resistance to medication has been reported.

Ibadronate. Ibadronate (ibadronic acid) is a third-generation aminobisphosphonate indicated for intravenous use (usual dose 2 mg) [168]. In animal studies ibadronate is capable of preserving bone quality and inhibiting bone resorption. This drug may also inhibit bone formation, but only at high doses (10 $\mu\text{g/kg}$ per day). In animal studies, ibadronate has proven to be more potent than etidronate, clodronate, pamidronate, and alendronate, and equivalent if not more potent than risedronate in inhibiting induced hypercalcemia and bone resorption. In preliminary studies in patients with PD, a single IV ibadronate dose (2 mg) decreased serum alkaline phosphatase levels and urinary markers of bone turnover, and inhibited bone resorption.

Reported adverse effects were: increased body temperature, hypocalcemia, hypophosphatemia, and, less commonly, flu-like symptoms and gastrointestinal intolerance [39].

Aminohydroxybutylidene bisphosphonate. Aminohydroxybutylidene bisphosphonate (ABDP), or 4-amino-1-hy-

droxybutylidene-1,1-disphosphonate is a new bisphosphonate with promising treatment for active PD [113, 119]. This drug is administered intravenously at a dose of 5 mg per day for 4–5 consecutive days and profoundly inhibits bone resorption, as evidenced by a significant decrease in bone biochemical markers [113].

Bone biopsies undertaken in ten patients indicated no adverse effects on mineralization.

The only noted side effect was a transient fall in total white cell count, particularly the lymphocyte and neutrophil fractions, associated with short-lived fever in 1% of the tested patients [113].

Olpadronate. Olpadronate (OPD) is one of the latest bisphosphonates; it is characterized by the dimethylation of the aminogroup [(3-dimethylamino-1-hydroxypropylidene) bisphosphonate].

A 12-day course with 200 mg per day of OPD proved to be a very effective and well-tolerated treatment for PD [57]. Its potency is similar to alendronate, but it is more soluble in the digestive system than other aminobisphosphonates.

Zoledronate. Zoledronate (dimethylaminohydroxypropylidene bisphosphonate) is a third-generation imidazole ring containing bisphosphonate. Oral zoledronate was well tolerated, and a dose of 200 mg per day for 10 days was sufficient to induce remission in the majority of patients, with a recurrence-free period of 22 months [146].

It has been shown, in animal studies, to be 850 times more potent than pamidronate. A single infusion of microgram amounts (400 μg dose) of zoledronate was capable of inhibiting bone resorption without observable clinical or biochemical toxicity [10]. Biochemical remission was obtained in 82% of treatments [146].

This potent new bisphosphonate appears to be a promising drug, but merits further study to determine its optimal dose and safety.

Calcitonin

Three forms of calcitonin are available: porcine, salmon, and human synthetic for intramuscular or subcutaneous administration. The dose of human synthetic calcitonin is 0.25–0.5 mg per day by subcutaneous injection [151]. Salmon calcitonin is also available in intranasal spray, suppositories, and oral form. The last two forms are still being tested in clinical trials. The potency of salmon and porcine calcitonin is expressed in MRC (Medical Research Council) units. The initial dose of salmon calcitonin was 50–160 MRC units [12], given either daily or three times a week in a single or divided dose for a prolonged period of 6–12 months. Salmon calcitonin has been introduced as a nasal spray or suppository at doses of 200–400 units and 300 units, respectively. It seems that

the injection of salmon (100 IU) calcitonin is more effective than nasal spray (200 IU). Nasal spray was ineffective in three patients with severe PD as compared to the injectable form [58]. The fall in serum alkaline phosphatase after 3 months of nasal calcitonin is expected to average 24–33% of pretreatment values [52].

The ease of administration and patients' acceptance makes this form a suitable alternative for geriatric patients [53]. The exposure to intranasal synthetic salmon calcitonin by patients previously treated with parenteral calcitonin may cause secondary antibody response and clinical resistance [93]. Human calcitonin can be used when salmon becomes ineffective because of antibody formation against calcitonin.

Calcitonin acts directly on osteoclasts, with immediate inhibition of osteoclast activity and marked reduction in the number of osteoclasts [24]. Calcitonin enhances production of 1,25-dihydroxyvitamin D₃ [54]. Calcitonin also promotes renal excretion of phosphate, calcium, sodium, and water [65]. Responses to salmon calcitonin (100 MRC units thrice weekly) and disodium etidronate (EHDP 400 mg daily) given for 6 months were similar [115, 135]. The reduction in alkaline phosphatase was 53% and 56%, respectively. Combination therapy produced a 71% reduction in alkaline phosphatase, which is significantly greater than in the non-combined treatment. More sustained control of the disease activity was achieved when salmon calcitonin was combined with EHDP.

Mithramycin (plicamycin)

The recommended dose for mithramycin (plicamycin) is 15 µg/kg body weight per day, administered in an IV glucose injection over 6–8 h, for 5 days. The same regimen should be repeated after a 7-day interval.

Mithramycin acts on bone resorption through osteoclastic toxicity. This inhibits the DNA-directed RNA synthesis of osteoclasts [140]. Mithramycin has a quick response on bone remodeling, and dramatic normalization of bone scan activity [68, 140]. Mithramycin (plicamycin) is indicated for severe spinal cord compression, especially when disease is in the osteolytic phase [61, 68]. Mithramycin is toxic to the liver, kidneys, and platelets. Monitoring of patients receiving mithramycin should include a platelet count, hematocrit, measurement of blood urea nitrogen, and liver-function tests every second day. We did not encounter permanent kidney, liver, or bone marrow complications in the regimen described. Mithramycin may predispose to hypokalemia that may result in death, especially in patients with predisposing cardiac disease receiving diuretics [14]. Reports indicated that patients may die of bleeding diathesis with large doses (37.5–50 µg/kg body weight) given for cancer therapy [83].

Gallium nitrate

Gallium nitrate is a new drug in the treatment of PD. The drug is administered either as IV, at a dose of 2.5 µg/kg body weight per day in 5% glucose for 7 consecutive days, or by subcutaneous injection at a dose of 0.25–0.5 mg/kg body weight per day for 14 days, followed by a 2-week interval free of medication, in a monthly cyclical fashion [17, 166].

The action of gallium nitrate seems to be long lasting [100] and safe [17], but the response duration is variable, lasting from 6 to 42 weeks. The effectiveness of treatment is proportional to the dose of the drug administered. Response to IV treatment was more marked than to subcutaneous injection [165].

The exact mechanism of action is unknown, but may be related to a similar inhibitory effect of calcitonin on osteoclasts, [108] and is dependent on cellular function.

Treatment with gallium nitrate significantly reduces serum levels of alkaline phosphatase and urinary excretion of hydroxyproline. A fall in hydroxyproline precedes alkaline phosphatase suppression, suggesting that suppression of osteoclastic bone resorption (reduced hydroxyproline) leads to bone formation by osteoblasts (decreased alkaline phosphatase).

Transient hyperparathyroidism has also been recorded secondary to the drop in serum calcium levels during treatment.

The treatment is still experimental, and larger trials are required to evaluate the safety and effectiveness of this drug.

Ipriflavone

Ipriflavone (7-isopropoxy-3-phenyl-4h-1-benzopyran-4-1) is an isoflavone that has been found to have a beneficial effect on Paget's disease of bone [1]. At a dose of 600 mg daily for 30 days, there was a significant alleviation of pagetic bone pain and improvement of biochemical bone markers [2].

The drug was well tolerated, and only some mild gastrointestinal intolerance was reported [118]. The drug apparently acts indirectly on bone, inhibiting bone resorption by stimulating the release of calcitonin [110]. This drug is still experimental, and is available only in Europe.

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.

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 [19]. Quantitative bone scan scintigraphy allows early and objective assessment of PD when evaluating the effects of therapy [120]. Radiographic images should be obtained before treatment and every 1–2 years thereafter to monitor the modeling (bone expansion) and remodeling changes (phase of the disease activity). Although PD is diagnosed economically with conventional radiography, magnetic resonance (MR) imaging is well suited to demonstrating specific characteristics of certain complications, including basilar invaginations, spinal stenosis, and secondary neoplasm [20].

Biochemical bone markers

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

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

1. In serum: total alkaline phosphatase (tAP) and bone alkaline phosphatase (β AP), procollagen type I N-terminal polypeptide (PINP), β -carboxyterminal telopeptide of type I collagen (SCTX); osteocalcin and serum bone sialoprotein.
2. In urine: hydroxyproline (Hyp) and 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. Urinary calcium is also an indicator of bone resorption.

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. Osteocalcin produced by osteoblast or released during osteoclast degradation of bone matrix may indicate either formation when resorption and formation are coupled or turnover when they are uncoupled. Therefore, this is not a practical bone marker. Resorption markers respond approximately

1–3 months after treatment intervention, whereas markers of formation respond much later, usually after 6–9 months [27].

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

Bone alkaline phosphatase and PINP seem to best reflect pagetic activity [9, 18, 120]. Total alkaline phosphatase can also be considered as a sensitive marker for therapeutic monitoring of Paget's disease. However, more specific markers may improve the usefulness of the biochemical assessment of PD in certain situations [164].

Urinary N-telopeptide (NTX) has also emerged as a sensitive marker for bone resorption in the management of pagetic patients [34, 120]. Serum levels of pyridinium cross-links correlate well with its urinary excretion (a sensitive index of bone resorption) [8] in patients with PD. Therefore, the determination of serum levels of pyridinium cross-links avoids the usual problems related to urinary specimen collection [148]. 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 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 [34, 56].

Patients should be followed by measuring bone markers every 3–6 months, depending on the activity of the pagetic lesions and the drug used [4]. Retreatment is suggested when remodeling indices rise above the upper limits of normal or by 25% above the previous nadir [139].

Other tests

Hematologic profile, serum electrolytes, and kidney and liver function tests are helpful in assessing the overall medical condition of patients with PD of the spine who are within the geriatric age groups [66], especially when administering antipagetic drugs such as mithramycin or the new-generation bisphosphonates.

Conclusions

The altered remodeling unit in PD results in abnormal bone remodeling, producing structural changes precipitating or leading to facet joint osteoarthropathy and spinal stenosis (see Fig.2). 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, exhibited constant spinal pain attributed to the pagetic pathologic remodeling process.

About one-third of patients with spinal involvement exhibited symptoms of clinical spinal stenosis. Ten distinct

mechanisms have been implicated as producing neural element dysfunction. Bone compression by the expanding pagetic vertebrae is by far the most common cause of neural dysfunction. However, severe stenosis, as seen on CT scan, may remain asymptomatic, suggesting adaptability of the thecal sac and its neural elements to severe spinal stenosis without significant loss of neurofunction. 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.

The natural history of PD affecting the spine is therefore progressive, characterized by bone proliferation, vertebral expansion, and structural changes (see Fig. 2), leading to spinal stenosis and facet arthropathy – clinical entities that are not always symptomatic.

One must be careful before attributing back pain to PD, otherwise the results of antipagetic treatment may be disappointing. Treatment of pagetic spinal stenosis symptoms should start with medical antipagetic therapy. If the symptoms persist in spite of normalization of bone remodeling markers, surgery is the alternative treatment.

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