

The Second Most Common Bone Disease: A Review on Paget's Disease of Bone

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Abstract

Paget disease of bone (PDB) is the second most common metabolic bone disease. It is a chronic disease with a mono- or polyostotic appearance that is characterized by an increased bone turnover. The orthopedic surgeon is often confronted with such symptoms and complications as bone pain, skeletal deformities, and pathologic fractures caused by the "out-of-balance bone remodeling process". Careful evaluation of the clinical and radiographic findings is necessary to determine whether treatment of PDB is indicated. The mode of action of effective pharmacological treatments consists of reducing the increase in osteoclast-mediated bone resorption that characterizes the disease. Bisphosphonates are the compounds of choice for PDB therapy; these are readily available and have received approval. Patients with PDB are at increased risk for surgical complications, such as blood loss and heterotopic bone formation, if operative treatment is necessary. However, advances in surgical techniques and accompanying medical treatment could potentially improve the overall outcome of these patients. To achieve that goal, careful perioperative interdisciplinary management and monitoring are essential.

Key Words

Epidemiology · Paget disease of bone · Treatment

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Introduction

Paget disease of bone (PDB) was first described by Sir James Paget in 1876. He observed several patients

throughout their lifespan with occasional pain at the skull and the left lower extremity. With disease progression, there was enlargement and deformity of both limbs and the skull as well as an antecurvature of the spine. Post-mortem examination revealed bone that was so "soft to be cut with a razor" [1].

Today, some 150 years later, it is now well established that PDB is characterized by a localized excessive uncontrolled osteoclastic bone resorption that is followed by compensatory increased osteoblastic activity, resulting in an unstable, unstructured fibroblastic and biomechanical less stable bone. However, the precise pathophysiology of PDB still remains to be established. Genome-wide searches have identified susceptibility loci – on the sequestosome-1 gene (SQSTM1) on chromosome 5q35, on the TNFRSF11A/B gene encoding for RANK on chromosome 18q21-22, and on the VCP gene encoding valosin-containing protein – associated with an increasing risk for developing PDB [2, 3]. Another potential cause discussed in the literature could be a viral infection, since nuclear inclusions of viral components have been observed in the osteoclasts of affected patients [4]. Interestingly, however, similar nuclear virus inclusions have also been described in patients with other skeletal disorders, such as the giant cell tumor of the bone, benign osteopetrosis, and pyknodysostosis [5, 6].

In most cases PDB is asymptomatic. It is generally diagnosed at a later stage of disease progression through chance radiological findings, such as widening of the bone and thickening of the cortex, and in blood tests, such as elevated serum alkaline phosphatase (sAP) concentration.

Pagetic bone lesions can occur at any site of the skeleton, and previous studies describe a polyostotic

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manifestation in approximately 60% of the cases. However, in more recently published European studies, there seems to be a shift towards monostotic manifestation, particularly in patients with PDB that are younger than 70 years of age [7, 8]. In a previous study involving 754 patients with PDB, we identified monostotic lesions in 77% of the cases [9]. In this same publication, we also discussed whether this trend to disease, which afflicts only one bone, may be due to an earlier diagnosis of disease progressions of PDB and an increased use of bisphosphonates in the treatment of PDB. Based on our data, which are in accordance with those of other studies, the majority of lesions were located in the pelvis (72.1%), followed by the spine (13.4%), femur (13.0%), skull (8.5%), tibia (6.5%), and humerus (5.6%) [9].

Symptoms specifically related to the disease are bone pain and deformities of the long bones [10]. Pain is usually caused by the lesion itself or from complications, such as bone deformities, fractures, osteoarthritis of afflicted or adjacent joints, and direct nerve compression. A rare but severe complication is a malignant transformation in an afflicted bone. In our series with 754 patients with PDB, we identified six patients developing a malignant transformation. The incidence of 0.8% corresponds with the quoted incidence of 0.1–1% from the literature [11]. However, because of the sparsity of Paget sarcoma, the majority of such studies are based on case reports [12], with the exception of four larger series, of which one is limited to osteosarcoma of the spine. Nevertheless, all studies describe a poor prognosis for patients independent of the location of the disease and its stage at presentation [11, 13–15].

Epidemiology of PDB

The prevalence of PDB ranges between 1 and almost 8%; as such, it is second-most common metabolic bone disease to osteoporosis. Marked geographical differences exist in the prevalence of the disease, with the highest rates, based on autopsies or radiographic surveys, being reported for UK, followed by New Zealand, the USA, and Western Europe. In contrast, PDB is virtually non-existent in Africa [16, 17]. Previous studies in Germany describe prevalences of between 1.8 and 3% [18, 19]. Epidemiological data from both European and non-European countries show a sex bias that varies from no difference at all to a 2:1 male bias. However, our earlier study on German residents did not find a preference for one sex. Interestingly, PDB is rare before the age of 50 years for

both sexes but shows a steep increase in prevalence thereafter [9]. Epidemiological studies from the UK demonstrated that the 2% prevalence among a patient group aged 55–60 years increased to almost 20% in the group of individuals older than 85 years [20].

There is a large body of evidence hinting at a decline in the frequency of PDB in recent years. In one follow-up study, the prevalence of PDB decreased from a rate of 6.2% in the 1970–1977 period to 2.5% in 1994 for men and from 3.9 to 1.6% for women [21]. In addition, while patients with PDB indeed display an increased mortality rates compared to skeletally healthy individuals, this rate has also been gradually declining in recent years [22].

The reasons for this large decrease in prevalence remain unclear. Although an environmental impact on PDB has been proposed – based on geographic and ethnic variation in prevalence rates – the decline may be a result of an increasing ethnic mix of the population. Another proposal has been that the increased use of vaccines against viral infections may have lowered the prevalence of PDB.

Diagnosis of PDB

In most cases PDB is diagnosed purely by chance when blood samples are drawn or conventional X-rays are performed for some other reason. Serum alkaline phosphatase is moderately or manifestly elevated in more than 90% of the patients with untreated PDB. Consequently, when only the sAP concentration is elevated and there is no manifest vitamin D deficiency, the recommended approach is to perform a bone scan to detect any mono- or polyostotic bone deformities. Should there be an additional liver disease, the bone-specific AP should be determined to differentiate between an elevated liver or bone sAP. Radiographic examination should be performed of painful skeletal areas if there is no history of trauma. Additional imaging is necessary in those skeletal areas that evoke suspicion after the radioisotopic bone scan [23].

Conventional X-rays of affected skeletal regions show a wide range of radiographic findings in PDB. These findings can be categorized into three different stages. The first stage (osteolytic phase) marks the initial phase with predominantly lytic lesions. These lesions occur in the metaphyseal area of the bones, with a sharp demarcation from unaffected bone (candle flame or blade of grass appearance), and expand in the epi- and diaphysis. In the second stage (mixed phase), osteosclerotic areas emerge, leading to the typically coarsening of the trabecular markings. The

involved vertebral bodies are enlarged in the spine, and a “picture frame” effect may occur due to cortical thickening. In some cases, a “Rugger–Jersey-vertebra” is visible, which is not only common in hyperparathyroidism or renal osteopathy, but also in PDB. In the pelvis the mixed areas of lucency and sclerosis lead to deformities, with a protrusion of the acetabulum and osteoarthritis of the hip joint. In the last stage (sclerotic phase), the remodeled bone increases in volume and density (Figure 1a). Radiodense foci can be observed in the skull – but also in other areas. The increased sclerotic alterations can ultimately lead to nerve tissue compressions and ensuing complications, such as amblycusia.

In most cases PDB is diagnosed by its radiographic appearance, and only rarely is bone biopsy used to establish the diagnosis. Histologically, the typical characteristics of trabecular bone (i.e., number, thickness, spacing distribution, and connectivity of trabeculae) that form the basis for their three-dimensional interconnected structure are altered in patients with PDB (Figure 1b). In addition, the otherwise clear separation of cortical and trabecular bone may be undetectable. Unfortunately, the broadening of the new structured bone does not follow bony trajectories which results in a reduced biomechanical stability compared to normal bone.

Trabecular bone mostly appears isolated with a ‘clumsy’ composition. Multinucleated osteoclasts that have more than 12 nuclei per cell cover the trabecular bone surface. In addition, the typical appearance of deep resorption lacunae with the so-called ‘swallowtail pattern’ can be observed. As an indicator of accelerated bone formation, the osteoid surface is enlarged and the amount of activated cuboidal osteoblasts is increased. In polarized light microscopy, the collagen fibers are not orientated into one direction; instead,

they display a rather random distribution, such as in woven bone.

Pharmacotherapy of PDB

Pharmacotherapy in patients with PDB is aimed at reducing bone pain at affected sites and to diminish the osteoclast-mediated bone resorption in order to avoid further progression of the disease. Therefore, indications for pharmacotherapy are pain caused by the lesion itself and if mechanical loaded sites are at an increased risk of developing deformities or even fractures. Pharmacotherapy is also indicated in those patients who present with hypercalcemia caused by polyostotic manifestation or neurological symptoms due to nerve compression. In some cases it can be difficult to differentiate whether the patient’s pain arises from PDB or from coexisting complications, such as osteoarthritis. Moreover, the extent to which a pharmacological treatment can prevent the progression of deformities or whether existing deformities can actually be corrected is still open to question. Kanis and coworkers [24] have shown that treatment with bisphosphonates results in only a mild regression in patients with deformities of the long bones. Consequently, in these cases, early surgical correction has to be considered. Finally, there are no controlled, prospective, randomized trials which demonstrate that the activity or the progressive character of PDB as documented on routine conventional X-rays can be reduced or revised. To date, published data only show an effective blocking of PDB activity, as reflected by a reduction in the sAP level, with this decrease being due to the anti-osteoclastic therapy.

Two classes of compounds are currently available and approved for PDB treatment: bisphosphonates and

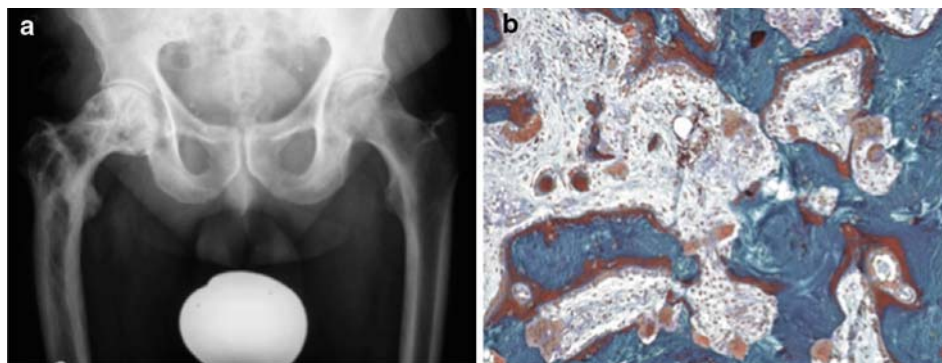


Figure 1. Radiological and histological appearance of patients with Paget disease of bone. a) Conventional X-ray with Pagetic involvement of the right proximal femur with varus deformity. b) Cancellous bone with broadened and plump trabeculae, wide red-stained seams of osteoid, and a highly increased number of both osteoclasts and osteoblasts (undecalcified preparation, Goldner's trichrome stain, $\times 100$).

calcitonin. Although calcitonin has been shown to reduce the activity of PDB, its importance as a pharmacotherapeutic drug for treating PDB has declined with the introduction of bisphosphonates. In addition, increases in the dosage or an extension of the treatment period with calcitonin does not result in a better suppression of PDB; rather, after its long-term use, a “resistance” to the calcitonin effects has been observed. In contrast, pharmacotherapy with bisphosphonates – including etidronate, tiludronate, pamidronate, alendronate, risedronate, and zoledronate – is currently the treatment of choice. Interestingly enough, treatment with third-generation bisphosphonates (alendronate, risedronate, and zoledronate) reduces the activity of the sAP towards the normal range more effectively than has been described for etidronate and tiludronate.

In a randomized study, the administration of 40 mg alendronate or 400 mg etidronate daily over 3 months led to a normalization of the sAP in 57% (alendronate) and 17% (etidronate) of the patients in each group, respectively [25]. Treatment with 5 mg zoledronate compared to 60 mg risedronate daily over 2 months resulted in a normalization of the sAP in 89% (zoledronate) versus 58% (risedronate) of the patients in each group, respectively [26]. In patients that do not show decreased sAP activity following the initiation of a bisphosphonate treatment, clinical recommendations include increasing the dosage, shortening the intervals of administration, and/or to changing the type of bisphosphonate. These recommendations are based on the fact that a resistance to bisphosphonate activities is not class specific but depends on the particular active ingredient administered. This rationale was proved by demonstrating that a change within the class of bisphosphonates (i.e., from one active ingredient to another) leads to a restart of the drug action [27]. Independent of the kind of bisphosphonate therapy, it is recommended that clinicians determine serum parathyroid hormone (PTH) and 25-hydroxy-vitamin D levels to assist in monitoring the calcium and vitamin D requirements. Calcium and vitamin D repletion must be performed, and normal serum concentrations must be maintained to avoid hypocalcemia.

Surgical Management of PDB

Although few patients with PDB need surgical treatment, successful surgical management of severe orthopaedic complications of this disease has markedly improved the quality of life for these patients [28]. Surgical procedures include long bone osteotomies, fracture fixation, spinal decompression, joint arthro-

plasty, and tumor resection. However, due to the hypervascularity and the high bone turnover rates in the pagetic lesions, certain specific characteristics of surgical treatment must be taken into account. In general, high output cardiac failure is not uncommon in elderly patients with a polyostotic involvement. The possibility of increased intraoperative bleeding should be anticipated; consequently, the use of an intraoperative cell saver is recommended [29].

Studies have shown that patients with PDB have an increased risk of developing heterotopic ossifications after hip arthroplasty [30]. Although it was feared that patients with PDB might develop early loosening of the implants, Parvizi and colleagues were able to demonstrate an excellent outcome in this patient group using uncemented implants. Their results in the PDB group were comparable to those for the patients of the control group [31–33]. However, some authors still recommend perioperative radiation and/or prophylactic bisphosphonate administration in patients who undergo total hip arthroplasty (THA). In summary, hip arthroplasty relieves pain and restores the mobility in patients with PDB.

Fractures are well-recognized complications in patients with PDB and need special attention. Although published data are rare, increased complication rates after surgical treatment have been described, such as bleeding, delayed union, and the development of compartment syndromes. All of these complications resulted in a prolonged rehabilitation period. In contrary to the potential problems elicited by surgical therapy, an increased mortality rate was reported for those patients whose fractures were treated conservatively [34].

Bowing deformities of the femur and tibia are generally accepted in elderly patients and do not warrant treatment – if they present as singular deformities. Despite this, severe bowing with a bone that is prone to fracture should be treated by a corrective osteotomy. Although published data are rare, Louette and coworkers described a higher rate of complications in such instances, such as delayed union in the patients with PDB.

The malignant transformation of PDB is the most devastating complication that can occur in this skeletal disease. In comparison to the juvenile, conventional osteosarcoma, the survival rate in patients with Paget sarcoma has not improved during the last decades despite the implementation of a neoadjuvant chemotherapy and better surgical skills in tumor therapy [13]. Paget sarcoma is mainly diagnosed in elderly patients with a polyostotic manifestation that presents at higher stages; consequently, neoadjuvant chemotherapy is

often limited due to the patient's general condition. If surgical resection is elected as the treatment option, it should be performed in experienced orthopaedic-oncology centers because of the large number of potential complications that put the patient at risk. In surgery, resection, which leaves a wide safety margin, is the treatment of choice. As an additional safety measure aimed at reducing peri- and postoperative complications, it is recommended that patients with PDB be treated with bisphosphonates 6 weeks to 3 months before they undergo elective surgery [23].

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