REVIEW

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Paget's disease of bone

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ABSTRACT

Paget's disease of bone is the most common metabolic bone disease after osteoporosis and affects 2-4% of adults over 55 years of age. Its etiology is only partly understood and includes both genetic and environmental factors. The disease may be asymptomatic and can be uncovered incidentally on x-ray or in biochemical tests performed for another condition. It can also manifest itself with bone pain, deformity, fracture or other complications. Paget's disease is diagnosed by x-rays and in general has very typical radiological features, but nuclear bone scans define the extent of the disease. Plasma total alkaline phosphatase activity is the most clinically useful indicator of disease activity. It is elevated in most untreated patients, but may be within the normal range in patients with monostotic or limited disease. Bisphosphonate therapy is indicated for patients with symptoms and should also be considered in patients with disease sites that suggest a risk of complications, such as long bones, vertebrae or base of the skull. Orthopedic surgery in Paget's disease patients includes almost the correction of fractures and arthroplasty.

KEYWORDS: paget's disease of bone, bone remodeling, bisphosphonates, alkaline phosphatase, treatment.

Introduction

Paget's disease of bone (PDB) is a chronic focal disorder of bone remodeling, affecting one (monostotic form) or more bones (polyostotic form) which are typically enlarged and deformed. The disease was first described in England, in 1877, by Sir James Paget who defined it with the name of "osteitis deformans" [1]. The disease mainly involves the axial skeleton, such that the pelvis (70%), femur (55%), lumbar spine (53%), skull(42%), and tibia (32%) are preferentially affected. Clinically,

the disease result in symptoms of bone pain, deformity, and pathological fracture. Osteoarthritis related to bone deformity and subchondral sclerosis is a common consequence and frequently requires arthroplasty. Patients with PDB also have

an increased risk of developing osteosarcoma, although rare (0.3% of PDB patients), and some families have been described in which PDB is accompanied by giant cell tumours [2].

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Epidemiology

PDB appears usually after the age of 40, being slightly more common in men than in women. It has been described almost worldwide, with an irregular geographical distribution. It primarily affects patients of British descent, being common (around 4%) in England , areas of Australia, New Zealand and North America and rare (less than 1‰)in Asia, Scandinavia and Africa.[3,4]. Most epidemiological studies

have documented a gradual decrease in the prevalence and incidence of PDB over the years, which is associated with a parallel decline in mortality and clinical severity[5],

Although the cause of this reduction is not completely understood, environmental changes, such as different migratory patterns, improved diet, sedentary lifestyle

and decrease in the exposure to viral infections and zoonoses, might play a role [4],

although no significant change in other regions such as Italy and the USA have been reported [6,7].

Etiopathogenesis

It is generally believed that the primary cellular abnormality in PDB is in the osteoclasts. Pagetic osteoclasts are mainly affected, experimenting an increase in number and size and containing more nuclei than normal osteoclasts and produce increased amounts of interleukin 6, and their precursors are hyper-responsive to 1,25-dihydroxy-vitamin D and receptor activator for nuclear factor κB (NFκB) ligand (RANKL) [8]. This results in an elevated metabolic osteolytic activity, coupled with increased bone formation by osteoblasts, which are apparently normal [9].

In PDB there is loss of the normal regulation of bone resorption and formation, with the process biased towards one or the other depending on the phase of the disorder.

There are three phases. The first is a lytic phase in which normal bone is resorbed by numerous, enlarged and more nucleated than normal osteoclasts and bone turnover is markedly increased. Secondly, a mixed phase of lytic and blastic activity characterised by rapid increases in bone formation from numerous osteoblasts.

The newly synhesised bone is abnormal with collagen fibres deposited in a haphazard way. There is both osteoblastic and osteoclastic activity, but formation becomes

dominant. Finally, there is sclerotic phase in which bone formation predominates, but the formed bone is disorganized (woven bone) and is weaker. The resultant bone has

altered and often abnormal architecture [10].

Despite the remarkable progresses of the last 2 decades, the pathogenetic mechanisms leading to these alterations in osteoclast phenotype and the development of PDB remain in part unknown and probably include either genetic or environmental causes.

Genetic factors

The presence of a familial predisposition in PDB has been known for many years.

Several genes and loci that predispose to familial PDB have been identified by a combination of linkage analysis in families and genome wide association studies (GWAS) in unrelated individuals.

Sequestosome 1 gene (SQSTM1): Mutations affecting the SQSTM1gene currently represent the major genetic cause of adult PDB and have been described in

approximately 25%–40% of familial cases and in up to 10%–15% sporadic cases in various patient series[11]. Despite SQSTM1 and other rarer mutations have been found in a relevant number of familial PDB-cases from different countries, their prevalence remains very low in patients with sporadic disease, and at up to 40%–50% of familial cases do not yet have a recognized mutation. This suggests the presence of

additional predisposition genes such as **Germline Mutations** associated with PDB and/or PDB related disorders such as: Tumour Necrosis Factor Receptor Superfamily Member 11A(TNFSRF11A) gene, Zinc Finger Protein 687 (ZNF687)gene, Profilin 1(PFn1)gene, Valosin containing protein(VCP)gene and **susceptibility**

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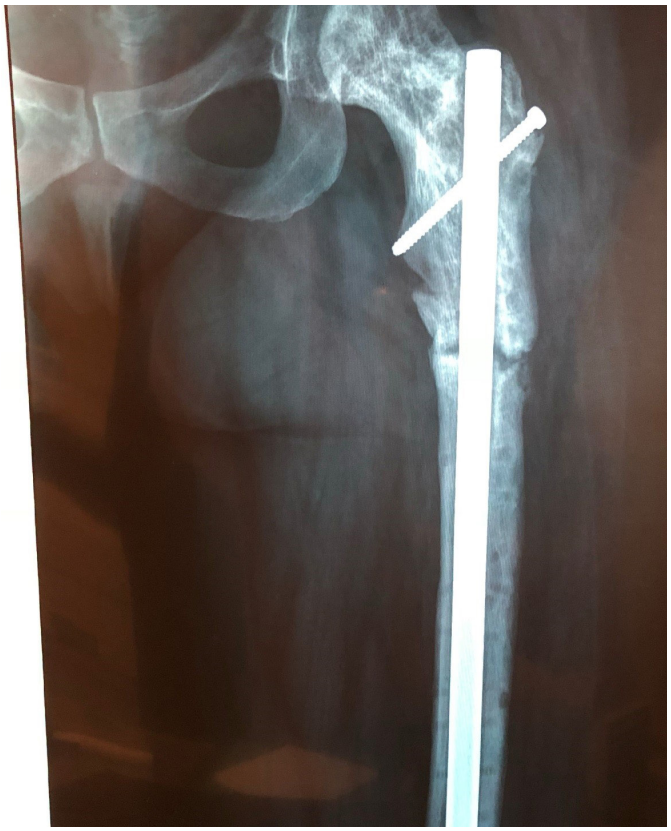

***Fig.1**. X-ray from a patient (37 years-old woman) with PDB affecting the left femur showing alternating areas of osteolysis and osteosclerosis with a pathologic fracture fixed intramedullary nail. (author's archive)*

variants like: Optineurin(OPTN)gene, Colony Stimulating Factor 1(CSF1)gene, Ras and Rab Interactor 3(RIN3)gene, Promyelocytic Leukaemia Gene(PML)gene,Transmembrane 7 Superfamily Member 4(TM7SF4) gene[12]etc.

Enviromental factors

The possible involvement of viral factors in the pathogenesis of PDB has been reported since the early 1970s [13], when virus-like inclusions were demonstrated first in the nucleus and then in the cytoplasm of pagetic osteoclasts using electron microscopy. These inclusions consist of groups of microtubules, which are present either in a compact paracrystalline array or are scattered in a more random fashion. The pagetic microtubules are similar to the nucleocapsids of two paramyxoviruses, measles virus (MV) and respiratory syncytial virus (RSV), showed identical dimension, and have been found in several studies in the past years[14,15).

Other research groups have hypothesized an association between another paramyxovirus, the canine distemper virus (CDV), and PDB[16]. The nature of these bodies is still controversial, since other attempts which were made to replicate these findings in bone and blood samples from PDB patients, report negative results [17,18] It has been suggested that they could be protein aggregates resulting from the dysregulation of the autophagy system [19]. However, recent studies have shown that the MVNP protein is associated with the upregulation of IL-6 and IGF1 in osteoclasts from mouse models and PDB patients, which could suggest a role for measles virus in the alteration of bone formation seen in these patients [20, 21].

PDB has also been linked to other factors such as poor calcium and vitamin D intake, consumption of uncontrolled beef meat during childhood , consumption of not purified water[22], contact with dogs during early years [23], an excessive mechanical loading on the skeleton and exposure to some environmental toxics [24].

However, despite all these environmental factors have been associated to an increased risk of PBD in some patient cohorts, no conclusive evidence can be drawn and complicate our understanding of the genetic mechanisms of the disorder. In this respect, a potential unifying mechanism linking genetic and environmental factor in the pathogenesis of PDB, yet to be demonstrated as such, could be represented by

epigenetics and miRNAs, although currently there are small preliminary studies about their role in the pathogenesis of skeletal pagetic abnormalities[25,26].

Clinical features and complications

Many patients with Paget's disease of bone are asymptomatic, and the disease is discovered when a radiograph or bone scan is performed for another clinical indication or when an elevated serum ALP level is found on a multiphasic screening chemistry panel. Most of the clini-

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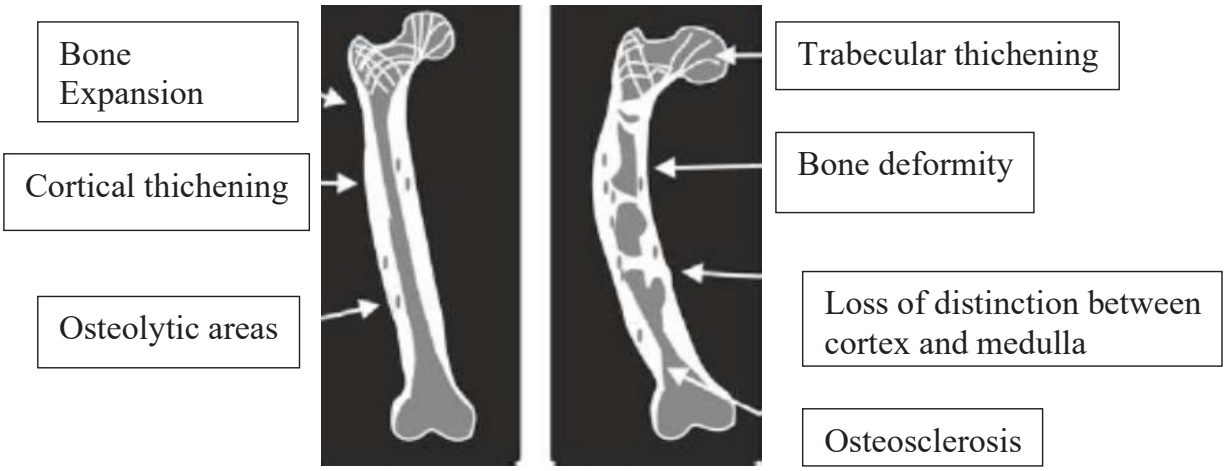

Fig.2 *Characteristic X-ray features of PDB*

cal manifestations of the disorder arise from the skeleton (Table1). In order of frequency, PDB affects the femur,spine, skull, sternum and pelvis, but can be found in any bone in the body [27]. The most common symptom is bone pain, which may be due to increased bone turnover or a complication such as osteoarthritis, spinal stenosis,or pseudofracture. Bone pain occurs in ~50% of cases presenting clinically and is usually mild to moderate in intensity and described as deep and aching. It can occur throughout the day and is often reported to be worse at night. Fractures with minimal trauma can occur through affected bone weakened by the elevated remodeling process with nonlamellar osteoid matrix. Approximately 10% of PDB patients sustain fractures. These fractures are termed "chalk-stick" or "banana"fractures because they are transverse and reflect the poor quality of the collagen matrix.(Fig 1). The most common neurological complication of Paget's disease is hearing loss associated with disease involving the

Skull. Originally thought to be caused by compression of the eighth cranial nerve, hearing loss is now believed to be due to cochlear damage [28]. With involvement of the skull, other cranial nerves can be affected. Rarely, basilar invagination may produce hydrocephalus. Paraplegia, quadriplegia, and other symptoms of spinal stenosis are rare, although the disease frequently involves vertebrae. Osteosarcoma is

a rare complication (present in less than 0.3% of cases) but should be suspected in patients who have a sudden increase in bone pain or swelling. Other rare complications include high-output cardiac failure, and hypercalcemia in patients who are immobilized. Clinical signs include bone deformity and warmth of the skin overlying an affected bone.

Diagnosis

A diagnosis of PDB is incidental in most cases, when an elevated level of alkaline phosphatase (ALP) is detected in the absence of liver disease in analyses that were performed for various reasons or the presence of suggestive radiographic changes ordered by other medical problems [29]. Other possible causes of increased ALP need to be excluded, including vitamin D deficiency, hyperparathyroidism, hyperthyroidism, renal osteodystrophy and malignancy. However, normal levels of alkaline phosphatase do not rule out the diagnosis[30]. Tests for specialized markers, such as bone-specific alkaline phosphatase(bALP) or procollagen type I N-terminal propeptide (P1NP), can be useful in patients with coexisting liver disease but otherwise offer little advantage over measurement of the total serum alkaline phos-

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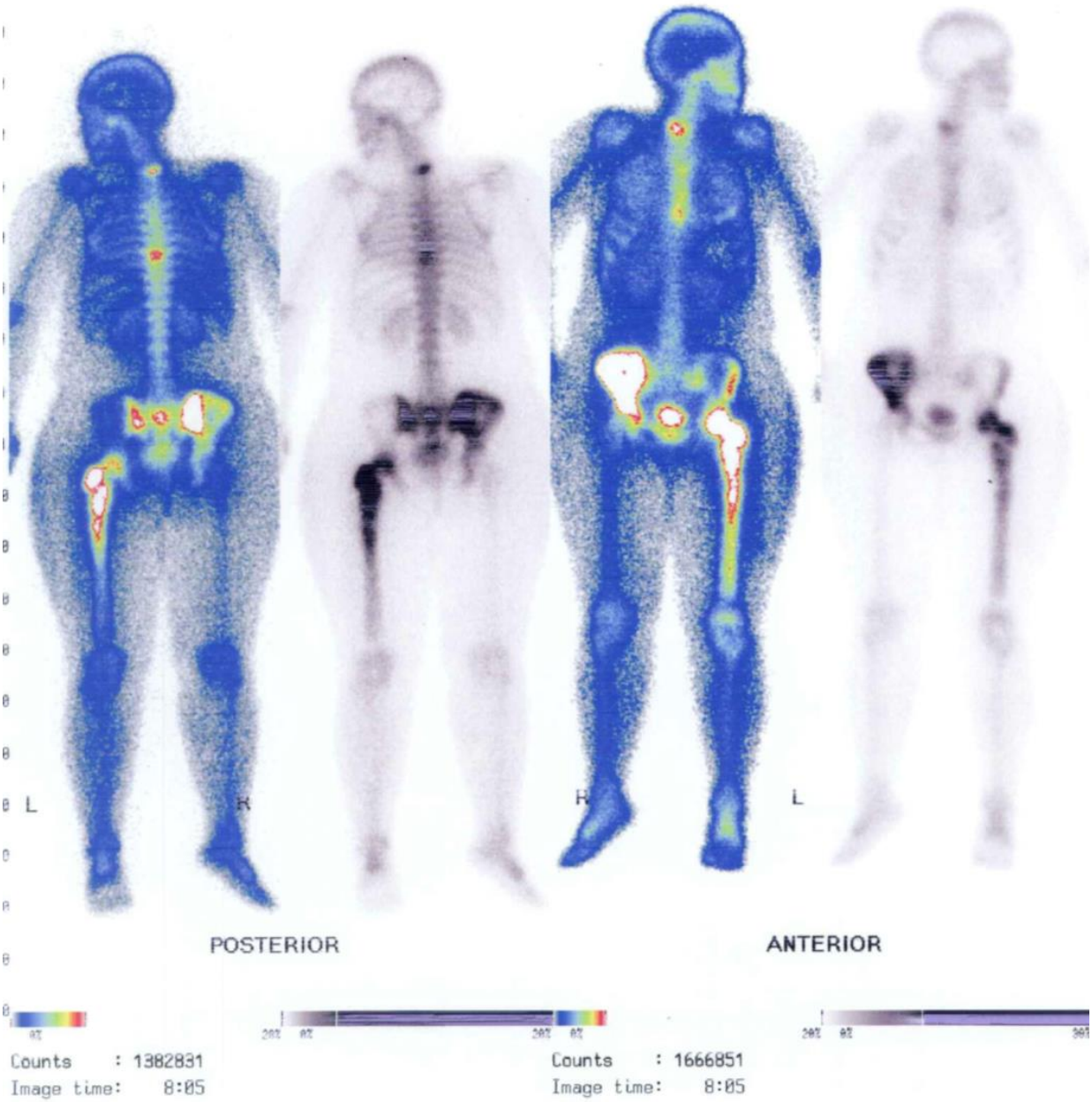

***Fig.3**. A radionuclide bone scan from the same patient of figure 1 shows intense tracer uptake in the upper part of the left femur. (personal archive)*

phatase level for the purpose of diagnosis [31]. Plain radiography is often the basis for diagnosis as its features are easily recognizable (focal osteolysis with coarsening of the trabecular pattern, bone expansion, and cortical thickening Fig.1and Fig.2). The differential diagnosis includes hyperostosis frontalis interna (a benign condition characterized by sclerosis of the frontal bones of the skull), fibrous dysplasia, pustulotic arthrosteitis (which can be manifested as sclerotic lesions of the clavicle and ribs), and osteosclerotic metastases. However, Paget's disease of bone is seldom confused with these other disorders, and biopsy of an affected site is rarely required for diagno-

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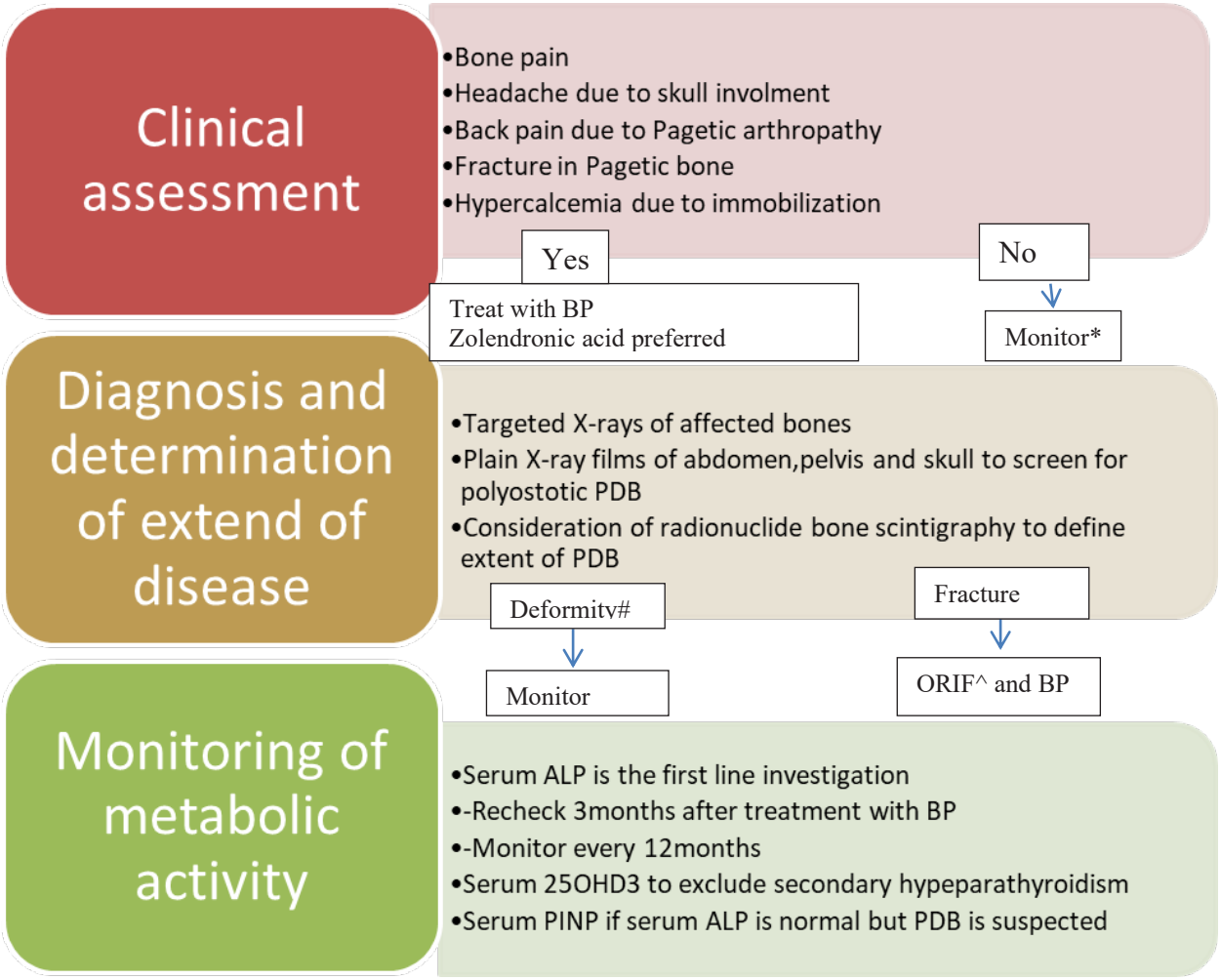

Fig. 4. *Management and treatment algorithm for Paget's disease of bone*

**Monitor serum ALP every 12 months, while treatment is indicated for symptomatic PDB.*

#There is insufficient evidence to recommend bisphosphonates to prevent bone deformity or progression of osteoarthritis in PDB.

^ORIF is recommended in treating fractures of pagetic bone. There is insufficient evidence to support use of pre-operative bisphosphonates to reduce intraoperative blood loss.

ALP, alkaline phosphatase; BP, bisphosphonates; ORIF, open reduction and internal fixation; PDB, Paget's disease of bone; P1NP, procollagen type 1amino-terminal propeptide

sis. Because a majority of the lesions of Paget's disease are asymptomatic, radionuclide imaging of the skeleton rather than a general x-ray survey has become the standard means to document the extent of skeletal involvement of Paget's disease [32]. Fig 3.

Other radiological modalities, such as computerized tomography, magnetic resonance imaging, and positron emission tomography, may be useful in individual patients, particularly if a neoplasm at a pagetic site is suspected, but they are not used routinely in the evaluation of patients with Paget's disease [33].

Further laboratory testing should include as-

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TABLE 1.

Symptoms and Complications of Paget'sDisease of Bone

SYSTEM	COMPLICATION
Musculoskeletal	Bone pain (52%) Bone deformity (22%) Osteoarthritis of adjacent joints (73%) Acetabular protrusion Fractures (9%) Spinal stenosis
Neurological	Spinal stenosis Neurological Hearing loss (9%) Tinnitus Cranial nerve deficits (0.4%) Basilar impression (2%) Increased cerebrospinal fluid pressure Paraplegia, quadriplegia, vascular steal syndrome
Cardiovascular	Congestive heart failure (3%) Increased cardiac output Aortic stenosis Generalized atherosclerosis Endocardial calcification
Metabolic	Immobilization hypercalciuria Hypercalcemia Hyperuricemia Nephrolithiasis
Neoplasia	Sarcoma (osteo/chondro/fibro) (0.3%) Giant cell tumor

sessment of renal function and measurement of levels of calcium, albumin, and 25-hydroxyvitamin D; Vitamin D deficiency is a common finding, probably reflecting the fact that Paget's disease of bone predominantly affects older people, among whom vitamin D deficiency is prevalent and liver function should be assessed to rule out the possibility that elevations in the alkaline phosphatase level are of hepatic origin [34].

Management

The primary goal of PDB treatment is to restore normal bone turnover in order to relieve symptoms such as bone pain and possibly prevent complications that result from the abnormal resorption and overgrowth of pagetic bone (table 2). most guidelines, including Endocrine Society Clinical Practice Guidelines, suggest antiresorptive treatment, **mainly bisphosphonates,** for most patients with active disease who are at risk for future complications [27]. However, it should be mentioned, there is no clear evidence that asymptomatic patients benefit from antiresorptive therapy. A recent trial in a large cohort of 1324 PDB cases form UK, the Paget's Disease, Randomized Trial of Intensive versus Sympto-

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TABLE 2.

Indications for treatment
1 Bone pain
2 Preparation for orthopedic surgery
3 Reversal of neurological deficit associated with vertebral disease
4 Hypercalcemia due to immobilization
5 High-output congestive heart failure
6 Prevention of complications including deformity and hearing loss

TABLE 3.

Bisphosphonates Used in the Treatment of Paget's Disease of Bone.

Drug	Dose	Common Adverse Effects
Oral		
Risedronate#	30mg/day for 2mo Retreatment may be required between 1 and 5 y	Dyspepsia, esophagitis
Alendronate# §	40mg/day for 5 mo	Dyspepsia, esophagitis
Intravenous		
Zolendronic acid¶	5mg single infusion. Retreatment is seldom required within 5 y	Acute phase response Hypocalcemia

 # This drug should be avoided in patients with an estimated glomerular filtration rate (GFR) of less than 30 ml per minute per 1.73 m2 of body-surface area.

§ Alendronate is not licensed for the treatment of Paget's disease of bone in the United Kingdom or other European countries.

¶ This drug should be avoided in patients with an estimated GFR of less than 35 ml per minute per 1.73 m2 of body-surface area.

matic Management (PRISM) study, compared the effects of a treat to target strategy aimed at normalizing bone turnover (as assessed by total alkaline phosphatase) with a strategy aimed at controlling symptoms. Most patients had previously been treated with bisphosphonates and a consistent proportion of them already presented complications such as hearing loss (22%), fractures (39%), bone deformity (36%) or had a previous surgery for PDB (16%).

The use of any licensed bisphosphonate was permitted, but risedronate was chosen as the first-line treatment because this was the most potent bisphosphonate available at the time when the study began. At 3 years, both strategies showed similar effects on the occurrence of fractures, or-

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TABLE 4.

Surgery in patients with paget's disease.
1 Total hip replacement
2 Total knee replacement
3 Femoral and tibial osteotomy
4 Correction of spinal stenosis or nerve root compression
5 Vertebroplasty for painful vertebrae
6 Ventricular-peritoneal shunting for hydrocephalus
7 Suboccipital craniectomy and cervical laminectomy for basilar impression

thopedic procedures, hearing loss, bone pain, quality of life and adverse events [35]. A 3-year extension study of the trial was performed on 502 patients in which the same treatment strategies were continued but where the most potent bisphosphonate zoledronic acid was used as the treatment of first choice in the intensive arm. In keeping with the original trial, there were no clinically relevant differences in quality-of-life measures or bone pain between the treatment groups. However, intensive treatment arm was associated with a nonsignificant increase in fractures (HR 1.90; 95% CI 0.91-3.98), orthopedic procedures (HR 1.81; 95% CI 0.71-4.61), and serious adverse events (RR 1.28; 95% CI 0.96-1.42).

Thus, it was concluded that long-term intensive bisphosphonate therapy to suppress bone turnover confers no clinical benefit over symptomatic therapy.

Agents used to treat PDB are antiresorptive in nature and mainly nowadays are bisphosphonates although Calcitonin has been the first antiresorptive agent to be used for effective treatment of PDB and is still approved for the treatment of PDB in several countries.

Even these drugs may also reduce bone pain, symptomatic treatment with analgesic agents or anti-inflammatory drugs may be required in some patients. Moreover, since hypocalcemia and secondary hyperparathyroidism are common after the suppression of bone turnover, daily supplements of calcium and vitamin D should be also recommended to PDB patients in addition to antiresorptive therapy.

While all bisphosphonates have been shown to be effective in PDB (alendronate, risedronate, pamidronate, neridronate, ibandronate and zoledronic acid),Table 3 summarizes the bisphosphonates currently used in treatment.

Denosumab is an alternative antiresorptive therapy used for patients with osteoporosis; however, it has been less studied in PDB than bisphosphonates.

While case reports of its use in PDB show its effectiveness in reducing bone turnover markers for up to five months after administration, its effect on bone pain, fracture risk and progression of pagetic lesions is less clear. At this stage, it is not recommended as treatment for PDB but

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may considered for the treatment of giant cell tumor(GCT) complicating PDB when the tumor is nonresectable[37].

Treatment response is best assessed by measuring serum total ALP 3–6 months after treatment and then annually once levels are normalised. If there are osteolytic lesions, the plain film should be repeated at 12 months to assess for improvement.

A single infusion of zoledronic acid has long-term benefits, with sustained remission rates of 87% at 6.5 years[36]. If symptoms recur and serum ALP rises above the normal range, retreatment with zoledronic acid should be considered [27].

Surgery

Although there no randomized trials, various surgical procedures have been beneficial for many patients. Table 4 lists the variety of procedures that have been used in the management of patients with Paget's disease.

Conclusion

Since the description of the first case, in 1877, PDB has remained for many years a challenging disorder either concerning the pathogenesis or the necessity of effective treatments, able to prevent disease progression and complications. Over the last two decades, thanks to the development in technology, remarkable advances have been provided on either the pathogenetic mechanisms or the clinical management of the disease. Despite these remarkable advances in the genetics of the disease there are still major gaps in knowledge, particularly concerning the understanding of the exact molecular mechanisms underlying osteoclast dysfunction and the occurrence of pagetic lesions in the presence of all these mutations. Importantly, since the development of more potent antiresorptive compounds such as aminobisphosphonates

PDB has become a treatable disorder, particularly after the recent introduction of

zoledronic acid which now allow a long-term remission in the majority of patients [38,39].

A graphical summary of the recommendations for diagnosis and management of PDB is shown in Fig 4.

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