

Latest Research Advances in Paget's Disease of Bone

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Abstract: Paget's disease of bone (PDB) is a non-inflammatory, metabolic skeletal disease. It is characterized by excessive bone resorption and irregular bone reconstruction. Its onset is often associated with both genetic and environmental factors. PDB is characterized by a very distinct geographical distribution, being more common in Western countries and rarer in Asia. The most significant susceptibility gene at the moment is *SQSTM1*. The imbalance between osteoclasts and osteoblasts is the main mechanism of its pathogenesis. The pelvis, spine, skull, femur, and tibia are most commonly involved, with less involvement in the upper limbs, clavicle, ribs, and scapula. It is less common before the age of 40, is predominantly male, and has a positive correlation between age and incidence. Pain and bone deformities are common manifestations of PDB. The diagnosis of PDB depends on imaging and biochemical markers. For the detection of PDBs, radionuclide bone scan is a more accurate test. Bisphosphonates are currently the leading therapeutic agent, and it has been shown that intravenous zoledronate provides remission in most patients and can prevent disease progression. In recent years, the number of related cases in China has gradually increased. The article summarizes relevant literature and analyzes relevant progress in order to provide help in the diagnosis and treatment of PDB.

Keywords: Paget disease of bone; Bisphosphonate; Diagnosis; Treatment

1. Introduction

Paget's disease of bone is a rare benign osteometabolic disorder that usually presents with abnormal bone remodeling in one or more regions of the skeleton, including osteolysis and abnormal bone formation. The early stage of the lesion is usually characterized by excessive osteoclast activity, which sometimes leads to radiolytic lesions. Subsequently, osteoblasts predominate, which is manifested on imaging as a localized increase in bone density, sometimes leading to localized deformities. These alterations result in skeletal regions becoming disorganized, with increased vascularization and increased skeletal fragility. Some diseases are consistent with PDB and need to be identified, including familial expansive osteolysis, expansive bone hyperphosphatemia, early-onset familial Paget's disease, juvenile Paget's disease, and whole bone expansion bone disease. These diseases are rare hereditary bone diseases, and the age of onset is earlier and more serious. PDB has long been considered a difficult disease to treat, and since the first clinical case was reported in 1876^[1], disease activity could not be fully controlled until the advent of the use of calcitonin. However, over time and with the discovery of bisphosphonates, the treatment of PDB has improved significantly. We are now able to treat it for temporary relief of bone pain and long-term relief of symptoms and prevention of common complications such as bone deformities, fractures and eventually tumor degeneration. At present, PDB has made some progress. First, the prevalence of PDB has significantly decreased in many nations, and second, the effectiveness of a single intravenous zoledronate injection in the management of PDB has been demonstrated. Intravenous injection of zoledronic acid once or twice can normalize bone cell activity and prevent disease progression.

This review summarizes the recent advances in the etiology, epidemiology, histopathology, clinical manifestations, diagnosis and evaluation, treatment and prognosis of PDB in this analytical paper.

2. Etiology

Genetic factors play a key role in the pathogenesis of PDB^[2]. The majority of the possible pathways associated with germline mutations in various genes are connected to the regulation of osteoclast differentiation and function. Six loci that predispose to the condition have been found through genome-wide association studies, and an additional eight genes have been found through family-based genetic research to be involved with PDB. With this, there are now 14 genes and loci in PDB. Nearly all are connected to the biology of osteoclasts. The genetic basis of PDB is complex and involves a number of genes. Among them, the SQSTM1 mutant gene is the most important susceptibility gene known, and about 30% of patients with familial PDB and about 10% of disseminated cases carry the SQSTM1 mutant gene^[3]. The majority of SQSTM1 mutations disrupt proteins' ubiquitin-binding domains and are linked to PDB clinical manifestations that are more severe^[4]. An autosomal dominant inheritance pattern is followed by at least one-third of patients, and as they age, their performance rate gradually rises, increasing the risk of first-degree relatives to as much as 50%. Within familial PDB, the disease is usually inherited in an autosomal dominant pattern of inheritance, albeit with an incomplete penetrance, is often diagnosed at a young age, and is more likely to be accompanied by polyostotic symptoms^[5, 6]. The percentage of patients who have a family history varies greatly by nation, from roughly 5% in the Netherlands to 50% of the French Canadian population. 12% to 15% of PDB patients in the UK and Italy had a family history. The stark differences between races serve to emphasize the significance of genetic variables even more. These variations in prevalence and severity imply an intimate relationship between environmental factors and the development of many diseases.

Environmental factors also play a role in PDB, including calcium or vitamin D deficiency, toxin exposure, chronic viral infection, skeletal trauma, etc. The probability of skeletal involvement in PDB is quite similar to the probability of skeletal involvement in hematogenous osteomyelitis, suggesting that circulating infectious agents may play a role in the pathogenesis of the disease. Studies of lentiviruses of the paramyxoviridae family have provided some support for this pathogenesis hypothesis, but there are conflicting results on the presence of viruses in PDB osteoclasts^[7, 8]. Nevertheless, there is ample proof that paramyxoviruses and viral proteins can encourage the development of osteoclasts that resemble PDB osteoclasts^[9, 10]. In contrast, the interaction between genetic variation and environmental factors and the mechanism of affecting susceptibility and disease severity are currently unknown. Clinical and experimental observations imply that, in the absence of concurrent interventions by related variables like viral infection, genetic susceptibility may not be a necessary requirement for the clinical development of PDB, at least in a portion of individuals^[4]. Although it is currently thought that genetic and environmental variables interact to generate PDB, more research is still needed to fully understand the pathophysiology of this medical disorder.

3. Epidemiology

PDB is the second most common bone metabolic disease after osteoporosis. An analysis of archaeological skeletons in the north of England found an overall prevalence of PDB of 2.1% in cases over the age of 40. The prevalence was 1.7% before 1500 and 3.1% after 1500^[11]. Additionally, because PDB typically begins beyond the age of 40 and is asymptomatic for a very long time, its prevalence may be overestimated. PDB has a very distinct geographical distribution, with different prevalence rates in different ethnic/geographic groups. It is common in England, the United States, Australia, New Zealand, Canada, South Africa and France, but rare in Asia. A report based on the study of the bones by archaeologists, the disease might have started in England before spreading to the rest of Europe and beyond^[12]. PDB is rarely diagnosed before the age of 40, and the prevalence increases with age, with a higher incidence in men than in women. In areas that were once considered to have no PDB, the number of reports of the disease has gradually increased. However, this situation may be more a reflection of increased awareness of the disease more than increased prevalence. In addition, there is evidence that in recent decades, the incidence of PDB in some countries has decreased significantly^[13, 14], and the severity has also been alleviated^[15].

4. Histopathology

In the early osteolytic stage of PDB, the number and volume of osteoclasts in the lesion increased, and the number of nuclei increased significantly with polymorphic nuclei^[16]. And there is an increased capacity to take up osteoclastogenic factors and some resistance to apoptosis. In addition, alterations in

the bone marrow microenvironment may also reinforce the osteoclast defect. At the same time, PDB lesions are associated with an increased number of immature osteoblasts in the region^[17]. As osteoclast activity progresses, the normal bone marrow in the medullary cavity is replaced by highly vascularized fibrous tissue^[18]. When bone is absorbed, they are phagocytized by osteoclasts and inhibit farnesyl pyrophosphate synthase, which is a key enzyme in the mevalonate pathway. This can lead to osteoclast cytoskeleton fracture and death^[17]. In the stage of coexistence of osteogenesis and osteolysis, osteoblasts form new woven bone, and repeated bone resorption and deposition form many irregular lamellar bone fragments. Lamellar bone and woven bone are mixed to form the 'mosaic' or 'jigsaw' pattern^[19]. As the disease is controlled, osteogenesis dominates, bone sclerosis becomes thicker, the structure is disordered, the pressure-bearing capacity is reduced, the vascular fibrous tissue is reduced accordingly, the bone marrow hematopoietic function is restored, and the biochemical markers return to normal. However, newborn bones are disorganized and lack the normal laminar pattern, so they are of poor quality and prone to deformities and fractures.

5. Clinical manifestation

The main symptoms of PDB are bone pain and deformity, and its signs and symptoms depend largely on the location involved. The most common bones involved in PDB were pelvis, femur, spine, skull and tibia, while upper limbs, clavicle, ribs and scapula were less affected^[20]. Lesions involving the vertebral body or articular surface may produce serious symptoms, whereas relatively extensive jaw involvement may not cause obvious dysfunction. PDB often causes bone pain, and the bone pain is more serious at night. If there are osteolytic lesions, bone pain may be more serious during weight-bearing. In the study by Tan et al^[21], 52.2% of cases were bone pain followed by deformity (21.5%) while deafness and fracture were found in 8.9% and 8.5% respectively, whereas most of the idiosyncratic manifestations including obstructive hydrocephalus and spinal stenosis were caused by abnormal bone remodeling. Nevertheless, the mechanism of pain in PDB is not fully known yet. The most serious consequences of PDB include osteosarcoma, chondrosarcoma, and fibrosarcoma, although their incidence is less than 1%^[2]. The skeletal malformations caused by PDB are mainly the protrusions of skull or forehead and the bending deformity of long bones. Long bone deformities often occur in patients who have not been treated for a long time, and the bending limbs are usually shortened, resulting in an abnormal fixed gait, which leads to abnormal mechanical stresses and a possible fissure fracture on the convex side of the bone^[22]. The typical symptoms of cranial PDB are enlargement of the skull or flattening of the occipital region. Facial skeletal deformities are more common, resulting in a lion-like appearance^[23]. Approximately 17 % of patients diagnosed with PDB have jaw involvement, and maxillary involvement is more common^[19]. In addition to bone pain, the progression of PDB usually leads to a number of complications, including osteoarthritis, hearing loss, and other neurological manifestations of nerve compression, and more rarely, tumor degeneration. PDB has long been a difficult disease to treat until calcitonin became the first antiresorptive agent and the subsequent discovery of the more effective bisphosphonates. Treatment at an early stage is essential in order to halt the progression of abnormal bone morphology lesions, as well as to prevent complications caused by abnormal bone transformation and overgrowth.

6. Diagnosis and evaluation

PDB is usually diagnosed on the basis of typical findings on plain radiographs. Common abnormalities include osteolysis, coarsening of the trabecular pattern, osteosclerosis, and bone deformities. The most unusual observations included the existence of aberrant trabeculae, crooked cementum lines, increased vascularity, and an increase in the quantity and size of osteoclasts. The early osteolytic phase of PDB is shown by decreased bone density and altered trabecular patterns, most commonly in the frontal and occipital bones of the skull, followed by the long bones of the lower extremities, with lesions usually appearing at one end of the bone and seldom in the diaphysis. In the absence of treatment, the margins of the lesion extend into normal bone at an average rate of about 1 centimeter per year^[24]. While older lesions frequently have a mixed appearance of sclerosis and solubility, early PDB may mostly present as lytic lesions. The osteogenic stage of PDB is characterized by patches of sclerotic bone formation. The patchy hardened area is usually described as a 'cotton wool-like' sign^[25]. With the development of the sclerosis period, the long bones of the lower limbs often appear bending deformity. Another radiological feature of PDB in the long bones of the lower extremities is the presence of a linear transverse fissure fracture in the cortex of the convex surface of the arched bone^[26]. Although it usually remain stable, a small percentage of patients progress to a

complete fracture. Sclerosing lesions, bone growth and deformation, and apparent radiographic patterns are the hallmarks of late PDB. One defining characteristic of PDB is increased bone diameter^[27].

Radionuclide bone scan is a more sensitive method to detect PDB^[28]. In 1974, the use of Technetium-99m (Tc-99m) labeled bisphosphonates opened the era of routine use of bone scanning in clinical medicine. Five minutes after intravenous injection of Tc-99m-labeled bisphosphonates (most commonly Tc99m-methylene diphosphonates), radionuclide activity in the affected bones increased. Multiple bone involvement can be discovered using radioisotope bone scanning. But during the early stage of osteolysis, the metabolic activity decreased, the lesion was not active, and the bone scan may be negative^[22]. Therefore, it should not be used as the sole basis for diagnosing PDB in clinical diagnosis, but should be combined with X-ray or CT.

Several biochemical markers of bone turnover can be used to diagnose and monitor PDB. Serum total alkaline phosphatase is the most widely used biochemical marker of bone turnover, and it is often used clinically to measure PDB activity, but there are limitations and the accuracy is reduced in patients with liver disease^[29]. Therefore, liver function tests should be performed when measuring serum total alkaline phosphatase to ensure that the source is bone rather than liver. Serum procollagen type I N-propeptide (PINP) and bone-specific alkaline phosphatase are markers of osteoblast activity, with sensitivity and specificity superior to non-specific total alkaline phosphatase activity, but with the disadvantage of higher cost^[30, 31]. The level of PINP can better indicate the PDB disease activity in patients with liver disease. Bone resorption markers are also significantly increased in active PDB. The commonly used bone resorption markers are serum C-terminal telopeptide, urine C-terminal telopeptide and urine N-terminal telopeptide. A correlation analysis showed that PINP had the highest correlation with PDB disease activity, and when it is unavailable, total alkaline phosphatase and urine N-terminal telopeptide are recommended to track disease activity after treatment^[29].

It is important to note that when in the early osteolysis stage, or when there is only localized skeletal involvement, biochemical markers may be normal despite the presence of imaging abnormalities. Therefore, normal biochemical markers cannot completely rule out PDB.

Early treatment is essential in order to halt the progression of PDB lesions and prevent some of the complications caused by abnormal bone transformation and overgrowth. It may not be sensitive enough to reliably detect PDB in early and asymptomatic cases if just genetic or bone indicators are used. For detection, it is therefore best to combine a number of diagnostic indicators. The PDB phenotype can be identified more precisely by screening for SQSTM1 gene mutations in conjunction with gene panels or a combination of genetic and biochemical assays^[32]. The lack of symptoms in about 70% of PDB patients makes early identification difficult. First-degree relatives are more susceptible to sickness, and 15% to 40% of patients have a positive family history. For family members at risk, serum alkaline phosphatase testing is advised every two to three years. For patients to have a better outlook and avoid problems, early detection and treatment are crucial.

7. Therapy

7.1. Medication

PDB is a chronic disease and progresses slowly. Patients with limited and asymptomatic bone involvement in the early stages of the disease usually do not require treatment. When bone pain develops, bisphosphonates and analgesics and nonsteroidal anti-inflammatory drugs are recommended for control. Other anti-PDB drugs, such as calcitonin and bisphosphonates, can reduce bone turnover and improve abnormalities in biochemical markers.

Calcitonin is one of the earliest drugs used to treat PDB. Calcitonin is a peptide hormone secreted by thyroid parafollicular cells that binds directly to receptors on the surface of osteoclasts. Calcitonin is the earliest effective drug for the treatment of PDB. Salmon calcitonin has a faster inhibitory effect on osteolysis. If patients cannot tolerate parenteral and oral bisphosphonates, it is recommended to consider the use of calcitonin for treatment. Calcitonin is also the first choice for patients with impaired renal function who cannot use bisphosphonates. Calcitonin is also the first choice for patients who pursue rapid pain relief^[33]. Salmon calcitonin has now been shown to reduce vascular distribution in PDB-affected bones, so that preoperative administration of salmon calcitonin can reduce bleeding during orthopedic surgery^[34]. However, since salmon calcitonin is a foreign protein, the patient's body will produce antibodies, and long-term use will produce significant drug resistance^[35]. In addition, salmon calcitonin may cause nausea and facial flushing in 10-20 % of patients. Other uncommon side

effects include vomiting, abdominal pain, diarrhea, and polyuria. Due to the need for daily injections and the frequent occurrence of side effects such as flushing or nausea, patients have limited acceptance of it. After stopping treatment, the disease will relapse rapidly. With the development of bisphosphonates in recent years, the use frequency of salmon calcitonin has decreased significantly.

Bisphosphonates are currently considered as the first choice for the treatment of PDB^[36]. The main effect is to inhibit osteoclasts thereby reducing bone resorption. At present, pamidronate, alendronate, risedronate and zoledronate are commonly used^[37]. Alendronate and risedronate are orally administered and need to be taken with water. (1)The dose of alendronate was 40 mg / d for 6 months. (2)Risedronate was administered at a dose of 30 mg / d for 2 months. The patient must be taken with water on an empty stomach in the morning, and fasted for 30 min after taking the medicine to achieve full absorption. It is generally recommended that patients stay upright for at least 30 min after taking the drug to minimize esophageal stimulation. Pamidronate and zoledronate are given intravenously. (3)The standard regimen of pamidronate was intravenous injection of 30 mg within 4 h for 3 consecutive days; a common regimen is that a single 60-90 mg infusion can be given to less severe patients, while more severe patients can receive multiple 90 mg infusions. (4)The dose of zoledronate is 5 mg administered intravenously within 15 min, with the vigilance that the patient's creatinine clearance rate must be greater than 35 ml/min, as bisphosphonates can cause kidney injury and are contraindicated in patients with severe kidney damage^[38]. Vitamin D deficiency and hypocalcemia need to be corrected before infusion, and 1500 mg of calcium and 1000 units of vitamin D3 need to be given daily for two weeks after infusion to reduce the risk of hypocalcemia after infusion. The first intravenous injection of pamidronate or zoledronic acid may cause transient acute reactions such as bone pain, myalgia, headache, nausea, fever and fatigue after infusion^[39]. Reinjection rarely produces side effects. Vitamin D deficiency can aggravate the acute phase response, so vitamin D supplementation in patients with vitamin D deficiency is effective in preventing acute phase response^[40]. There was no significant difference in the therapeutic effect between the two routes of administration^[27].

At present, it is generally believed that a single intravenous injection of 5 mg zoledronic acid is the first-line treatment for PDB^[27, 33]. This is because it is superior to other drugs in inducing biochemical remission and continuous remission time. A single infusion can restore the biochemical markers of bone turnover to the normal range and last for up to 6 and a half years in most patients^[41].

7.2. Operation

Although bisphosphonates are the main treatment for PDB, disease-related complications may require surgical treatment. Arthroplasty is a common method for the treatment of osteoarthritis associated with bone deformity and subchondral bone sclerosis^[42]. Total hip arthroplasty (THA) and total knee arthroplasty (TKA) are common orthopedic surgeries for PDB patients and most patients can relieve pain and improve mobility^[43-45]. Postoperative heterotopic ossification is usual but mostly not serious. Osteotomies are effective for curved deformities of the tibia and femur. Preoperative medication control is needed to minimize neovascularization and reduce the risk of blood loss. One study showed that the risk of surgical complications in patients with PDB after hip or knee arthroplasty did not increase compared with the normal population^[42]. However, one patient who was not diagnosed with PDB before surgery had prosthesis loosening after hip replacement and failed after revision, indicating that untreated PDB patients may lead to loosening of joint replacement components^[46].

Normalization of markers is often used clinically as the endpoint of PDB treatment. However, minimal disease activity has been found in some patients with normal biochemical markers, while the second infusion of zoledronic acid was completely relieved. For spinal PDB paraplegia and femoral and tibial lytic lesions, it is important to confirm imaging healing, not just normal markers. Symptom relief, improvement of quality of life, and cessation of disease progression are the treatment endpoints that should be pursued.

8. Conclusions

PDB is a rare metabolic bone disease in China, which is characterized by osteolysis and abnormal reconstruction. Untreated PDB is not an inert disease, on the contrary, it is a progressive disease that spreads along the affected bone, resulting in pain, deformity, and even disability. Overly conservative treatment may lead to unpredictable disease progression in patients. Therefore, the main goal of treatment is to restore normal bone turnover process, to reduce bone pain or other symptoms, and to

prevent complications^[47]. Intravenous injection of zoledronate is the first line of treatment for PDB, which can prevent the progression of skeletal malformations, heal osteolytic lesions, reduce pain and improve quality of life. Single infusion can well control disease activity for a long time, which is helpful to significantly improve the prognosis and clinical management of PDB. Compared with Western countries, the age of onset of PDB patients in China is earlier and the symptoms are more serious. In China, the misdiagnosis rate of PDB is as high as 36.0%, and it is often misdiagnosed as malignant tumor bone metastasis and fibrous alloplastic hyperplasia^[20]. Patients with mild or asymptomatic symptoms are also easily overlooked, and most clinicians are not familiar with the disease. Combined with the current situation of PDB in China and the differences between China and the West, we believe that in the later stage, we should further expand the scope of research, formulate more comprehensive and localized diagnosis and treatment norms, and discover, diagnose and intervene in the occurrence of diseases earlier.

Acknowledgement

[Foundation Project]: Changzhi City Science and Technology Bureau Fund Project (NO.2022sy008)

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