Diagnosis and management of Paget's disease of bone

Diagnóstico e tratamento da doença de Paget óssea

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ABSTRACT

Objective: To conduct a literature review on the diagnosis and management of Paget's disease of bone. **Materials and methods:** This scientific statement was generated by a request from the Brazilian Medical Association (AMB) to the Brazilian Society of Endocrinology and Metabolism (SBEM) as part of its Clinical Practice Guidelines program. Articles were identified by searching in PubMed and Cochrane databases as well as abstracts presented at the Endocrine Society, Brazilian Society for Endocrinology Annual Meetings and the American Society for Bone and Mineral Research Annual Meeting during the last 5 years. Grading quality of evidence and strength of recommendation were adapted from the first report of the Oxford Centre for Evidence-based Medicine. All grades of recommendation, including "D", are based on scientific evidence. The differences between A, B, C and D, are due exclusively to the methods employed in generating evidence. **Conclusion:** We present a scientific statement on Paget's disease of bone providing the level of evidence and the degree of recommendation regarding causes, clinical presentation as well as surgical and medical treatment. Arq Bras Endocrinol Metab. 2014;58(6):587-99

Keywords
Paget's disease of bone; diagnosis; treatment

RESUMO

Objetivo: Conduzir uma atualização das últimas evidências científicas a respeito da apresentação, diagnóstico e manejo clínico da doença de Paget óssea. **Materiais e métodos:** Este documento foi concebido pelo Departamento de Metabolismo Ósseo da Sociedade Brasileira de Endocrinologia e Metabologia (SBEM) a partir daquele oriundo do Programa de Diretrizes da Associação Médica Brasileira (AMB). Realizamos uma revisão dos artigos mais relevantes obtidos nos bancos de dados PubMed e Cochrane, além de abstracts apresentados nos encontros anuais da *Endocrine Society*, Sociedade Brasileira de Endocrinologia e da *American Society for Bone and Mineral Research* dos últimos cinco anos e classificamos as evidências em níveis de recomendações de acordo com a força científica por tipo de estudo, adaptando o primeiro relato do "*Oxford Centre for Evidence-based Medicine*". Todos os graus de recomendação, incluindo-se o "D", foram baseados em evidência científica, sendo as diferenças entre o A, B, C e D devidas exclusivamente ao desenho empregado na geração da evidência. **Conclusão:** Apresentamos uma atualização científica a respeito da doença de Paget óssea, classificando e graduando em níveis de recomendações as principais evidências científicas sobre as suas causas, as variadas formas de apresentação, seu diagnóstico e tratamento. Arq Bras Endocrinol Metab. 2014;58(6):587-99

Descritores
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INTRODUCTION

Paget's disease of bone is a metabolic bone disease characterized by very high rates of bone remodeling which lead to bone expansion, trabecular disorganization with a consequent decreases in strength and quality (1). It has avariable geographic distribution worldwide,

being most commonly encountered in white Europeans, and those of European descent over 55 years of age (2,3). In Brazil, a prevalence study in a city originally colonized by Europeans identified rates comparable to those encountered in southern Europe (3). The etiology of the disease remains controversial, but genetic factors are involved as well as environmental factors (1,4). The diagnosis is made primarily by characteristic radiological findings and the most common complications are pathologic fractures, bone deformities and osteoarthrosis.

MATERIALS AND METHODS

This scientific statement was generated by a request from the Brazilian Medical Association (AMB) to the Brazilian Society for Endocrinology as part of its Clinical Practice Guidelines program. Through the Brazilian Society for Endocrinology's Department of Bone Metabolism, a task force was established. A draft of this report was submitted for comment to the membership of the Brazilian Medical Association and Brazilian Society of Endocrinology. This report represents the completion of this process.

Grading quality of evidence and strength of recommendation were adapted from the first report of the Oxford Centre for Evidence-Based Medicine, detailed described elsewhere (5) and summarized in table 1. Grades of recommendation are reported, as follows:

A: More consistent experimental or observational trials.

B: Less consistent experimental or observational trials.

C: Case reports (non-controlled trials).

D: Opinion without critical evaluation, based on consensus, physiological studies or animal models.

Table 1. Grades of recommendation and strength scientific evidence

A	1 A	Systematic review of randomized controlled trials Systematic reviews of prospective cohort studies
	1 B	Individual RCT with narrow confidence interval Prospective cohort studies
B	2 A	Systematic review of retrospective cohort studies
	2 B	RCT with > 20% dropout Retrospective cohort studies
	3 A	Systematic review of case-control studies
	3 B	Individual case-control studies
C	4	Case series
D	5	Expert opinion

RCT: randomized controlled trials.

Articles were identified by searching in PubMed and Cochrane databases, as well as abstracts presented at the Endocrine Society, American Society for Bone and Brazilian Society for Endocrinology Annual Meetings during the last 5 years. References are listed numerically in order of appearance in the text, followed by the levels of evidence.

EPIDEMIOLOGY

The highest prevalence of Paget's disease of bone is found in England, the United States, Australia and New Zealand, mainly among patients older than 55 years (4). In other locations, such as Asia, it is a rare disorder (6,7) (C4), as it is in Scandinavia (4) and most of Latin America (8) (C4).

PDB has been linked to white ancestry in European and other countries, being less common in people who are not of European origin. A study published in 2006 on reported cases of Paget's disease in Latin America over the past 30 years showed that a total of 1,149 cases of Paget's disease had been previously published in Latin America, more than half of them in Argentina and Brazil (9) (C4).

One report from Italy showed a 0.74% radiographic prevalence (n = 8 of 1,068 patients evaluated) of pelvic PDB in rural regions of Calabria, located in the southern part of the Italian peninsula, with a male: female ratio of 5:3 and a mean age of 71.6 ± 13.1 years (10) (C4). The region of Campania, also in southern Italy, was shown to be an area with a high prevalence of Paget's disease (11) (C4).

PDB rarely appears before the age of 40, but its prevalence tends to double every decade starting at the age of 50, rising to approximately 10% after ninth decade (12).

Seitz and cols. retrospectively evaluated the bone biopsies and medical records of 754 patients historically proven to have PDB and found the peak incidence to occur between the ages of 70 and 80 years (13) (B3b).

A study from Spain evaluated 4,528 radiographs, including all those of the lumbar vertebrae, pelvis, sacrum and femoral head in 13 centers studied, reporting a 1% incidence of PDB (95% CI: 0.7 to 1.3) in subjects over 55 years age and an estimated prevalence ranging from 1.1% (95% CI: 0.8 to 1.4) to 1.6% (95% CI: 1.1 to 2.1), with pelvic involvement reported in 60-90% of patients considered to have PDB. The prevalence was slightly higher in men than in women and significantly greater

in individuals over 75 years of age. A considerable geographical variation in the prevalence was observed (p = 0.004) in Spain, with 73% of the patients unaware of their disease when the radiographs were taken (14) (B3b).

One study, from the US, found a diagnosis of PDB in 236 residents of Olmsted County, Minnesota, with a mean age of 69.9 years at diagnosis, 55% of those affected being men (15) (C4).

Paget's disease of bone is extremely rare in Asia (16), especially in Korea (17), and among ethnic Chinese (18) (C4). It is also very rare in Japan. A review of the literature was carried out of all cases reported in Japan from January 1990 to December 2002. Most cases (72.1%) were reported by the Department of Orthopedic Surgery and a prevalence of 2.8 cases per million capita was detected, confirming the rareness of the disease in Japanese (19) (B3b).

There is little information available on the existence of the PDB in the Arab world. A recent study reported four cases of Arab patients with PDB, with variable presentations, characterizing the existence of the disease in the country studied (20) (C4).

A number of studies have reported an unexplained downward trend in the prevalence of PDB, some postulating that the disease will become increasingly rare in the future (21,22) (B3b). A review of approximately 2,000 pelvic radiographs, estimated the prevalence of the disease in individuals of European descent, over 55 years of age, in two New Zealand cities (Dunedin and Auckland). The prevalence rate increased with age (p = 0.022), being higher in men (p = 0.014), but showing no significant gender difference in either of the two cities. The Dunedin data was compared to that of another study in the year 1983 in the same city, with the prevalence now being roughly half the previous level (p = 0.012). In Auckland, the prevalence of an isolated raised plasma alkaline phosphatase level (> 150 U/L, normal range < 120 U/L) was estimated in over 80,000 blood samples processed at a community laboratory. The prevalence of "biochemical Paget's disease", as measured, was very similar to that seen in a radiographic study of the same city involving subjects under 80 years of age, but not for dose over 80 (23) (B3b).

There are also reports, as in an Australian study, of a decrease in incidence and severity of the disease in newly diagnosed cases, but for unknown reasons (24), with more cases of monostotic disease, whose incidence has doubled in the last 30 years. Some reports suggest that these findings are more evident in women, as in a study conducted in England (25) (B3b).

The prevalence of PDB in Italy was assessed based on radiography, scintigraphy, and biochemical data from two Italian cities, Siena (central Italy) and Turin (northern Italy). At the end of the radiological survey, 16 of 1,778 cases of pelvic PDB (8 men and 8 women) were observed in Siena, and 41 of 6,609 cases (27 men and 14 women) in Turin. Disease prevalence was 0.89% in Siena, and 0.62% in Turin. Since pelvic involvement is normally described in 60 to 90% of the patients with PDB, the overall estimated prevalence ranged from 1.0 to 1.5% in Siena, and 0.7 to 1% in Turin. No decrease in the prevalence of PDB was evident after comparison of prevalence rates during different time periods. Biochemical analyses showed that 296 of 7,449 subjects had elevated levels of alkaline phosphatase and normal liver enzymes, 87 of whom had a confirmed diagnosis of PDB. The estimated biochemical prevalence was 1.5%. The scintigraphy study showed an estimated prevalence of PDB in 194 of 7,906 cases (2.4%), which was significantly higher than radiological and biochemical estimates. This study suggests that PDB in Italy has an estimated prevalence of at least 1%, comparable to what has been observed in the United States, and some European countries, but lower than that reported in Great Britain and New Zealand. No secular trend indicating decreased prevalence of PDB was observed in this study (26) (B3b).

Figure 1 illustrates the extensive geographical variation in prevalence of PDB worldwide.

Figure 1. Worldwide prevalence studies of Paget's disease of bone.
Prevalence studies.
Case series: 145.
Data from references 3,14,21,24,26-33.

EPIDEMIOLOGY OF PDB IN BRAZIL

Epidemiological data on Paget's disease of bone in Brazil are scarce. There are case reports from Rio de Janeiro, published in 2000, of PDB involving the maxilla (34)

(C4) and in 2002 a case series from Recife retrospectively analyzed the characteristics of 89 cases (35)(C4).

The colonization of Pernambuco was strongly influenced by immigrants from Portugal and Holland, many of whom were Jews. In Recife, the occupation by the Dutch and Jews continued after the initial colonization by the Portuguese for political and administrative reasons, which may explain the high frequency of PDB in the state of Pernambuco (8,36) (C4).

Bandeira and cols. reported an analysis of 108 cases diagnosed in two centers in Recife between 1984 and 2005 and found that about 90% of the patients were of European ancestry. The mean age at diagnosis was 66.2 years; 49.1% were men; the polyostotic form of the disease was the most common; light-colored eyes were observed in 22.2% of the patients (data on Brazilian general population is not available); 23.1% of the patients were shown to have a family history of PDB. The most affected skeletal locations in this study were the pelvis, lumbar vertebrae, femur and cranium. It was also found that zoledronate was the most effective drug in reducing alkaline phosphatase in these patients (8) (C4).

A Brazilian study about the epidemiology of PDB in Brazil evaluated patients aged 45 years or older attending the Osteoporosis Center of the Department of Endocrinology and Diabetes of Pernambuco between January of 2006, and December of 2009. The age-related period of prevalence and incidence density were both calculated, separately for men and women for each year. A total of 7,752 patients were evaluated, 53 of whom had PDB. The mean age of patients was 69.53 ± 8.51 years. The overall prevalence of PDB was 6.8 per 1,000 patients (p = 0.013, 95% CI 5.1 to 8.9), and the incidence density of PDB was 50.3 per 10,000 person-years (p = 0.026 95% CI 35.8 to 68.8). The prevalence and incidence both increased in both sexes during this period. These data shows that both the prevalence and incidence of PDB in Recife are comparable to the corresponding rates in southern Europe (3)(B3b).

A case series from the city of Florianopolis, retrospectively evaluated data from patients enrolled in 6 centers between 1995 and 2009. A total of 134 patients with PDB were identified, with a mean age at diagnosis of 63.2 + / -10.5 years, of whom 67.2% were women and 91.1% white. A positive family history was observed in only 8.2% of patients. Polyostotic disease was found in 75.0%, bone pain in 77.9%, and bone deformities in 15.9%. Higher levels of alkaline phosphatase showed a significant association with both the
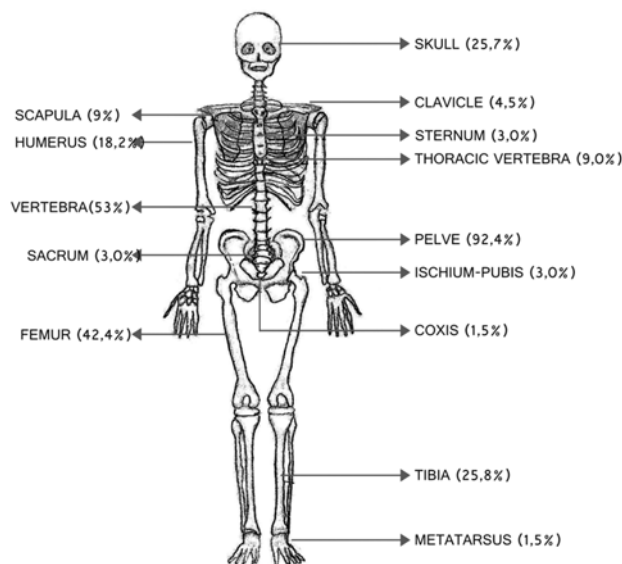
Figure 2. Sites of bone involvement in 108 cases of polyostotic Paget's disease of bone (PDB).
Data from reference 8.

polyostotic form of the disease and involvement of the cranium. The pelvic bones were the most frequently affected (53.7%). Treatment with zoledronic acid produced the best results, with only 2.9% of the patients failing to show anadequate response (37) (C4).

ETIOLOGY

The etiology of the disease remains controversial, with evidence that genetic along with environmental factors are involved. *SQSTM1 (sequestosome 1 encoder)* is the most important gene that has been associated with the disease up to now (38) (B3b).

Various loci of susceptibility have been linked to the disease, including *SQSTM1* and *TNFRSF11A (encoder of the RANK)* on chromosome 18q21-22.*SQSTM1*, also known as p-62 or sequestosome 1, located on chromosome 5q35, which is a signaling protein that appears to be involved in the pathogenic mechanisms that increase the activity of osteoclasts. Random mutations (*P392L*) of this gene were detected in over 30% of PDB family members. The role of *SQSTM1/p62* has yet to be fully elucidated. There is evidence that mutations may reduce the ability to sequester cytoplasm proteins, altering nuclear factor kB (NF-kB), resulting in increased osteoclastogenesis (4). The action of osteoprotegerine (OPG) on the RANK receptor has also been described. The inhibitory effect of the OPG in the RANK/RANKL system suggests that mutations

causing function loss in the *TNFRSF11B* gene, encoding the OPG, could also lead to an activating effect in the signalization of NF-kB (39) (C4) and there are also evidence that *TNFRSF11A* gene allelic variants interact with *SQSTM1* mutations to cause the severity of the disorder (40) (B3b).

Not only genetic causes have been proposed as the etiology of PDB, biological hybridization studies (*in situ*), along with immunohistochemistry, have also suggested the possibility of infection of the osteoclasts by a virus, mainly paramyxovirus, as being the cause of PDB (4) and a study published in 2010 suggested that measles virus nucleocapsid gene expression and the *SQSTM1* mutation both contribute to the increased osteoclast activity in PDB (41) (B3b) (42) (C4).

A French study found that half of PDB familial forms carried a *SQSTM1* mutation (43) (B3b). Other loci that predispose to PDB were recently identified by genomic association studies that have identified variants at seven loci predisposing to the disease. These alone increase the risk of PDB from 1.3 to 1.7 times, but they have combined effects that affect about 86% of the PDB at-risk population with negative *SQST1* (42) (C4).

Recent studies also suggest that pro-inflammatory cytokines are involved in the pathophysiology of Paget's disease of bone. A recent control case study evaluated the genomic DNA for functionally active polymorphism of the genes of pro-inflammatory cytokines (interleukin-1α, interleukin-1 β, interleukin 6), and tumor necrosis factor α, involving 144 PDB patients and 115 healthy controls. The frequency of genotypes and alleles of the polymorphisms examined demonstrated practically identical results in both cases and controls. Regarding pro-inflammatory genes, patients with PDB genotype C/C gene of interleukin 6 (IL-6) showed significantly (p < 0.001) greater hearing loss and primary hyperparathyroidism. There were no significant differences in the other clinical features. This study does not support the hypothesis that the pro-inflammatory genes examined represent an important genetic risk factor for PDB. However, data suggests a role for the IL-6 gene in modifying the clinical characteristics of the disease (44) (B3b).

A study from New Zealand evaluated the relationship between family history, phenotype, and the state of *SQSTM1* mutation in patients with a family history, and/or severe phenotype of PDB. The severity of the phenotype was significantly associated with the *SQSTM1* mutation status, but not with family history (p < 0.005). *SQSTM1* mutations were found in 10.5% of the patients with early onset, and/or severe disease, but without a family history of the disorder (38) (B3b).

An earlier study of genomic association had already identified variants in loci *CSF1*, *OPTN* and *TNFRSF11A*, as risk factors for Paget's disease of bone, and an extension of this study identified three new loci and recently confirmed these associations with PDB in 2,215 affected individuals (cases), and 4,370 controls from seven independent population groups. The new associations were with *rs5742915* within *PML* on 15q24, *rs10498635* within *RIN3* on 14q32 and *rs4294134* within *NUP205* in 7q33 and also confirms the association of *TM7SF4* with PDB. These seven loci account for the familial risk for PDB in approximately 13% of cases (45) (B3b).

There are studies investigating the relationship between genetic polymorphisms and sporadic PDB, with the aim of identifying polymorphisms representing susceptibility to the disease. A recent study investigated the association between polymorphisms in three candidate genes and the functional development of PDB, *TNFSF11* (activator receptor of the nuclear factor Kb ligand, RANKL), *VCP* (valosina-containing protein), and IL-6 (interleukin-6), in 196 patients with sporadic PDB, and 212 Belgian control subjects, and revealed that *VCP SNP (rs565070)* was associated with PDB in this population study (p = 0.5). Through the use of genetic testing in the study, no association linking *TNFSF11* or IL-6 with PDB was confirmed. More data are therefore needed because when the VCP data is combined with data from other regions, involving susceptible genes in previous studies (i.e. the *TNFRS11A*, *CSF1*, *OPTN* and *TM7SF4* genes), the independent effect of each gene region was confirmed and the accumulated population attributable risk was 72.7% (46) (B3b).

Recent studies of genomic association (GWAS) confirm the role of the RANK gene in PDB, and also indicate the involvement of chromosomal regions that harbor the CSF1 and OPTN genes with PDB. A study in the Belgian and Dutch populations that attempted to replicate these findings also found an association between these genes and PDB, being most significant in the region of CSF1, followed by the OPTN and TNFRSF11A genes. A significant association was also discovered with a polymorphism in the chromosomal region of the TM7SF4 gene that encodes the DC-

STAMP, which had no significance in association with the genomic GWAS, but because of its effect on osteoclasts, can be considered a strong candidate gene. The cumulative risk attributable to these four loci calculated for the two populations studied was shown to be approximately 67%, indicating that the major part of the genetic risk for PDB comes from genetic variants close to these four genes (47) (B2b).

Patients with PDB without mutation of the *SQSTM1* gene seem to be susceptible to genetic polymorphisms in regions of the genes *CaSR*, *ESR1*, *TNFRSF11B (OPG)*, *TNFRSF11A (RANK)*, *CSF1 (M-CSF)*, *OPTN*, *TM7SF4 (DC-STAMP) VCP*, *NUP205*, *RIN3*, *PML*, and *GOLGA6A*, resulting in an increased risk for developing PDB. The nature of these genes suggests that the regulation of osteoclastogenesis has a key role in the pathogenesis of PDB. Moreover, the involvement of SQSTM1 and VCP in autophagy and the formation of protein aggregates suggest that the disruption of these processes may represent a risk factor (48,49).

There are also reports of a high prevalence of vitamin D deficiency in patients with PDB. One possibly reason for this is that osteoclast precursors have a high responsiveness and sensitivity to 1.25 (OH) 2D3, resulting in increased expression of co-activators of vitamin D receptors (VDR) in PDB (50) (C4).

In recent years there has been significant progress in the study of the epidemiology of PDB. However, we still lack a combined evaluation of genetic and environmental factors to enable us to fully understand their interaction with the etiology of the disease (D5).

CLINICAL MANIFESTATIONS

Most patients with Paget's disease of bone (PDB) are asymptomatic (51), having been incidentally diagnosed through findings from imaging or because of high serum levels of alkaline phosphatase (52) (C4).

The clinical spectrum of PDB is highly variable and depends on the sites affected, the type and magnitude of the complications, and the metabolic activity (53). Although the disease may affect any part of the skeletal structure, the pelvis, spine, cranium and long bones are the most often affected (15,54) (C4).

Bone pain is the most common symptom. In two recently published studies pain was found to be present in 40-45% of the patients. It is usually deep, precisely located and persists when the patient is at rest,

constant, exacerbated both at night and by weight overload. It may occur suddenly as a result of pagetic injury, or more frequently, from complications caused by the breakdown of bone structure, leading to conditions such as degenerative arthritis, nerve compression or sarcomatous degeneration (a rare occurrence present in only 1% of cases) (15,55) (C4).

Bone deformities are the second most common manifestation with a prevalence ranging from 12 to 36%. They occur most commonly in the femur and tibia, causing bending, which is characteristically anterolateral in the femur and anterior in the tibia. These deformities can lead to changes in gait and mechanical stress, increasing the likelihood of joint degeneration. Involvement of the cranium begins with circumscribed osteoporosis, followed years later by increases in volume, regions of sclerosis, an enlarged diploe and frontal bossing (15,55) (C4).

We suggest evaluation for PDB in all individuals over 50 years of age who present an unexplained elevation of serum alkaline phosphatase, as well as bone pain or deformities (C).

LABORATORY AND IMAGING PROCEDURES

PDB is associated with increased bone turnover, indicated by the elevation of biochemical markers for bone formation and resorption. This occurs because a high correlation between formation and resorption is maintained with PDB. The increase in these markers is proportional to the intensity, size, and number of lesions, and may be more pronounced in cases involving the cranium. Serum alkaline phosphatase, a bone formation marker, has been used for the diagnosis and monitoring of patients affected by the disease. However, none of the biochemical markers of bone remodeling are entirely specific to bone alone. Serum alkaline phosphatase has a sensitivity of 78%, and a specificity of almost 100%. However it may be normal in up to 20% of patients with monostotic disease (4,56,57). In a study by Bandeira and cols. serum alkaline phosphatase was shown to be elevated in 92% of the cases. The mean increase was significantly more pronounced in patients with the polyostotic form than in those with monostotic form of the disease (5.9 ± 2.8 *vs.* 2.2 ± 1.9 times the ULN) (58).

Osteocalcin, considered a specific marker for bone formation, was of limited value, whether for the diagnosis (normal in 40% of cases) of PDB or for the follow-up. Among the new markers of bone resorption, NTX and CTX-β have been shown to have the great-

est diagnostic accuracy (59). Recent data has demonstrated a significant reduction in CTX after use of oral ibandronate. After six months of treatment, the mean decrease in CTX was 65.24 ± 9.28%, with reductions greater than 80% in seven of the patients. One patient with normal sCTX showed a reduction of 97.5% by the end of the treatment (60) (B2b). As with beta-CTX, there was evidence of a greater reduction in the ratio of urinary αC-telopeptide of type 1 collagen tocreatinine (mg/nmol of creatinine) with the infusion of zoledronic acid, when compared to risedronate (61) (B3b).

Serum calcium and phosphorus levels are normal in most patients. Hypercalcemia and hypercalciuria may occur in the case of immobilization or fracture. The finding of hypercalcemia normally points to a secondary disorder such as hyperparathyroidism.

Bone scintigraphy followed by radiography of the affected areas determines the extent of involvement of the bone in Paget's disease. Sites of increased uptake occur as a result of the high rate of bone formation and blood flow. As a more sensitive method, bone scan with Tc 99-MDP can be positive even before the lytic changes seen on plain radiography. For this reason, about 10-15% of lesions detected by scintigraphy appear normal on plain radiographs. Comparing results from both methods, bone scintigraphy and radiography show alterations 56 to 86% of the time, with 2-23% of the cases showing alterations only in the scintigrams, and 11-20% only in the radiographs. The late stages of the disease may show a normal uptake of the radiopharmaceuticals, owing to the declinein metabolic activity and alterations in the findings of plain radiography. The characteristic findings of plain radiography are hyperostosis, osteosclerosis and bone expansion. CT and MRI provide little additional information when dealing with uncomplicated cases of the disease. They can be useful when complications associated with PDB are suspected, such as fractures or sarcomatous degeneration of pagetic bone. Due to the excellent resolution, MRI is the method of choice for the staging of sarcomatous degeneration (62). It can also be useful in the evaluation of neurological complications, such as compression of spinal nerve roots and cranial nerves (62-65) (C4).

COMPLICATIONS

Clinical manifestations of the disease are usually related to the presence of complications, which can be classified according to the particular system involved: skeletal (bone pain, osteoarthrosis, fractures, deformities and hypercalcemia), cardiovascular (high output heart failure, vascular calcifications, and valvular stenosis), neurological (deafness, increased intracranial pressure, and cranial nerve dysfunction), metabolic (hyperuricemia, hypercalciuria, hypercalcemia and nephrolithiasis) and neoplastic (osteosarcoma and giant cell tumors) (66-68) (D5).

Osteoarthritis is a common complication, most often affecting the knee and hip joints, resulting in the modification of bone biomechanics that causes bone and cartilage degeneration. Rheumatoid arthritis and its variants, as well as arthropathy from crystal deposition, have also been associated with the disease (69) (D5). Deformities and fractures are the result of abnormal bone formation, and associated with high morbidity due to the high incidence of associated pain (70) (D5). The involvement of cranial bones can cause neurological complications such as hearing loss (either neurosensorial or conductive), headache, dizziness, and more rarely, vascular dementia and hydrocephalus. Involvement of the jaw bones may lead to periodontal disease and dental malocclusion (66,67) (D5).

Malignant transformation of pagetic bone involving osteosarcoma or giant cell tumor is rare, occurring in less than 1% of cases. It classically affects individuals with the polyostotic form of the disease, and manifests itself accompanied by an increase in bone pain, swelling, and more rarely, pathologic fracture (71-74) (D5).

Hypercalcemia is often associated with prolonged immobilization or dehydration. Cardiovascular changes, although described, are rarely evident in clinical practice (75) (D5). Because PDB is a chronic disease, and diagnosed belatedly, it is important to be aware of the signs and symptoms that indicate the need for further radiological investigation.

TREATMENT

Pharmacological treatment seeks to promote pain relief and reduce the rate of bone remodeling. Restoration of typical bone turnover normalizes the rate of bone deposition, reducing bone vascularization, and slowing progression of the disease.

Symptomatic patients (with secondary symptoms of metabolically active disease) should be treated. The most common symptom is bone pain at a pagetic site. The exact cause of pain in these patients may be difficult to determine, and the initiation of drug therapy in

these cases is usually indicated by a concomitant elevation of serum alkaline phosphatase (76-78) (D5).

The asymptomatic form of the disease is often detected by imaging studies, motivated by suspicion of other diseases, or by observation of persistently elevated levels of serum alkaline phosphatase. Therapeutic decisions involving affected patients should take into account the location of the disease in sites that are susceptible to complications, such as the cranium and spine, in addition to abnormally high alkaline phosphatase levels (two to four times above the upper limit considered normal), and the presence of co-morbidities (79).

Other indications for treatment of asymptomatic patients include planned surgery at an active pagetic site in order to reduce the risk of bleeding (including blood loss during surgery), along with the rare possibility of developing hypercalcemia associated with the immobilization of patients with the polyostotic form of the disease (76) (D5).

We suggest the initiation of pharmacological treatment for all symptomatic patients, for preoperative asymptomatic patients requiring bone surgery, those with hypercalcemia, and cases involving locations liable to present complications (C).

PHARMACOLOGICAL TREATMENT MODALITIES

Several treatment modalities have been employed in an effort to care for patients with Paget's disease. They involve agents that target osteoclasts, the primary cells responsible for the disease, and that act by suppressing bone resorption within days or weeks. Most researchers conclude that these drugs are best considered as tools for helping to control the disease, rather than being a definitive therapy (80) (A1b).

The first therapy used for Paget's disease (in the 1970s) involved salmon calcitonin, followed later by human calcitonin. The medication acts directly on calcitonin receptors located on the osteoclasts. Owing to its short duration of action, partial response, and acquired resistance, it is used only in those with intolerance to bisphosphonates (81) (D5). Although radiological improvement has been reported during treatment, recurrence is common after the medication is discontinued. Side effects are common, including flushing, nausea and vomiting (22) (D5).

The efficacy of parenteral salmon calcitonin was evaluated in a trial involving 85 patients. Alkaline phosphatase levels and urinary hydroxyproline excretion de-

creased by approximately 50% after the first few months of therapy. However, in 22 of the 85 patients, despite the continued treatment, these parameters returned to pretreatment levels. Nineteen patients were considered treatment-resistant, presenting elevated amounts of antibodies to calcitonin (82) (B2b). The usual initial dose is 50 to 100 units per day (as tolerated), and the maintenance dose is normally 50 units daily, or 50 to 100 units every three days. The intranasal formulation, easy to administer, can be as effective as parenteral therapy, but has not yet been approved in the United States for this specific purpose (83,84) (D5).

Currently, the most widely used agents for treating the disease are the bisphosphonates, a broad class of medications that work by blocking osteoclastic bone resorption. Nitrogenous bisphosphonates (alendronate, risedronate, pamidronate, and zoledronic acid) are the drugs of choice (60,79) (A1b).

The first bisphosphonate used for the treatment of Paget's disease (in 1971) was the etidronate form, a non-nitrogenous bisphosphonate. The recommended dosage is 5 mg/kg per day (mean dose 400 mg/day) for six months. In general, patients with very active forms of the disease experience moderate clinical and biochemical improvement, followed by rapid relapse after stopping the medication. In addition, there is a tendency to become resistant to the medication after repeated courses of therapy (85) (D5).

Clodronate has greater potency than etidronate, and does not lead to mineralization defects. It should be administered intravenously at dose levels of 300 mg daily for 5 days. However, it is generally less effective than pamidronate (86) (B2b).

In the non-nitrogenous class of bisphosphonates, tiludronate is recommended in doses of 400 mg/day for 3 months, normalizing alkaline phosphatase in 35% of patients. It is more effective than etidronate, and does not cause bone demineralization. In a randomized, placebo-controlled trial, 149 patients used tiludronate at doses of 400 and 800 mg/day for three months, presenting a significant reduction in bone markers and pain (87) (A1b).

Alendronate is used at dose levels of 40 mg daily for six months. It is generally a well-tolerated drug, effective in normalizing serum alkaline phosphatase. It should not be used in patients with creatinine clearance below 35 ml/min (88) (A1b).

In a study involving 89 patients with active disease, a group treated with 40 mg of alendronate daily for six months showed a significantly greater reduction in alka-

line phosphatase (79% *vs.* 44%), and urinary deoxypyridinoline (75% *vs.* 51%) than a group treated with 400 mg of etidronate (p < 0.001 in both cases). Alendronate was well tolerated, and had a safety profile similar to that of etidronate (89) (A1b). In an open trial lasting two years, 72 patients with Paget's disease were assigned to receive either 60 mg of pamidronate every 3 months or 40 mg of alendronate daily for 3 months. The study concluded that alendronate and pamidronate have similar efficacy in achieving biochemical remission (90) (A1b).

Risedronate is used in 30-mg doses daily for two months, but should not be administered to patients with a creatinine clearance of less than 30 ml/min. In an American multicenter study, 62 patients received risedronate, 30 mg daily for 2 months, and 61 patients received etidronate, 400 mg daily for 6 months. Serum levels of alkaline phosphatase were controlled in 73% of the patients treated with risedronate, compared with 15% of the patients who received etidronate (P < 0.001). The average time for normalization was 91 days for the patients treated with risedronate, and 360 days for the patients treated with etidronate (P < 0.001). Relapse rates were 3% in the risedronate group and 15% in the etidronate group (P < 0.05). Pain reduction was statistically significant in the risedronate group, but not in the etidronate group. Both drugs were well tolerated (91) (A1b).

Pamidronate is well tolerated and can be used with a clearance above 30 ml/min. It is administered intravenously in 30 mg doses daily for three days. One drawback to its use is the development of resistance, which may influence the effectiveness of retreatment (92) (A1b). It may lead to a fall in serum alkaline phosphatase by 70% and about 60-80% will normalize it. The response is better in patients with higher values at baseline (93).

Ibandronate has been used safely and effectively in treating Paget's disease with 2 mg intravenous doses (94) (B2b). Recent data from a series of cases shows a significant reduction in the levels of sCTX, and in the algic aspect following oral use of ibandronate with 150 mg doses per month for six months. After six months of treatment, there was a mean reduction in sCTX of 65.24 ± 28.9%, and reduction of more than 80% in 58.3% of the patients studied. One patient with normal sCTX showed a reduction of 97.5% at the end of the treatment period. The mean reduction in alkaline phosphatase was 49.21 ± 37.9%, with all patients presenting normal levels after the treatment. There was a significant clinical response in all patients, with a marked improvement in bone pain (60) (C4).

Zoledronic acid is the most potent bisphosphonate approved for use in cases of Paget's disease. Administered in a single intravenous dose of 5 mg, it is not recommended for patients with a clearance below 35 ml/min. Sustained remissions are achieved in most patients, lasting up to two years (61) (A1b). This finding was confirmed when the study was extended for 6.5 years (95). Zoledronic acid can lead to a more rapid and prolonged remission during the treatment of Paget's disease when compared to risedronate. When evaluated for six months, using a single 5 mg infusion administered over 15 minutes, the effective response being considered normalization of alkaline phosphatase (or a decrease of at least 75%), it resulted in a 96% reduction in alkaline phosphatase, compared with a 74.3% reduction with risedronate when administered in daily 30 mg doses for 3 months. Normalization of alkaline phosphatase levels was more frequently achieved in patients treated with the zoledronic acid (88.6% *vs.* 57.9%) than in with those receiving risedronate (96) (A1b).

We indicate the use of nitrogenated bisphosphonates (alendronate, risedronate, pamidronate, and zoledronic acid) for the treatment of Paget's disease, emphasizing that zoledronic acid is the most potent bisphosphonate for use with this disease. (C)

MONITORING DISEASE ACTIVITY

Alkaline phosphatase, being a marker for bone remodeling, is commonly used as a parameter for measuring the biochemical response to treatment with bisphosphonates. Normalization of the alkaline phosphatase level is associated with biochemical remission, histological evidence of normal bone turnover, and its elevated level is related to the increase in disease activity. The measurement of alkaline phosphatase levels should be conducted after the first three to six months of treatment, in order to evaluate the initial response, followed by two annual measurements as a marker of bone activity (92) (D5).

Tiludronate, a weak bisphosphonate is available in some countries, mainly to treat monostotic disease. In a clinical trial involving twenty-one patients with PDB receiving 400 mg of tiludronate daily for three months, treatment response was observed six months after discontinuation of therapy, while the relapse of the disease, when present, was observed one year after the end of treatment (97) (B2b).

In a case series study, significant reductions in the levels of alkaline phosphatase and serum CTX were demonstrated after six months of treatment with orally administered ibandronate at dosages of 150 mg per month for six months. After 6 months of treatment, the mean reduction in CTX was 65.24 ± 28.9%, deceasing more than 80% in 7 patients. One patient with normal CTX showed a reduction of 97.5% at the end of the treatment period. The average reduction in alkaline phosphatase was 49.21 ± 37.9%, with all patients presenting normal levels after the treatment, suggesting that the follow-up of patients with PDB should also include CTX levels (60) (B2b).

Remission is considered to have been achieved when normal levels of alkaline phosphatase are attained, and partial remission when there is a decrease in levels greater than 75% after three to six months of treatment. Treatment should be resumed when alkaline phosphatase levels begin to rise again (when treatment involves normalization), or when there is a 25% increase compared to post-treatment levels (98) (D5).

We suggest the measurement of serum alkaline phosphatase after three and six months from the start of treatment in order to monitor the initial response, followed by biannual measurements of markers indicating disease activity (B).

NATURAL HISTORY OF PDB

Several clinical guidelines cast doubt on the belief that the treatment of Paget's disease alters the history of disease complications. Results from the PRISM study showed that most treatment approaches have limited impact on quality of life, pain and hearing loss, and highlighted the need for further studies to examine whether the effects of bisphosphonates on bone remodeling can actually translate into a clinical improvement and lower risk of complications in the individuals affected (99) (B2b). On the other hand the follow-up was too short to show the expected beneficial effects on chronic complications of the disease. Long-term studies are therefore needed in order to assess the impact of treatment on the natural history and progression of PDB.

CONCLUSIONS

Paget's disease of bone has a variable geographic distribution worldwide, being most commonly encountered in white Europeans, and those of European descent over 55 years of age. In Brazil, a prevalence study in a city originally colonized by Europeans identified rates comparable to those encountered in southern Europe. The etiology of the disease still remains controversial, with evidence that genetic factors are involved, particularly those relates to SQTM1 and genetic polymorphisms in sections of the following genes: *CaSR, ESR1, TNFRSF11B (OPG), TNFRSF11A (RANK), CSF1 (M-CSF), OPTN, TM7SF4 (DC-STAMP), VCP, NUP205, RIN3, PML* and *GOLGA6A* (1,4). Environmental factors, along with viral and proinflammatory cytokines may also be involved. The clinical presentation is quite extensive, with bone pain, fractures, skeletal deformities and secondary arthrosis comprising part of the picture. The diagnosis is made primarily by characteristic radiological findings and high alkaline phosphatase. The most common complications include pathologic fractures, bone deformities and osteoarthrosis. Malignant transformation of pagetic bone is rare. Treatment should be recommended for all symptomatic or asymptomatic patients, during the preoperative phase of bone surgery, or when hypercalcemia or support bones are involved. Nitrogen contained bisphosphonates are the medications of choice, with zoledronic acid being the most potent bisphosphonate approved for pharmacological treatment. Newer compounds such as denosumab, a monoclonal antibody against RANKL may show promises for the treatment of PDB, although data are still lacking. Serial measurements of serum alkaline phosphatase should be used to monitor disease activity, combined with clinical monitoring of the patient.

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