

Paget's disease of bone: there's more than the affected skeletal – a clinical review and suggestions for the clinical practice

Alberto Falchetti, Laura Masi and Maria Luisa Brandi

Regional Center for Hereditary Endocrine Tumors, Unit of Metabolic Bone Diseases, Department of Internal Medicine, University of Florence, Florence, Italy

Correspondence to Maria Luisa Brandi, MD, PhD, Department of Internal Medicine, University of Florence, Viale Morgagni 85, 50135 Florence, Italy
Tel: +39 055 4296586; fax: +39 055 4296585; e-mail: m.brandi@dmi.unifi.it

Current Opinion in Rheumatology 2010, 22:410–423

Purpose of review

New acquisitions have been recently obtained on molecular pathogenesis, genetics and treatment of the Paget's disease of bone. Utmost importance to the skeletal manifestations of this disease has been given, even though extraskeletal abnormalities have been reported over the years. Consequently, the clinical aspects of extraskeletal complications have been less extensively investigated. This review will focus primarily on epidemiological, clinical and diagnostic features of skeletal and extra-skeletal clinical manifestations and will include either the hypotheses or new findings on their underlying molecular pathophysiology. A practical suggestion for an optimal management path of Paget's disease of bone is given.

Recent findings

It has been revealed that osteoblasts and osteocytes participate in impaired bone remodeling; in a North American study on pagetic patients, the survival rate was better than expected; the frequency of neurological complications and hearing loss could be different than previously reported; and somatically acquired mutations of *SQSTM1/p62* gene have been found in both the diseased bone and tumor samples from sporadic patients with Paget's disease of bone.

Summary

Through an improved and more complete clinical characterization the 'old' complications could be better managed and new ones could emerge as entities potentially associated with Paget's disease.

Keywords

clinical diagnosis of Paget's disease of bone, ideal path for an optimal clinical management of Paget's disease of bone, Paget's disease of bone, pathophysiology of Paget's disease of bone, skeletal and nonskeletal complications of Paget's disease of bone

Curr Opin Rheumatol 22:410–423
© 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins
1040-8711

Introduction

Paget's disease of bone (PDB) [1] is a focal alteration of bone remodeling in which the normal architecture is replaced by not organized bone tissue, with a consequent tendency to bone pain, deformities and fractures in the affected areas and arthritis in the adjacent joints. Recent epidemiological data indicate a reduction in the prevalence and clinical severity of PDB, even if confounding factors may influence such findings and not necessarily correspond to a real view. In general, utmost importance has been given to the skeletal manifestations of this disease, even though extraskeletal abnormalities have been reported over the years. New important acquisitions have been recently obtained on the molecular pathogenesis, genetics and treatment of PDB-related skeletal abnormalities, but the purely clinical aspects

of the extraskeletal complications have been less subject to extensive clinical observations or trials, remaining in part anchored to the relatively few and 'old' reports.

Review of the above PDB-related clinical aspects, addressed also to readers who are lacking the clinical experience of this disease, describes in a simple and schematic way the main issues associated with the clinical aspects related to PDB, suggesting an ideal and virtuous clinical-diagnostic path for an appropriate management of PDB patients. We will focus primarily on the epidemiological, clinical and diagnostic features of both skeletal and extraskeletal PDB-related clinical manifestations and will include the hypotheses on possible common underlying molecular pathogenic mechanisms. General practical considerations, where they can be undertaken, have been also incorporated in this manuscript.

Table 1 Sites of involvement in order of frequency

Pelvis	67%
Vertebrae	34%
Femur	32%
Tibias	25%
Skull	23%
Humerus	11%
Ribs	7%
Calcaneus	4%
Ulna	2%
Scapula	2%
Hands	2%
Mandible	1%
Sternum	1%

Data from [4].

Finally, due to the need not to unduly expand this review, the discussion of any PDB therapy cannot be dealt with within the context of this manuscript.

Monostotic and polyostotic forms of Paget's disease of bone

According to the number of involved skeletal sites within the affected individual, two major forms of the disease are defined as monostotic and polyostotic. In the last three decades, the severity of the disease in newly presenting patients seems to be felt down, with an increasing proportion of patients having monostotic type – nearly 40% of patients nowadays have only one bone involved [2]. Although PDB may potentially affect any skeletal site, some segments are more frequently affected by PDB (Table 1) [3,4], and the reason for this is still unknown.

Recently, a large study [3] on PDB patients reported that 34% of them had a monostotic lesion, with an overall average of 5.5 bone lesions per patient in the whole group. Although frequently asymptomatic, mainly the monostotic form, PDB may also cause a variety of clinical complications resulting in considerable morbidity and reduced quality of life [5].

Histological appearance of Paget's disease of bone

The main histological features rely on evidence in the affected skeletal segment(s) of giant multinucleated osteoclasts (OCLs), metabolically hyperactive and containing 3–30 nuclei per cell with respect to one to seven of normal OCLs [6]. Recently, osteoblasts (OBLs) and osteocytes have also been described to participate in impaired bone remodeling. In particular, an increased number of OBLs, the presence of osteosclerosis due to increased thickness of trabecular elements and an increased number of osteocytes (per mm³ of bone), with an abnormal grade of organization of their canalicular net, can be observed in specimens from affected bones [7**].

Pathological phases of Paget's disease of bone

Three phases of pagetic bone activities have been determined: initial/incipient-active corresponding to the osteolytic appearance to the radiographs (Figs 1a and 2) with hyperactive bone resorption [8]; mixed/active corresponding to mixed radiographic features (Fig. 1b) with coexistence of bone osteolysis and sclerosis in which activities of OBLs gradually prevail, as suggested by the highly increased alkaline phosphatase (ALP) levels, with a tissue level bone formation rate that may be increased six-fold to seven-fold above normal levels [7**]; and late/inactive representing an exhaustive stage that appears osteosclerotic to radiographs (Fig. 1c).

What are the ethnic and age groups mostly at risk to develop the disease?

PDB, the second metabolic bone disorder, is quite common among older people of Caucasian European descent (particularly British descents and also French, Dutch, Spanish and Italian descents) [9–11] and mainly affect individuals over 55 years of age [12,13]. It is uncommon in Scandinavia, eastern Europe and Asia [14,15].

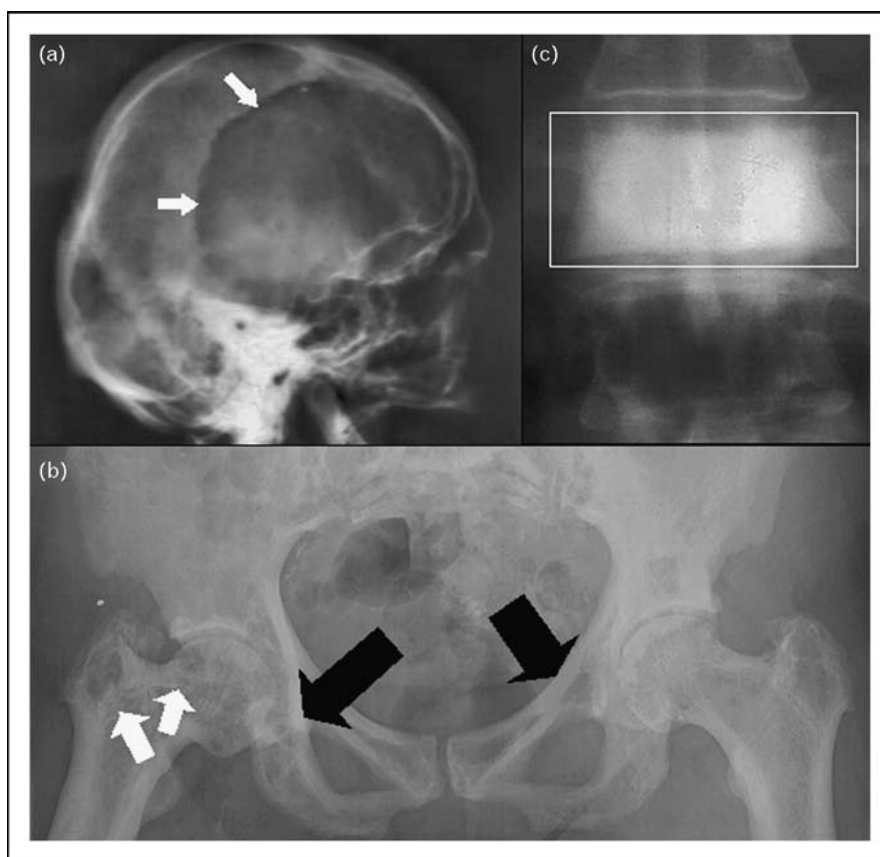
Morbidity and mortality of Paget's disease of bone

A large epidemiological study on a UK population suggested an increased morbidity in PDB patients vs. age-matched and sex-matched controls with relative risk (RR) of skeletal pain, fractures, deafness, osteoarthritis in adjacent joints and osteosarcoma of 2.1, 1.2, 1.6 and 1.7, respectively. The survival of these PDB patients was reduced with respect to controls [16]. After a 5-year follow-up period, deaths represented 32.7% in PDB and 28.0% in controls [12]. Bone [17] reported a significantly higher prevalence of conditions and states of morbidity in PDB patients than in controls.

More recently, in contrast to the findings by van Staa *et al.* [12], a North American study on the impact of PDB on mortality revealed that survival among PDB patients was better than expected, especially in affected male patients [18**]. Clinical surveys also demonstrated a decrease in the severity of the PDB-related clinical expression [13,19–22], even if an Italian study of PDB patients from Campania, a southern region, showed greater clinical severity and increased frequency of neoplastic degeneration among patients who live or are descended from people who live in this region [23].

Secular trends of Paget's disease of bone

A decline in the frequency of PDB has been reported in recent years. A UK follow-up prevalence study [13]

Figure 1 Radiographic images exemplifying each one of three phases of Paget's bone disease

(a) Phase 1 or initial, incipient-active. Arrows indicate the osteolytic appearance to the radiographs. (b) Phase 2 or mixed, active. Coexistence of both bone osteolysis (white arrowheads) and sclerosis (black arrows) of the affected pelvis. (c) Phase 3 or late, inactive. Osteosclerotic vertebra (within the white box).

described that the PDB prevalence (age-standardized and gender-standardized) fell down drastically between 1974 and 1994, as observed also in other European countries.

Possible explanations for the reduced prevalence of Paget's disease of bone

It is highly possible that the reported reduced prevalence of PDB is strongly linked to important and massive immigration into western nations, in a relatively short period, which has moved masses of individuals from Africa and Asia, 'diluting' the real frequency of PDB and its related mortality.

Finally, PDB diagnosis in the past was accidentally performed, particularly in asymptomatic or slightly symptomatic forms, when classical radiology was intended to evaluate abdominal symptoms, back pain, pelvic pain or hip pain. The advent of ultrasonography in evaluating abdominal disorders, including gallstones and kidney stones, has supplanted the traditional radiology in the

diagnosis of these diseases and consequently reduced the possibility of accidentally identifying a bone disease such as PDB. However, in other European countries, such as Italy, the prevalence showed no tendency to decrease [24].

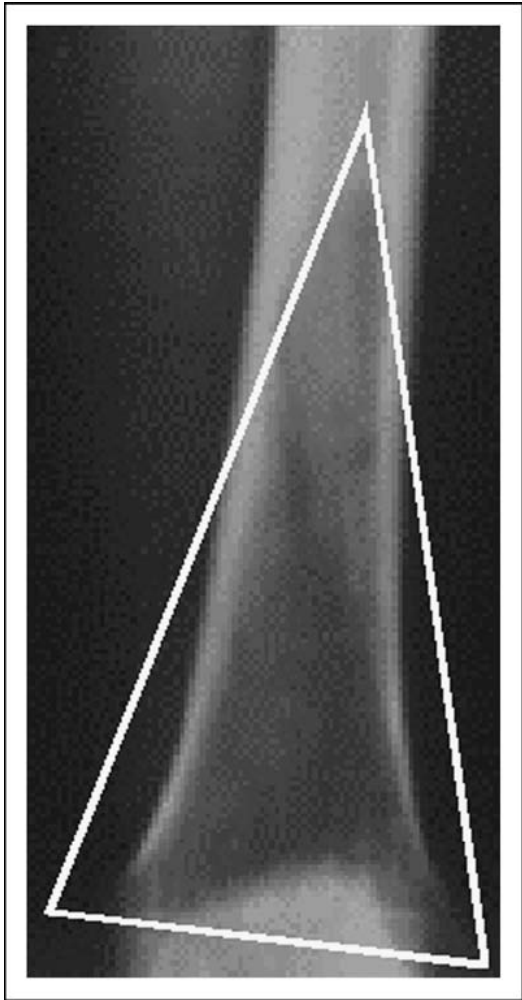
Etiopathogenesis

Viral infection (environmental factors) and genetic hypotheses are currently most crediting the cause of PDB.

Viral (environmental) hypothesis

The presence of nuclear and cytoplasmic inclusions, similar to the nucleocapsid paramyxovirus, the detection of mRNAs or proteins from measles, canine distemper and respiratory syncytial viruses in samples from PDB patients suggest the possibility that a viral infection may be involved in the genesis of the disease. Many conflicting results have been reported concerning this hypothesis of PDB either in the past [25–33] or more recently [34–36,37**].

Figure 2 'V'-shaped resorption front



However, very recently, in an Italian PDB series from Campania, a higher prevalence of contact with animals (livestock or pets) has been reported, with no difference between patients with/without mutation *SQSTM1/p62* (see below) with a greater number of sites covered when compared with patients without animal contact [38**].

Genetic hypothesis

Evidence of a strong familiarity in many cases of PDB clearly indicates the inheritance of this condition as an autosomal dominant trait.

SQSTM1/p62 gene germline mutations

The most frequent genetic alterations involve the *Sequestosome1* (*SQSTM1*) gene encoding the scaffold protein *p62*. Germline mutations of this gene have been evidenced both in familial and sporadic PDB cases [39–44,45*].

Protein *p62* is capable of binding chains of ubiquitin and together with other cytoplasmic proteins acts as a

modulator of the function of nuclear growth factor κ B, NF κ B, a major factor for the recruitment of preosteoclasts and osteoclastic activation. It is still unclear how these mutations could justify either the acquisition of a pagetic phenotype or the skeletal focal nature of PDB, although in-vitro evidence suggests a reduced capacity for repression of the function of NF κ B [46,47,48**,49].

SQSTM1/p62 gene somatic mutations

A search for somatic mutations of *SQSTM1/p62* gene has been performed on primary cultures of OBLs and bone marrow cells from PDB patients. The findings of this study suggest that somatic mutations of *SQSTM1/p62* are not commonly present in pagetic bones [50**]. On the contrary, an almost simultaneous study [51**] revealed the presence of somatically acquired *SQSTM1/p62* mutations in the affected bone and tumor samples from sporadic PDB cases and pagetic osteosarcoma, suggesting this disease as fitting more closely with the cancer model of somatically acquired mutations.

Clinical presentation of Paget's disease of bone

The clinical manifestations of PDB range from no symptoms (patients diagnosed either accidentally, mainly with a limited extension of PDB, or precociously identified by the fact that they belong to families in which PDB occurs in one or more members and consequently subjected to regular biochemical–clinical screening) to painful deformities/fractures in symptomatic patients.

Asymptomatic vs. symptomatic form

Accidental discovery of PDB may often occur through the finding of elevated serum and/or bone-specific alkaline phosphatase (sAP and/or bAP) activity on a biochemical screening, rarely on radiograph or scintiscan taken for some other purpose, and then followed by radiological assessment of the disorder. On the contrary, many PDB patients have symptoms for long periods before the disease is recognized [6]. The main clinical features of PDB are summarized in Table 2.

The presence of a positive familial history of PDB and the possibility to perform DNA testing in PDB patients

Table 2 Clinical features of Paget's disease of bone

Pain	Bone pain Pain
Deformity	Inclination of the long bones Cranial deformities
Fractures	Enlargement of the segments involved Complete Fissures of the cortex
Neurological complications	Deafness Paralysis of other cranial nerves Spinal cord compression
Transformation tumor	Sarcoma

and their relatives can help the early detection of individuals at risk to develop PDB.

A positive familial history of Paget's disease of bone enables an early identification of asymptomatic patients at risk to develop Paget's disease of bone

It has been reported that 12–40% of index cases had at least one first-degree relative affected [49], with 7–10 times increased risk to develop PDB for the first-degree relatives of PDB patients with respect to general population. In particular, this risk is even greater in relatives of patients with bone-deforming disease and those with an early age at diagnosis [52].

Detection of germline mutations in familial form of Paget's disease of bone: a further help to identify asymptomatic mutant gene carriers

Numerous germline mutations affecting the *SOSTM1/p62* gene have been found in patients with either familial or sporadic PDB [39–44,45*,47,53–58,59**,60**,61*]. *SOSTM1/p62* mutations may account for up to 50% of familial and 10–20% of sporadic PDB cases [62]. Thus, mutant gene carriers, especially from the new generations, can be identified at an asymptomatic stage of PDB. Consequently, the detection of both a positive PDB familial history and asymptomatic mutant carriers may provide a powerful tool to precociously identify an asymptomatic PDB individual or some of those patients who have symptoms for long periods before the disease is recognized. Finally, it should be always considered that possibly some of the PDB cases originally reported as sporadic cases may become new familial forms.

Paget's disease of bone-related signs and symptoms: clinical, biochemical and radiological diagnosis

The diagnosis of PDB may result from the appearance of specific signs and symptoms (Table 2) or be totally random.

Clinical diagnosis

Signs and symptoms are more likely to occur in patients with polyostotic PDB. Bone pain, from mild to moderate, and deformities are easily identified when the skull and facial bones, and also the extremities, are affected (Fig. 3).

Biochemical diagnosis: bone turnover markers

Since PDB is characterized by an accelerated remodeling of the affected skeletal, the biochemical assay of bone turnover markers is important for both diagnostic and clinical management purposes.

Figure 3 Bowing of the affected tibia



Bone formation markers

Serum AP and/or bAP increased levels represent the most important biochemical marker(s) of PDB activity, generally depending on increased number of OBLs in the sclerotic lesions. Their increased levels reflect the rate of bone formation and correlate directly with the extent of the skeletal involvement [63]. In monostotic PDB, or

in forms with a limited bone extent, only the evaluation of bAP has a sufficient sensitivity. However, in very limited forms, bAP can be normal too [64,65]. In untreated patients, the levels of sAP or bAP correlate well with the degree of bone scintigraphic uptake [6,66,67].

Bone resorption markers

Type 1 procollagen peptides, P1NP and P1CP, or osteocalcin levels might also be found increased in PDB [68], even if their serum variations are not generally evaluated in those patients who are not suspected of having bone disease. They are less sensitive and accurate than sAP [64]. Apart from P1NP, probably more useful in terms of pretreatment values being clearly elevated in PDB of limited extent and showing the greatest changes with treatment and on relapse of PDB, these markers provide scarcely useful additional information regarding diagnosis or effectiveness of treatment with respect to sAP, especially when it is clearly elevated at presentation [66,67]. Currently, only sAP/bAP serum levels can be used as a predictor of PDB-related activity.

Is there any role for other bone turnover markers in biochemical assessment of Paget's disease of bone?

Various breakdown products of type I collagen and the osteoclast-derived enzymes TRAP5b and cathepsin K have also been investigated in PDB patients, but their potential role in clinical practice seems to be still insufficient [66].

Other biochemical markers investigated in Paget's disease of bone patients (not currently used)

Higher level of endothelin-1 (ET-1) has been reported in PDB patients, suggesting both its pathophysiological role in the disease and the fact that metabolism in the pagetic bone affects endothelial cell metabolism, and maybe also modulated by endothelial cell products [69,70]. Larger studies replicating these findings are needed before considering ET-1 as a possible new useful marker of PDB-related activity.

Radiological/nuclear medicine diagnosis

The diagnosis of PDB is typically radiographic and based on a broad range of disorders (Table 3) [71–73]. Classical radiographs and total bone scintigraphy represent the main radiological tests to be considered for PDB skeletal localization and extension. When individually considered, radiological lesions are not specific to PDB and numerous differential diagnoses must be taken into account [6], especially against primitive neoplasms of the skeleton or bone metastases. Computerized tomography (CT) may be sometimes an aid in differential diagnosis. The traditional radiography represents the most important diagnostic tool to identify complications (e.g. osteoarthritis secondary to joints adjacent fractures, deformities or to follow their evolution).

Table 3 Radiographic features of Paget's disease of bone

Initial form: mainly lytic	'V' shaped fissures of the cortex of long bones
Intermediate phase (lytic and sclerotic)	Circumscribed osteoporosis of the skull Thickening of the cortex Indistinguishability of the cortico-medullary border
Late stage: mostly sclerotic	Accentuation of the trabecular pattern Thickening of long bones Increased bone section Sclerosis

Bone scintigraphy with bisphosphonate labeled with Tc 99 is more sensitive than radiology in identifying pagetic lesion [74], although its specificity is very low because many other diseases of bone remodeling, including skeletal metastases, can be associated with a positive scintigraphy. The bone scan is therefore recommended after the radiological evidence of a skeletal segment affected by PDB. A possible involvement of the skull, not yet symptomatic, is a particularly important finding since this localization requires a more aggressive therapy.

General considerations on radiological diagnosis

Due to scintigraphy's low diagnostic specificity, and given the high prevalence of PDB, a-priori exclusion of the combination of two diseases in the same individual is not possible, e.g. PDB and osteoporosis and/or neoplastic disease of the skeleton. Therefore, the nature of a lesion detected by scintigraphy has always to be thoroughly evaluated by radiology. The bone scan is preferable to total body radiographic mapping due to the total radiation dose (Table 4). Double X-ray emission absorptiometry (DEXA) is useful to detect a coexisting osteopenic/osteoporotic condition in PDB individuals, considering that a clear overlap in the age of prevalence for both this bone metabolic disorders exists.

Bone biopsy

Bone biopsy is rarely required for diagnosis of PDB and may be useful in the presence of radiological figures not easily distinguished from osteosclerotic metastases (e.g. prostatic cancer or Hodgkin's disease). It is needed when the suspicion of a development of osteosarcoma in a PDB affected segment is strong.

Table 4 Radiant exposure of different diagnostic techniques in Paget's disease of bone

Survey	mSv
Traditional bone scintigraphy	3–5
Pelvic radiographs	0.7–1.4
Lumbar spine radiographs	1.3–2.7
Total body radiographs	>7
Trunk computed tomography	5–15

Table 5 Skeletal-related complications of Paget's disease of bone

Skull	Hearing loss [18**] Tinnitus Rarely, symptoms of hydrocephalus even when there has been marked enlargement of the cranium
Jaw	Malocclusion Interdental diastema (migration of teeth) Loss of teeth
Edentulia, pain, and sometimes osteomyelitis can worsen the health status of PDB patients [76]	
Spine	Enlarged sclerotic vertebrae (the most common finding in spinal PDB) Vertebral compression and kyphosis
Lumbar spine and sacrum are most commonly involved sites in PDB [71–74]	
Fractures of long bones (more frequently in the lytic disease) and their features	Lower extremities, typically transverse in nature Femur fractures localization (more frequent than tibia) Femoral fractures are more likely with nonunion of bone segments [78] Incomplete fissure fracture, usually not painful (more common than complete) [79,80]

PDB, Paget's disease of bone.

Classical complications

It is known that pagetic bone predisposes to pain, fracture and skeletal deformity, but in relation to the bone segment affected, other clinical manifestations may also be present.

Skeletal-related complications

PDB may cause visible skeletal deformities particularly in the skull, legs, arms and also in long bones, as reported in Table 5 [16,75–80].

Joint-related complications

When PDB affects bone segments adjacent to large joints, there is frequently arthritic degeneration of the joint. Table 6 reports such complications [12,63].

Neurological complications of Paget's disease of bone

Neurological complications occur in 30% of PDB patients, with cranial nerve lesions and spinal cord/nerve root as the most common forms of involvement [17]. For many years the most common neurological problem has been considered hearing loss due to compression of cranial nerve VIII and cochlear dysfunction.

These complications may occur either in patients with a long history of PDB or in patients with previously unrecognized disease. At spine level, ischemic myelitis and nerve compression due to bone hypertrophy represent the main mechanisms of nerve damage in PDB [81*].

Recently, it has been estimated that up to 76% of PDB patients may have some form of neurological involvement. However, neurological sequelae of PDB may be underappreciated [81*]. In a North American study [16], neurological complications were much lower than previously described, with only 0.4% of patients developing cranial nerve compression and 5.5%, developing nerve root or peripheral nerve impingement. However, as the authors themselves stated, several limitations existed in this study, such as the relatively small population from a midwestern community with a higher prevalence of whites and slightly younger participants than the US population.

Hearing loss

The prevalence of hearing loss has been reported to be 2.4–13.5% [19,82]. The hearing impairment may be sensorineural, mixed, or, rarely, only conductive. General mechanisms supposed to contribute to the occurrence of

Table 6 Joint-related complications and their features

Arthritis due to altered distribution of the mechanical load secondary to skeletal deformities of affected segments	Spine
	Pain due to associated degenerative arthritis Nerve root or spinal cord impingement (less commonly)
	Pelvis
	Pelvic PDB is associated with degenerative arthritis of the hips It is probably the most common severe complication [63]
	Hip
	Impairment of the mobility and autonomy to walking over time due to pain Arthritis of the hip is probably the most frequent cause of hip replacement in PDB

PDB, Paget's disease of bone.

hearing loss in PDB patients with skull involvement are described below [83].

- (1) Reduced bone mineral density (BMD) in the cochlear capsule, without evidence of dysfunction of the acoustic nerve.
- (2) Involvement of the otic capsule and increasing hat size (a complaint less often heard in this nonhat-wearing era).
- (3) Acoustic nerve entrapment due to the expansion of the bone structure at the level of the ear canal.

Recently, always in the North American study, hearing loss has been reported in nearly two-thirds of the investigated PDB cohort, significantly higher than the above described prevalence estimates [16].

A new possible pathophysiological hypothesis for hearing loss: a recent and isolated finding

Degeneration (cystic) of the spiral ligament, probably altering the flow of ionic homeostasis, has been reported in two PDB patients determining a cochlear hearing loss of sensorineural type. This degeneration had never been described before and could be typical of PDB and may be explaining the neurosensory loss in the absence of other anomalies [84]. However, such an isolated finding should be thoroughly investigated in larger series of PDB patients before considering it as a real new pathological hypothesis.

General considerations on osteoarthritis and deafness

It is important to take into account that knee and hip osteoarthritis and deafness result from more or less permanent structural changes that develop over decades. However, it is also true that since musculoskeletal symptoms, back pain, osteoarthritis and deafness are common symptoms in the elderly, it can be difficult to clearly define what symptoms can be genuinely attributable to PDB.

Eye's fundus complications

The ocular fundus of a PDB patient may demonstrate a linear opacity representing a crack in Bruch's membrane, known as angioid streak [85].

Cardiovascular complications of Paget's disease of bone

Cardiovascular complications, including an increased arterial calcification propensity, are known to be not unusual in the aging population of PDB patients [12,16,86–88]. Such complications are summarized below.

- (1) High-output chronic heart failure (CHF) when there is extensive skeletal involvement 3% of PDB patients (increased vascularity of bone and of the overlying muscle and skin) [12,16,86–88].
- (2) Calcifications of the media or atherosclerotic calcifications (more frequent than controls). Arterial calcification in the aorta, iliac, femoral, gluteal and pelvic arteries [70] (cause unknown).
- (3) Calcification of the aortic valve [88] and the interventricular septum.
- (4) PDB-related calcifications are longer and thicker than age-matched non-PDB patients [87].
- (5) Generalized atherosclerosis.
- (6) Endocardial calcification.

When bone involvement may influence thoracic-cardiovascular operations

Although rare, the localization of PDB at the sternum, for those patients needing sternotomy and harvesting of internal mammary arteries, may reveal problems because of a thickened sternum and substernal adhesions. It has been suggested that saphenous vein graft or other arterial grafts may be used and it has been reported that in appropriate patients, an operation through a thoracotomy or noninvasive balloon and/or stent techniques may be good choices [89].

Is there any link between abnormal calcification of the vascular wall and bone remodeling in Paget's disease of bone?

Overall, the number, length, and thickness of the vascular calcifications in PDB patients are higher than controls [87]. Interestingly, studies on the quantification of vascularity in iliac bone biopsies of castrated rats, before and after treatment with bisphosphonate, evidenced a reduction of the vascularization, suggesting that this parameter should be considered in the planning of drug therapy [90].

Suggested hypotheses to link vascular calcifications and bone remodeling: with pathogenesis?

According to the literature, the following three hypotheses can be suggested: 1) malfunction/anomaly of mesenchymal vascular cells wall with acquisition of an osteoblastic phenotype. There may be viral contamination of bone cells, but also of the connective cells of the vessel walls, leading to this dysfunction [91]; 2) circulating systemic factors: sAP, noncollagen protein abnormally secreted by pagetic bone cells, may promote calcification by acting on the vessels [87]. It has been suggested that IL-6 could be a potential candidate to link PDB and vascular calcification. In fact, when excessively secreted by pagetic bone cells, IL-6 may intervene in the genesis of atheromatous plaques, as observed in mice [92]; 3) genetic factors: a) osteoprotegerin (OPG). OPG-knockout mice have vascular calcifications; b) germline mutations in *SQSTM1/p62* gene, accounting for classical PDB. These mutations alter ubiquitin binding domain of p62 protein, thereby leading to activation of nuclear factor (NF)- κ B signal (RANK) [93]. The RANK-RANKL system is also involved in the pathogenesis of vascular calcification [94].

Neoplasms

PDB features such as locally invasive behavior and relapse after treatment are suggestive of a benign neoplastic disease. Effectively, skeletal tumors are sometimes found in PDB individuals, and also non skeletal ones [95]. Occasionally, PDB can be complicated by benign or rarely malignant giant-cell tumors (GCTs). The incidence of such tumors is low (probably <1%): osteosarcoma (~86% of cases), fibrosarcoma (~5%) and chondrosarcoma (~2.5%) [96,97,98**]. However, true malignancy can develop probably as the result of somatic genetic mutation [12], and carcinomas can metastasize to pagetic lesions, perhaps because of increased blood supply to affected bone, and bone marrow malignancies may also occur in patients with PDB.

Osteosarcoma

The presenting symptom is generally an acute bone pain, which might be recent in onset or might be a worsening of existing pain.

Sarcomatous degeneration represents the most serious complication of PDB, even if it occurs in less than 1% of PDB patients and its incidence is possibly lower than estimated in the past [99]. A UK study reports that pagetic sarcoma has become increasingly rare over the last few decades and that this rate of decline is greater than the well recognized fall in the incidence of PDB per se. The age of presentation of pagetic sarcoma in this study has significantly increased over the last few decades continuing the previously manifesting trend 50 years ago. Moreover, the increase of sAP levels in these patients correlates with the extent of the underlying PDB, suggesting that the number of affected sites still continue to affect sAP even in the presence of sarcoma [98**].

Comparison of the anatomical distribution between adolescent and pagetic osteosarcoma

Comparison of the anatomical distribution between adolescent and pagetic osteosarcoma revealed that while the adolescent osteosarcoma localizes primarily to the lower limbs (femur and tibia, respectively 47 and 15%), the pagetic osteosarcoma appears more frequently to ilium (26%), skull (8%) and humerus (19%), with a frequency also to sacrum, ribs and vertebrae (3% each) greater than adolescent osteosarcoma [99]. However, not all PDB associated tumors are sarcomas; metastatic cancer has been seen to metastasize to pagetic bone, and also hematological malignancies may occur.

Paget's disease of bone osteosarcoma is always keeping the same aggressiveness in the years: possible explanations

In two distinct observational clinical series (from 1942 to 1967 and from 1976 to 2001), it has been observed that treated PDB sarcoma usually had a poor survival. The following considerations should be taken into account to

explain it: 1) pagetic sarcoma is a tumor more malignant than other connective tissue tumors (generally diagnosed at stage III); 2) the excessive vascularity of the pagetic bone; 3) age and general health status of PDB patients may limit the use of chemotherapeutic agents; 4) the localization of tumors in the PDB mainly to pelvis, proximal femur, and proximal humerus; and 5) patients with polyostotic disease may be less aware of the development of a malignant tumor due to, for example, physical and/or mental impairment or the co-existence of chronic pain (see below) [97,100].

- (1) No improvement in the treatment of Pagetic sarcoma in terms of discoveries, treatment or survival although recent advances in diagnostic imaging, systems of radiation in the surgical technique.
- (2) Not easy application of adjuvant chemotherapeutic agents in elderly people with polyostotic disease (already metastasized at the time of diagnosis).
- (3) Need of specific and targeted genetic studies of this disorder in light of recent acquisitions in this sector of the pathophysiology of PDB.

The mortality rate of Paget's disease of bone osteosarcoma did not significantly exhibit a reduction trend

Through the comparison between the mortality rate for malignant bone tumors associated and not associated with PDB, in both males and females from 1951 to 1970, it was shown that while the rate of mortality was significantly reduced in tumors not associated with PDB, the PDB-related bone tumors had not behaved in the same manner, showing only a slight declining trend [97].

The recent discovery of somatic somatically acquired *SQSTM1/p62* mutations in both the diseased bone and tumor samples from sporadic PDB and pagetic osteosarcoma indicates that PDB fits more closely with a cancer model of somatically acquired mutations, acquired throughout life, occurring at the site of the disease [51**]. Thus, mutations somatically acquired over the life of the individual are linked to the PDB phenotype.

Giant-cell tumors

GCTs are rare (~2.5% of cases) with a benign outcome (see below).

- (1) Sarcoma: <1% (mainly osteoblastic or fibroblastic osteosarcoma; more rare chondrosarcoma, fibrosarcoma and angiosarcoma).
- (2) Metastatic (solitary metastasis).
- (3) Hematological malignancies (lymphoma non Hodgkin).
- (4) GCT (prevalently benign and rarely malignant): it occurs more frequently in polyostotic forms.

This unusual tumor is most commonly reported in people from the Italian region of Campania with a high

prevalence for PDB [101,102]. This probably could reflect, at least in part, a genetic predisposition, but it remains still unknown, as descendants of migrants from this area develop this cancer [103]. GCTs, usually benign, are less common than sarcomas and are often painful [104].

Metabolic abnormalities frequently observed in Paget's disease of bone patients

Several metabolic abnormalities have been frequently described in PDB patients.

Calcium metabolism disturbances

It is well known that hypercalcemia, particularly in polyostotic patients, can be a consequence of immobilization, although not commonly reported [105]. Hypercalcemia is more likely to occur in patients with PDB as a consequence of a hyperparathyroid status [106], but a considerable confusion among primary, secondary and tertiary forms of hyperparathyroidism is still existing. Increased parathormone (PTH) levels are present in 12–18% of PDB patients [107] and the prevalence and sex distribution of primary hyperparathyroidism in PDB resemble figures in the elderly. Moreover, PDB and secondary hyperparathyroidism may also coexist and dietary supplementation with calcium and vitamin D is effective in the treatment of PDB [108].

Thus, it should always be considered that an excess of PTH should be likely to have an exaggerated impact at skeletal sites affected by PDB [109]. Moreover, the influence of severity of hyperparathyroidism on post-operative improvement in bone turnover in PDB has also been demonstrated [106]. In fact, a correlation between PTH, sAP and serum calcium levels has been described in 39 patients with PDB [109]. Finally, interesting similarities between PDB and primary hyperparathyroidism may exist (see below).

- (1) Both diseases are capable of causing bone pain.
- (2) Bone biomarkers are elevated in both.
- (3) Increased marrow fibrosis and vascularity are common histological features of both.
- (4) Hypercalcemia and hypercalciuria occasionally occur in PDB and are common findings in hyperparathyroidism.
- (5) Increased PTH levels are present in 12–18% of PDB.

Although hypercalciuria has been reported in a subset of patients, the incidence of renal stones does not seem to be increased [108].

Hyperuricemia

Hyperuricemia has been mainly observed in male PDB patients [63] and it might occur as a consequence of the

high turnover of nucleic acids in pagetic lesions. Gout occurrence has been reported with a variable incidence.

General considerations on Paget's disease of bone and hyperparathyroidism

As described above for osteoarthritis and deafness, the association of PDB and primary hyperparathyroidism may also be due to a chance association of two common diseases of the elderly. However, by the practical clinical point, biochemical screening of PDB should also include evaluation of calcium/phosphate/vitamin D axis, including PTH, supporting the management of PDB. In patients with both disorders, parathyroidectomy is indicated and in those patients affected by primary hyperparathyroidism who exhibit high bone turnover after parathyroidectomy, a diagnostic screening for PDB has to be proposed.

Peyronie's disease: an unrecognized or infrequent phenotype associated with male patients of Paget's disease of bone?

Peyronie's disease consists of an idiopathic disorder featured by an inflammatory fibrosis of tunica albuginea of the corpora cavernosa determining deformation of erectus penis [110] and the prevalence of which is approximately 1% in men over 50 years of age, with a peak occurrence at 52 years of age [111]. In a study [110] on a population of US PDB male patients, Peyronie's disease was reported in 31% of PDB patients with normal erection. No statistical differences were observed in PDB patients with or without Peyronie's disease in terms of age, years of PDB and sAP levels. Interestingly, only 0.4% of the patients affected by Peyronie's disease were found to be also affected by PDB, whereas in the PDB population Peyronie's disease has been found with a prevalence of 14.5%. Consequently, it has been suggested that Peyronie's disease may be associated with PDB and may be an unrecognized complication of PDB. However, as also stated by authors themselves, the mentioned study had some limitations, particularly regarding the lack of an adequate control group to compare the prevalence rates of Peyronie's disease [111]. Unfortunately, no other studies on the possible association between these two disorders in male PDB patients have been conducted so far.

Conclusion

PDB, especially in the monostotic or limited skeletal extension form, can have an asymptomatic course for a long time. Consequently, its clinical diagnosis is often later than the onset of its related signs/symptoms. The diagnosis may be suspected on the basis of an elevated sAP level and confirmed by radiographic assessment. Bone scintigraphy is the most convenient imaging test to accurately detect the extent of skeletal segments

involved. Sometimes, the differential diagnosis with other bone pathologies may request a CT scan.

An early diagnosis of the disease favors an early start of treatment and, consequently, a limitation of the skeletal involvement thereof and a rapid remission of symptoms related to the increased bone turnover, even if definitive evidences of its effectiveness on other PDB-related symptoms are lacking.

In first-degree relatives of index cases a higher risk to develop PDB, with respect to general population, has been reported [49], and this risk is even greater in relatives of patients with deforming disease and those with an early age at diagnosis [52]. Moreover, a positive PDB familial history associates to either an early age of onset or a higher incidence of bone deformities, and also a higher fracture rate, in comparison to cases lacking a familial history [22].

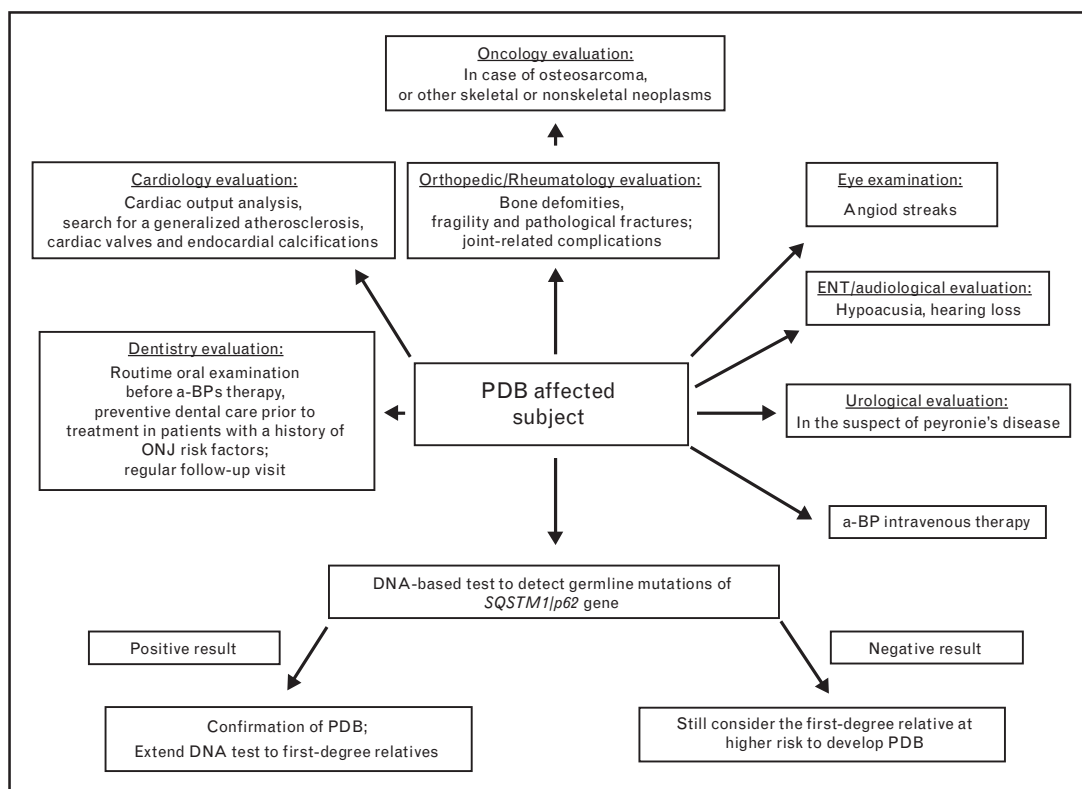
Germline mutations of *SQSTM1/p62* gene have been reported with a variable frequency of between 30 and 50% of cases of familial PDB and approximately 5% of sporadic cases [39–44,45*] and this strongly suggests the opportunity to extend the genetic test to relatives of mutant affected individuals. This may represent a real and concrete strategy to increase the diagnostic sensitivity

for PDB at least in most of the asymptomatic patients resulting to be mutant carriers who, consequently, will undergo periodical biochemical/clinical evaluation. Thus, gene testing could contribute to decrease the morbidity associated with PDB and this is particularly important for familial younger generations whose mutant members can remain symptomatic for many years before expressing the disease and in whom the disease may occur late, with a mild onset, and therefore not to be diagnosed unless their carrier status since a young age is already known.

However, in a still indefinite percentage of PDB cases, the disease evolves giving its typical result of skeletal and extra-skeletal complications. Up to date most of clinical, genetic and interventional reports have been focusing mainly on bone specific aspects of PDB, but it is clear that although PDB is a predominantly metabolic bone disorder, specific complications involving different tissues and organs can be an active part of a more complex clinical phenotype. Unfortunately, assuming it exists, a pathogenic hypothesis unifying all clinical manifestations of PDB, skeletal and extra-skeletal, is still missing.

Randomized clinical trials indicate that antiresorptive treatment is able to effectively reduce the PDB-related pain and lowers the elevated levels of sAP, marker of disease extent and activity [65,112–115]. In particular,

Figure 4 Suggested flow chart for an ideal path that an affected Paget's disease of bone patient could undergo for an adequate clinical evaluation and management



therapy with amino-bisphosphonates (a-BPs), especially through intravenous administration, is able to prevent skeletal complications of PDB [113–115], such as bowing of the limbs and fracture. Unfortunately, such benefits on prevention and progression of extraskeletal complications, such as osteoarthritis, neurological and cardiovascular abnormalities, loss or reduced hearing, eye alterations, and neoplasms are still definitively unproven.

Larger prospective studies evaluating the effectiveness of a precocious start of therapy with a-BPs on prevention of either skeletal or extraskeletal complications are needed.

However, considerable controversy regarding the hierarchy of diagnostic procedures and the medical treatment threshold still remain.

All the above reported evidences must be taken into account in the clinical management of PDB patients. Figure 4 suggests a flow chart of the ideal path that a PDB-affected patient should undergo for a complete view of all potential clinical complications that he/she may or will suffer. Anyway, an accurate collection of familial and personal history of a patient and an equally accurate physical examination, noting any anomalies, skeletal and extra-skeletal, known to be associated with PDB, are mandatory. In fact, clinical examination still represents the richest source for an appropriate and complete clinical description, characterization and management of the disease that needs of multidisciplinary expertise. Only through a proper application of commonly shared clinical protocols, preferably within the context of large multicenter studies, will also be possible to report underestimated or newly appearing clinical signs/symptoms in order to build up most updated clinical management recommendations based primarily on the evidence-based medicine.

Finally, important findings could merge out from longitudinal familial study of PDB affected kindred and from longitudinal long-time clinical observation of the asymptomatic mutant carriers.

Acknowledgement

This review was supported by an unrestricted grant from F. I. R. M. O. Fondazione Raffaella Becagli (to M.L.B.).

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 463–464).

- 1 Paget J. On a form of chronic inflammation of bones (osteitis deformans). *Trans Med-Chir Soc* 1877; 60:37–63.

- 2 Cundy HR, Gamble G, Wattie D, *et al.* Paget's disease of bone in New Zealand: continued decline in disease severity. *Calcif Tissue Int* 2004; 75:358–364.
- 3 Haddaway MJ, Davie MW, McCall IW, Howdle S. Effect of age and gender on the number and distribution of sites in Paget's disease of bone. *Br J Radiol* 2007; 80:532–536.
- 4 Gennari L, Merlotti D, Martini G, Nuti R. Paget's Disease of Bone in Italy. *J Bone Miner Res* 2007; 21:14–21.
- 5 Gold DT, Boisture J, Shipp KM, Pieper CF, *et al.* Paget's disease of bone and quality of life. *J Bone Miner Res* 1996; 11:1897–1904.
- 6 Kanis JA. Pathophysiology and treatment of Paget's disease of bone. London: Martin Dunitz Ltd; 1991.
- 7 Seitz S, Priemel M, Zustin J, *et al.* Paget's disease of bone: histologic analysis of 627 patients. *J Bone Miner Res* 2009; 24:62–69. This study analyzed PDB in terms of incidence, skeletal distribution, malignant transformation, and histological and histomorphometric characteristics through the revision of bone biopsies and patient files of 754 PDB cases. For the first time, a quantitative histomorphometric approach in more than 200 cases revealed an increase of both osteoclast and osteoblast indices.
- 8 Renier JC, Audran M. Progression in length and width of pagetic lesions, and estimation of age at disease onset. *Rev Rheum Ed Fr* 1997; 64:35–43.
- 9 Gardner MJ, Guyer PB, Barker DJP. Paget's disease of bone among British migrants to Australia. *Br Med J* 1978; 2:1436–1437.
- 10 Gomez Acotto C, Mautalen CA. European origin of patients with Paget's disease of bone in the Buenos Aires area. *Eur J Epidemiol* 2001; 17:409–411.
- 11 Griz L, Caldas G, Bandeira C, *et al.* Paget's disease of bone. *Arq Bras Endocrinol Metabol* 2006; 50:814–822.
- 12 van Staa TP, Selby P, Leufkens HG, *et al.* Incidence and natural history of Paget's disease of bone in England and Wales. *J Bone Miner Res* 2002; 17:465–471.
- 13 Poor G, Donath J, Fornet B, Cooper C. Epidemiology of Paget's disease in Europe: the prevalence is decreasing. *J Bone Miner Res* 2006; 21:1545–1549.
- 14 Barker DJ, Gardner MJ. Distribution of Paget's disease in England, Wales and Scotland and a possible relationship with vitamin D deficiency in childhood. *Br J Prev Soc Med* 1974; 28:226–232.
- 15 Detheridge FM, Guyer PB, Barker DJP. European distribution of Paget's disease of bone. *Br Med J* 1982; 285:1005–1008.
- 16 Cooper C, Harvey NC, Dennison EM, van Staa TP. Update on the epidemiology of Paget's disease of bone. *J Bone Miner Res* 2006; 21 (Suppl 2): 3–8.
- 17 Bone HG. Nonmalignant complications of Paget's disease. *J Bone Miner Res* 2006; 21 (Suppl 2):64–68.
- 18 Wermers RA, Tiegs RD, Atkinson EJ, *et al.* Morbidity and mortality associated with Paget's disease of bone: a population-based study. *J Bone Miner Res* 2008; 23:819–825. Before this study, only limited information was available about the clinical aspects of Paget's disease of bone among unselected patients in the community. Authors examined morbidity and mortality associated with Paget's disease of bone in a large inception cohort of a Minnesota's County. No clinical risk factors were identified to be associated with an increased risk of death.
- 19 Gardner MJ, Barker DJ. Mortality from malignant tumours of bone and Paget's disease in the United States and in England and Wales. *Int J Epidemiol Int J Epidemiol* 1978; 7:121–130.
- 20 Cundy T, McAnulty K, Wattie D, *et al.* Evidence for secular change in Paget's disease. *Bone* 1997; 20:69–71.
- 21 Cooper C, Schafheutle K, Dennison E, Kellingray S, *et al.* The epidemiology of Paget's disease in Britain: is the prevalence decreasing? *J Bone Miner Res* 1999; 14:192–197.
- 22 Seton M, Choi HK, Hansen MF, *et al.* Analysis of environmental factors in familial versus sporadic Paget's disease of bone: the New England Registry for Paget's Disease of Bone. *J Bone Miner Res* 2003; 18:1519–1524.
- 23 Rendina D, Gennari L, De Filippo G, *et al.* Evidence for increased clinical severity of familial and sporadic Paget's disease of bone in Campania, southern Italy. *J Bone Miner Res* 2006; 21:1828–1835.
- 24 Gennari L, Di Stefano M, Merlotti D, *et al.* Prevalence of Paget's disease of bone in Italy. *J Bone Miner Res* 2005; 20:1845–1850.
- 25 Rebel A, Basle M, Pouplard A, *et al.* Bone tissue in Paget's disease of bone: ultrastructure and immunocytology. *Arthritis Rheum* 1980; 23:1104–1114.
- 26 Mills BG, Frausto A, Singer FR, *et al.* Multinucleated cells formed in-vitro from Paget's bone-marrow express viral antigens. *Bone* 1994; 15:443–448.

- 27 Reddy SV, Singer FR, Roodman GD. Bone marrow mononuclear cells from patients with Paget's disease contain measles virus nucleocapsid messenger ribonucleic acid that has mutations in a specific region of the sequence. *J Clin Endocrinol Metab* 1995; 80:2108–2111.
- 28 Mee AP, Dixon JA, Hoyland JA, *et al*. Detection of canine distemper virus in 100% of Paget's disease samples by in situ reverse transcriptase-polymerase chain reaction. *Bone* 1998; 23:171–175.
- 29 Helfrich MH, Hobson RP, Grabowski PS, *et al*. A negative search for a paramyxoviral etiology of Paget's disease of bone: molecular, immunological, and ultrastructural studies in UK patients. *J Bone Miner Res* 2000; 15: 2315–2329.
- 30 Ooi CG, Walsh CA, Gallagher JA, Fraser WD. Absence of measles virus and canine distemper virus transcripts in long-term bone marrow cultures from patients with Paget's disease of bone. *Bone* 2000; 27:417–421.
- 31 Kurihara N, Reddy SV, Mena C, *et al*. Osteoclasts expressing the measles virus nucleocapsid gene display a pagetic phenotype. *J Clin Invest* 2000; 105:607–614.
- 32 Reddy SV, Kurihara N, Mena C, *et al*. Osteoclasts formed by measles virus infected osteoclast precursors from hCD46 transgenic mice express characteristics of pagetic osteoclasts. *Endocrinology* 2001; 142:2898–2905.
- 33 Friedrichs WE, Reddy SV, Bruder JM, *et al*. Sequence analysis of measles virus nucleocapsid transcripts in patients with Paget's disease. *J Bone Miner Res* 2002; 17:145–151.
- 34 Kurihara N, Zhou H, Reddy SV, *et al*. Expression of measles virus nucleocapsid protein in osteoclasts induces Paget's disease-like bone lesions in mice. *J Bone Miner Res* 2006; 21:446–455.
- 35 Selby PL, Davies M, Mee AP. Canine distemper virus induces human osteoclastogenesis through NF-kappa B and sequestosome 1/p62 activation. *J Bone Miner Res* 2006; 21:1750–1756.
- 36 Ralston SH, Afzal MA, Helfrich MH, *et al*. Multicenter blinded analysis of RT-PCR detection methods for paramyxoviruses in relation to Paget's disease of bone. *J Bone Miner Res* 2007; 22:569–577.
- 37 Matthews BG, Afzal MA, Minor PD, *et al*. Failure to detect measles virus ribonucleic acid in bone cells from patients with Paget's disease. *J Clin Endocrinol Metab* 2008; 93:1398–1401.
- Measles virus sequences were not detected in any of the pagetic or control samples. The results of the study do not support the hypothesis that measles virus plays a role in the pathogenesis of Paget's disease.
- 38 Gennari L, Gianfrancesco F, Di Stefano M, *et al*. SQSTM1 gene analysis and ●● gene–environment interaction in Paget's disease of bone. *J Bone Miner Res* 2010. [Epub ahead of print]
- Among the Italian PDB population analyzed, patients from Campania region (southern Italy) showed the highest prevalence of animal contacts without any difference between patients with or without mutation of SQSTM1 gene. Animal contacts were observed in 90% of families from this region, suggesting that animal-related factors may be important in the cause of PDB and may interact with SQSTM1 mutation influencing disease severity.
- 39 Laurin N, Brown JP, Morissette J, Raymond V. Recurrent mutation of the gene encoding sequestosome 1 (SQSTM1/p62) in Paget disease of bone. *Am J Hum Genet* 2002; 70:1582–1588.
- 40 Hocking LJ, Lucas GJ, Daroszewska A, *et al*. Domain-specific mutations in sequestosome 1 (SQSTM1) cause familial and sporadic Paget's disease. *Hum Mol Genet* 2002; 11:2735–2739.
- 41 Lucas GJ, Hocking LJ, Daroszewska A, *et al*. Ubiquitin-associated domain mutations of SQSTM1 in Paget's disease of bone: evidence for a founder effect in patients of British descent. *J Bone Miner Res* 2005; 20:227–231.
- 42 Lucas GJ, Hocking LJ, Daroszewska A, *et al*. Novel UBA domain mutations of SQSTM1 in Paget's disease of bone: genotype phenotype correlation, functional analysis, and structural consequences. *J Bone Miner Res* 2004; 19:1122–1127.
- 43 Morissette J, Laurin N, Brown JP. Sequestosome 1: mutation frequencies, haplotypes, and phenotypes in familial Paget's disease of bone. *J Bone Miner Res* 2006; 21:38–44.
- 44 Bolland MJ, Tong PC, Naot D, *et al*. Delayed development of Paget's disease in offspring inheriting SQSTM1 mutations. *J Bone Miner Res* 2007; 22:411–415.
- 45 Falchetti A, Di Stefano M, Marini F, *et al*. Genetic Epidemiology of Paget's ● Disease of Bone in Italy: sequestosome1/p62 Gene Mutational Test and Haplotype Analysis at 5q35 in a Large Representative Series of Sporadic and Familial Italian Cases of Paget's Disease of Bone. *Calcif Tissue Int* 2009; 84:20–37.
- This is the larger genetic study on patients affected by Paget's disease of bone performed on a non British-descent Caucasian population. It confirms the data on the existence of both a mutational hotspot at the UBA domain of SQSTM1/p62 and suggests a founder effect in this PDB population.
- 46 Duran A, Serrano M, Leitges M, *et al*. The atypical PKC-interacting protein p62 is an important mediator of RANK-activated osteoclastogenesis. *Dev Cell* 2004; 6:303–309.
- 47 Rea SL, Walsh JP, Ward L, *et al*. A novel mutation (K378X) in the sequestosome 1 gene associated with increased NF-kappaB signaling and Paget's disease of bone with a severe phenotype. *J Bone Miner Res* 2006; 21: 1136–1145.
- 48 Layfield R, Searle MS. Disruption of ubiquitin-mediated processes in dis- ●● eases of the brain and bone. *Biochem Soc Trans* 2008; 36:469–471.
- This review, written by two known and qualified experts in this field, enables a clear understanding on how SQSTM1/p62 gene mutations impair the ability of p62 to bind to ubiquitin and determines the disordered osteoclast NF-κB signaling underlying the disease etiology. It is an extremely clear review of both the structural mechanism of ubiquitin recognition by the p62 UBA domain and the mechanisms by which different PDB mutations exert their negative effects on ubiquitin binding by p62 has been made. It is extremely helpful also to nonexpert readers.
- 49 Langston AL, Campbell MK, Fraser WD, *et al*. Clinical determinants of quality of life in Paget's disease of bone. *Calcif Tissue Int* 2007; 80:1–9.
- 50 Matthews BG, Naot D, Bava U, *et al*. Absence of somatic SQSTM1 mutations ●● in Paget's disease of bone. *J Clin Endocrinol Metab* 2009; 94:691–694.
- Although some genetic mechanisms have been revealed, the focal nature of Paget's is still unexplained. This study examines the possibility that somatic mutations in the SQSTM1 gene are present in the pagetic local lesions. It concludes that somatic mutations for SQSTM1 are not commonly present in Paget's disease.
- 51 Merchant A, Smielewska M, Patel N, *et al*. Somatic mutations in SQSTM1 ●● detected in affected tissues from patients with sporadic Paget disease of bone. *J Bone Miner Res* 2009; 24:484–494.
- SQSTM1(C1215T) mutation has been found in samples from sporadic pagetic osteosarcoma and not in the normal adjacent tissue, indicating an occurrence of somatic events. The discovery of somatic SQSTM1 mutations in sporadic PDB and pagetic osteosarcoma shows a role for SQSTM1 in both sporadic and inherited PDB. These findings of somatically acquired mutations in both the diseased bone and tumor samples suggests a paradigm shift in the pathogenesis of this disease.
- 52 Siris ES, Ottman R, Flaster E, Kelsey JL. Familial aggregation of Paget's disease of bone. *J Bone Miner Res* 1991; 6:495–500.
- 53 Johnson-Pais TL, Wisdom JH, Weldon KS, *et al*. Three novel mutations in SQSTM1 identified in familial Paget's disease of bone. *J Bone Miner Res* 2003; 18:1748–1753.
- 54 Falchetti A, Di Stefano M, Marini F, *et al*. Two novel mutations at exon 8 of the Sequestosome 1 (SQSTM1) gene in an Italian series of patients affected by Paget's disease of bone (PDB). *J Bone Miner Res* 2004; 19:1013–1017.
- 55 Eekhoff EW, Karperien M, Houtsma D, *et al*. Familial Paget's disease in The Netherlands: occurrence, identification of new mutations in the sequestosome 1 gene, and their clinical associations. *Arthritis Rheum* 2004; 50: 1650–1654.
- 56 Hocking LJ, Lucas GJ, Daroszewska A, *et al*. Novel UBA domain mutations of SQSTM1 in Paget's disease of bone: genotype phenotype correlation, functional analysis, and structural consequences. *J Bone Miner Res* 2004; 19:1122–1127.
- 57 Beyens G, Wuyts W, Cleiren E, *et al*. Identification and molecular characterization of a novel splice-site mutation (G1205C) in the SQSTM1 gene causing Paget's disease of bone in an extended American family. *Calcif Tissue Int* 2006; 79:281–288.
- 58 Collet C, Michou L, Audran M, *et al*. Paget's disease of bone in the French population: novel SQSTM1 mutations, functional analysis, and genotype-phenotype correlations. *J Bone Miner Res* 2007; 22:310–317.
- 59 Najat D, Garner T, Hagen T, *et al*. Characterisation of a non-UBA domain ●● missense mutation of sequestosome 1 (SQSTM1) in Paget's disease of bone. *J Bone Miner Res* 2009; 24:632–642.
- This study describes a functional analysis on a rare non-UBA domain mutations of SQSTM1/p62 gene. This represents the first characterization at the molecular, cellular, and functional level of a non-UBA domain missense mutation of SQSTM1/p62. The obtained finding indicates that non-UBA mutations, as already reported for UBA domain mutations, may exert their effects through a common mechanism involving dysregulated NF-κB signaling.
- 60 Rea SL, Walsh J, Ward L, *et al*. Sequestosome 1 mutations in Paget's ●● disease of bone in Australia: prevalence, genotype/phenotype correlation and a novel non-UBA domain mutation (P364S) associated with increased NFκB signaling without loss of ubiquitin-binding. *J Bone Miner Res* 2009; 24:1216–1223.
- This study examines the prevalence of SQSTM1 mutations in Australian PDB patients, genotype/phenotype correlations and the functional consequences of a novel point mutation (P364S) located upstream of the UBA. As demonstrated by [41], an increased NF-κB signaling may be essential in the pathogenesis of PDB associated with SQSTM1 mutations.

- 61 Chung PY, Beyens G, Guanabens N, *et al.* Founder effect in different European countries for the recurrent P392L SQSTM1 mutation in Paget's disease of bone. *Calcif Tissue Int* 2008; 83:34–42.
- This study sequencing reveals the existence of the common CGTG (H2) haplotype associated with the most frequent mutation of *SQSTM1/p62* gene, P329L. It provides strong evidence for a founder effect of the P392L-SQSTM1 mutation in Belgian, Dutch, and Spanish patients with PDB.
- 62 Layfield R. The molecular pathogenesis of Paget disease of bone. *Expert Rev Mol Med* 2007; 9:1–13.
- 63 Franck WA, Bress NM, Singer FR, Krane SM. Rheumatic manifestations of Paget's disease of bone. *Am J Med* 1974; 56:592–603.
- 64 Alvarez L, Guanabens N, Peris P, *et al.* Discriminative value of biochemical markers of bone turnover in assessing the activity of Paget's disease. *J Bone Miner Res* 1995; 10:458–465.
- 65 Delmas PD, Meunier PJ. Drug therapy: the management of Paget's disease of bone. *N Engl J Med* 1997; 336:558–566.
- 66 Reid IR, Davidson JS, Wattie D, *et al.* Comparative responses of bone turnover markers to bisphosphonate therapy in Paget's disease of bone. *Bone* 2004; 35:224–230.
- 67 Meunier PJ, Salson C, Mathieu L, *et al.* Skeletal distribution and biochemical parameters of Paget's disease. *Clin Orthop Rel Res* 1987; 217:37–44.
- 68 Shankar S, Hosking DJ. Biochemical assessment of Paget's disease of bone. *J Bone Miner Res* 2006; 21 (Suppl 2):22–27.
- 69 Tarquini R, Peretto F, Tarquini B. Endothelin-1 and Paget's bone disease: is there a link? *Calcif Tissue Int* 1998; 63:118–120.
- 70 Pirzer R, Tilly N, Sommer U, *et al.* Endothelin-1 levels in patients with Paget's disease of bone. *Exp Clin Endocrinol Diabetes* 2005; 113:598–601.
- 71 Khairi MR, Robb JA, Wellman HN, Johnston CC Jr. Radiographs and scans in diagnosing symptomatic lesions of Paget's disease of bone (osteitis deformans). *Geriatrics* 1974; 29:49–54.
- 72 Steinbach HL. Some roentgen features of Paget's disease. *Am J Radiol* 1961; 86:950–964.
- 73 Wilner D, Sherman RS. Roentgen diagnosis of Paget's disease (osteitis deformans). *Med Radiogr Photogr* 1966; 42:35–78.
- 74 Wellman HN, Schauwecker D, Robb JA, *et al.* Skeletal scintigraphy and radiography in the diagnosis and management of Paget's disease. *Clin Orthop Rel Res* 1977; 127:55–62.
- 75 Mackenzie I, Young C, Fraser WD. Tinnitus and Paget's disease of bone. *J Laryngol Otol* 2006; 120:899–902.
- 76 Smith BJ, Eveson JW. Paget's disease of bone with particular reference to dentistry. *J Oral Pathol* 1981; 10:233–247.
- 77 Hadjipavlou AG, Gaitanis LN, Katonis PG, Lander P. Paget's disease of the spine and its management. *Eur Spine J* 2001; 10:370–384.
- 78 Dove J. Complete fractures of the femur in Paget's disease of bone. *J Bone Joint Surg Br* 1980; 62-B:12–17.
- 79 Allen ML, John RL. Osteitis deformans (Paget's disease). Fissure fractures: their etiology and clinical significance. *Am J Roentgenol Rad Ther* 1937; 38:109–115.
- 80 Marr DS, Rosenthal DI, Cohen GL, Tomford WW. Rapid postoperative osteolysis in Paget disease: a case report. *J Bone Joint Surg Am* 1994; 76:274–277.
- 81 Rubin DJ, Levin RM. Neurologic complications of Paget disease of bone. • *Endocr Pract* 2009; 15:158–166.
- This is exhausting review on the epidemiology, evaluation, and management of the neurological complications associated with Paget disease of bone. It suggests that neurological sequelae of PDB may be underappreciated.
- 82 Briesacher BA, Orwig D, Seton M, *et al.* Medical care costs of Paget's disease of bone in a privately insured population. *Bone* 2006; 38:731–737.
- 83 Monsell EM. The mechanism of hearing loss in Paget's disease of bone. *Laryngoscope* 2004; 114:598–606.
- 84 Teufert KB, Linthicum F Jr. Paget disease and sensorineural hearing loss associated with spiral ligament degeneration. *Otol Neurotol* 2005; 26:387–391.
- 85 Smith R. Paget's disease and angiod streaks: one complication less? *Br J Ophthalmol* 1990; 74:577–578.
- 86 Haworth S. Cardiac output in osteitis deformans. *Clin Sci* 1953; 12:271–275.
- 87 Laroche M, Delmotte A. Increased arterial calcification in Paget's disease of bone. *Calcif Tissue Int* 2005; 77:129–133.
- 88 Strickberger SA, Schulman SP, Hutchins GM. Association of Paget's disease of bone with calcific aortic valve disease. *Am J Med* 1987; 82:953–956.
- 89 Sokullu O, Tabakan A, Sanioglu S, *et al.* Effect of coexisting Paget's disease on coronary artery bypass operations. *J Card Surg* 2006; 21:597–599.
- 90 Fournier P, Boissier S, Filleur S, *et al.* Bisphosphonates inhibit angiogenesis in vitro and testosterone-stimulated vascular regrowth in the ventral prostate in castrated rats. *Cancer Res* 2002; 62:6538–6544.
- 91 Reddy SV, Mena C, Singer FR, *et al.* Measles virus nucleocapsid transcript expression is not restricted to the osteoclast lineage in patients with Paget's disease of bone. *Exp Hematol* 1999; 27:1528–1532.
- 92 Mills BG, Frausto A. Cytokines expressed in multinucleated cells: Paget's disease and giant cell tumors versus normal bone. *Calcif Tissue Int* 1997; 61:16–21.
- 93 Cavey JR, Ralston SH, Hocking LJ, *et al.* Loss of ubiquitin-binding associated with Paget's disease of bone p62 (SQSTM1) mutations. *J Bone Miner Res* 2005; 20:619–626.
- 94 Sattler AM, Schoppet M, Schaefer JR, Hofbauer LC. Novel aspects on RANK ligand and osteoprotegerin in osteoporosis and vascular disease. *Calcif Tissue Int* 2004; 74:103–106.
- 95 Franchi A. Pathology of Paget's disease of bone. *Clin Cases Miner Bone Metab* 2004; 1:203–207.
- 96 Haibach H, Farrell C, Dittrich FJ, Wick MR. Neoplasms arising in Paget's disease of bone: a study of 82 cases. *Am J Clin Pathol* 1985; 83:594–600.
- 97 Mankin HJ, Hornicek FJ. Paget's sarcoma: a historical and outcome review. *Clin Orthop Relat Res* 2005; 438:97–102.
- 98 Mangham DC, Davie MW, Grimer RJ. Sarcoma arising in Paget's disease of bone: declining incidence and increasing age at presentation. *Bone* 2009; 44:431–436.
- Sarcomatous transformation is a rare complication of Paget's disease of bone, present among polyostotic cases, although a more widespread skeletal involvement by Paget's disease is not a significant risk factor for malignant transformation. A male predominance of this malignancy continues in pagetic patients. Although rare, it continues to have a poor prognosis and is often the presenting feature of the disease.
- 99 Hansen MF, Seton M, Merchant A. Osteosarcoma in Paget's disease of bone. *J Bone Miner Res* 2006; 21 (Suppl 2):58–63.
- 100 Reifenshtein EC Jr, Albright F. Paget's disease: its pathologic physiology and the importance of the complications arising from fracture and immobilization. *N Engl J Med* 1944; 231:343–355.
- 101 Jacobs TP, Michelsen J, Polay JS, *et al.* Giant cell tumor in Paget's disease of bone: familial and geographic clustering. *Cancer* 1979; 44:742–747.
- 102 Singer FR, Mills BG. Giant cell tumor arising in Paget's disease of bone: recurrences after 36 years. *Clin Orthop Relat Res* 1993; 293:293–301.
- 103 Shaylor PJ, Peake D, Grimer RJ, *et al.* Paget's osteosarcoma: no cure in sight. *Sarcoma* 1999; 3:191–192.
- 104 Gutteridge DH, Gruber HE, Kermod DG, Worth GK. Thirty cases of concurrent Paget's disease and primary hyperparathyroidism: sex distribution, histomorphometry, and prediction of the skeletal response to parathyroidectomy. *Calcif Tissue Int* 1999; 65:427–435.
- 105 Brandi ML, Falchetti A. What is the relationship between Paget's disease of bone and hyperparathyroidism? *J Bone Miner Res* 2006; 21 (Suppl 2):69–74.
- 106 Genuth SM, Klein L. Hypoparathyroidism and Paget's disease: the effect of parathyroid hormone administration. *J Clin Endocrinol Metab* 1972; 35:693–699.
- 107 Siris ES, Clemens TP, McMahon D, *et al.* Parathyroid function in Paget's disease of bone. *J Bone Miner Res* 1989; 4:75–79.
- 108 Ralph DJ, Mirakian R, Pryor JP, Bottazzo GF. The immunological features of Peyronie's disease. *J Urol* 1996; 155:159–162.
- 109 Nagant de Deuxchaisnes CN, Krane SM. Paget's disease of bone: clinical and metabolic observations. *Medicine (Baltimore)* 1964; 43:233–266.
- 110 Devine CJ Jr, Horton CE. Peyronie's disease. *Clin Plastic Surg* 1989; 15:405–409.
- 111 Lyles KW, Gold DT, Newton RA, *et al.* Peyronie's disease is associated with Paget's disease of bone. *J Bone Miner Res* 1997; 12:929–934.
- 112 Hosking D, Meunier PJ, Ringe JD, *et al.* Paget's disease: diagnosis and management. *Br Med J* 1996; 312:491–494.
- 113 Reid IR, Miller P, Lyles K, *et al.* Comparison of a single infusion of zoledronic acid with risedronate for Paget disease. *N Engl J Med* 2005; 353:898–908.
- 114 Hosking D, Lyles K, Brown JP, *et al.* Long-term control of bone turnover in Paget's disease with zoledronic acid and risedronate. *J Bone Miner Res* 2007; 22:142–148.
- 115 Tziomalos K, Florentin M, Krikis N, *et al.* Persistent effect of zoledronic acid in Paget's disease. *Clin Exp Rheumatol* 2007; 25:464–466.