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

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

<table>
<thead>
<tr>
<th>Site</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvis</td>
<td>67%</td>
</tr>
<tr>
<td>Vertebral</td>
<td>34%</td>
</tr>
<tr>
<td>Femur</td>
<td>32%</td>
</tr>
<tr>
<td>Tibias</td>
<td>25%</td>
</tr>
<tr>
<td>Skull</td>
<td>23%</td>
</tr>
<tr>
<td>Humerus</td>
<td>11%</td>
</tr>
<tr>
<td>Ribs</td>
<td>7%</td>
</tr>
<tr>
<td>Calcaneus</td>
<td>4%</td>
</tr>
<tr>
<td>Ulna</td>
<td>2%</td>
</tr>
<tr>
<td>Scapula</td>
<td>2%</td>
</tr>
<tr>
<td>Hands</td>
<td>2%</td>
</tr>
<tr>
<td>Mandible</td>
<td>1%</td>
</tr>
<tr>
<td>Sternum</td>
<td>1%</td>
</tr>
</tbody>
</table>

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 descendants and also French, Dutch, Spanish and Italian descendants) [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]
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**].
modulator of the function of nuclear growth factor κB, NFκB, 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 NFκB [46,47,48**].

**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 preclusively 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

<table>
<thead>
<tr>
<th>Pain</th>
<th>Bone pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deformity</td>
<td>Inclination of the long bones</td>
</tr>
<tr>
<td></td>
<td>Cranial deformities</td>
</tr>
<tr>
<td>Fractures</td>
<td>Enlargement of the segments involved</td>
</tr>
<tr>
<td>Neurological complications</td>
<td>Complete</td>
</tr>
<tr>
<td></td>
<td>Fissures of the cortex</td>
</tr>
<tr>
<td>Transformation tumor</td>
<td>Deafness</td>
</tr>
<tr>
<td></td>
<td>Paralysis of other cranial nerves</td>
</tr>
<tr>
<td></td>
<td>Spinal cord compression</td>
</tr>
<tr>
<td></td>
<td>Sarcoma</td>
</tr>
</tbody>
</table>

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 Seques-trosome1 (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
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 I 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 physiopathological 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

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial form: mainly lytic</td>
<td>V-shaped figures of the cortex of long bones</td>
</tr>
<tr>
<td>Intermediate phase</td>
<td>Circumscribed osteoporosis of the skull</td>
</tr>
<tr>
<td></td>
<td>Thickening of the cortex</td>
</tr>
<tr>
<td></td>
<td>Indistinguishability of the cortico-medullary border</td>
</tr>
<tr>
<td>Late stage: mostly</td>
<td>Thickening of long bones</td>
</tr>
<tr>
<td></td>
<td>Increased bone section</td>
</tr>
<tr>
<td></td>
<td>Sclerosis</td>
</tr>
</tbody>
</table>

Bone scintigraphy with biphosphonate 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 osteoelastic 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 bone metabolic disorders exists.

Bone biopsy
Bone biopsy is rarely required for diagnosis of PDB and may be useful in the presence of radiological features 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

<table>
<thead>
<tr>
<th>Diagnostic Method</th>
<th>Radiant Exposure (mSv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional bone scintigraphy</td>
<td>3–5</td>
</tr>
<tr>
<td>Pelvic radiographs</td>
<td>0.7–1.4</td>
</tr>
<tr>
<td>Lumbar spine radiographs</td>
<td>1.3–2.7</td>
</tr>
<tr>
<td>Total body radiographs</td>
<td>2.7</td>
</tr>
<tr>
<td>Trunk computed tomography</td>
<td>5–15</td>
</tr>
</tbody>
</table>
Table 5 Skeletal-related complications of Paget’s disease of bone

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

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

<table>
<thead>
<tr>
<th>Complication</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis due to altered distribution of the mechanical load secondary to skeletal deformities of affected segments</td>
<td>Spine, Pain due to associated degenerative arthritis, Nerve root or spinal cord impingement (less common), 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</td>
</tr>
</tbody>
</table>

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 non-heeling 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 bone homoeostasis, 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) malfunctions/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 gene expression 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)-κB 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 CIBS), 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 Paget’s 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].

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Metabolic abnormalities frequently observed in Paget's disease of bone patients
Several metabolic abnormalities have been frequently described in PDP 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 postoperative 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.

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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 erect 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.

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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,

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**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.

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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).

This study analyzed PBD in terms of incidence, skeletal distribution, malignant transformation, and histological and histomorphometric characteristics through the revision of bone biopsies and patient files of 764 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, Aidar M. Progression in length and width of pagetic lesions, and estimation of age at disease onset. Rev Rhum Ed Fr 1987; 64:35–43.
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.