

# Demographic and Clinical Features Related to a Symptomatic Onset of Paget's Disease of Bone

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**ABSTRACT** *Objective.* Paget's disease of bone (PDB) is a focal disorder of skeletal remodeling that can lead to bone pain, deformity, and fractures, but it can often be asymptomatic for a long time. This study investigated which factors may distinguish patients with clinical manifestations from asymptomatic patients.

*Methods.* The study group consisted of 224 patients with PDB referred to our Bone Disease Unit. For all patients, data were collected about clinical and demographic variables and diagnostic procedures. Logistic regression analyses were used to assess the role of recorded variables on the odds of being diagnosed clinically rather than by chance.

*Results.* Among the 124 patients with clinical manifestations leading to the diagnosis (55.4%), 36 subjects complained of bone pain, 32 articular pain, 42 back pain, 2 headache; 9 had fractures in Paget bone, and 3 had bone deformity. In 100 patients (44.6%) PDB was diagnosed by chance. At the multivariate analysis, only the number of bones involved (OR for 1 site increment = 1.18, 95% CI: 1.007-1.402;  $p = 0.04$ ) acted as an independent predictor for a clinical diagnosis. Some skeletal localizations were associated with a clinical diagnosis: the involvement of lumbar spine (OR = 2.085, 95% CI: 1.024-4.224;  $p = 0.043$ ) was more likely in symptomatic patients; pelvis and tibia showed a borderline statistical significance. The skull was predictive for asymptomatic PDB.

*Conclusion.* A systematic laboratory screening including serum alkaline phosphatase of an older subject complaining of bone pain, articular pain, or back pain is the sole strategy to improve the diagnostic sensitivity for PDB. (J Rheumatol First Release Dec 1 2009; doi:10.3899/jrheum.090674)

## Key Indexing Terms:

PAGET'S DISEASE OF BONE  
DIAGNOSIS

EPIDEMIOLOGY

CLINICAL FEATURES  
NATURAL HISTORY

Paget's disease of bone (PDB) is a focal disorder of skeletal remodeling that can lead to an abnormal bone structure responsible for bone pain, bone deformity, and fractures. Other possible complications of PDB can be related to joint involvement inducing secondary osteoarthritis, and nervous system involvement with neurological compression syndromes; in rare cases, a sarcomatous degeneration of Paget bone has been described<sup>1-4</sup>. The typical signs and symptoms of PDB and its complications may affect the quality of life of the patients, resulting in significant disability<sup>5,6</sup>. Clinical series from hospital referral centers usually involve a high rate of symptomatic patients such as those recognized because of clinical manifestations that lead to the diagnosis,

but it is generally accepted that most patients (up to 95%) are asymptomatic and often undiagnosed<sup>7</sup>. In these subjects, PDB is accidentally discovered during a routine laboratory screening showing an elevated serum alkaline phosphatase (SAP), or by radiological investigations performed for unrelated diseases. It has been suggested that the development of symptoms and complications of PDB is related to several features of the disease such as the number of involved bones, their anatomic distribution, the closeness to other structures, the level of disease activity, the rate of progression<sup>8</sup>, and familial disease<sup>9</sup>, but the question remains why some of the affected individuals become symptomatic and how many are diagnosed by means of these symptoms. This issue obviously influences the clinical outcome of the patients and the burden of medical care for PDB. To find diagnostic clues allowing an early diagnosis, we investigated which factors may distinguish patients with clinical manifestations evocative of PDB.

## MATERIALS AND METHODS

From January 2000 to July 2007, we recruited 224 patients with PDB referred for the first time to the Bone Disease Unit of our hospital. Only patients with a suspected but unconfirmed diagnosis or patients recently diagnosed (< 6 months) were recruited. The diagnosis was confirmed by

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radiological assessments, bone scan, and biochemical evaluation, performed on all patients. The scintiscan used  $^{99}\text{Tc}$ -labeled methylene bisphosphonate as a tracer; from the scintiscan, the total number of bones and the proportion of skeleton involved, as assessed by Coutris, *et al*<sup>10</sup>, were recorded. Most of the patients were untreated, but 6 had previously received treatments: calcitonin (2 patients) or bisphosphonates (etidronate: 1 patient, clodronate: 3 patients). Only biochemical data collected before treatment were considered for this study. To account for variation in reference ranges of SAP values among laboratories, the percentage increases with respect to maximum normal value of the individual laboratory were calculated before any specific treatment. No patients showed cholestatic liver diseases. Patients were interviewed by a consultant using a questionnaire that covered the following areas: demographics, education level, family history of PDB (a first-degree relative diagnosed as having PDB), age at diagnosis, and diagnostic procedures. For symptomatic cases, the patients were asked to state the age at the onset of symptoms connected to PDB. When the patient's presenting symptom was pain, attempts were made to define if pain was due to PDB or associated osteoarthritis. According to previous definitions<sup>11</sup>, pain was assumed to arise from joints if it was worsened by exercise and relieved by rest, if it limited the range of movement, if radiological findings showed a narrowing of joint space, and if the patient reported an improvement by using nonsteroidal anti-inflammatory drugs; pain was attributed to bone if it was more severe at night and was neither precipitated by exercise nor relieved by rest. Given the difficulty of assessing whether back pain arises as a consequence of PDB or as a result of degenerative changes, that symptom has not been classified according to these criteria.

**Statistical analysis.** Continuous variables were described by means of medians and quartiles (Q1-Q3). When percentiles were too flat and did not provide effective descriptions, mean values were used. The Wilcoxon rank sum test or the Kruskal-Wallis test were used to compare values of continuous variable distributions. The chi-squared test or the Fisher's exact test was applied to study the association between categorical variables. To assess linear relationships, the chi-squared test for trend (for categorical variables) or the Spearman correlation coefficient (for continuous variables) were calculated, as appropriate.

At multivariable analysis, the logistic regression model was used to assess the role of recorded variables on the odds of being diagnosed by symptoms rather than by chance. Two different models were calculated. The first model considered only demographic and clinical variables. The following covariates were included: age at diagnosis, gender, family history of PDB, education, residence, disease extent (mono vs polyostotic), SAP value (per 1-unit increment), and the number of affected sites (per 1-site increment). The choice of the covariates included in the multivariable model was made by considering the factors that had a relevant effect on the outcome (univariable analysis) plus other potential confounders. A further logistic regression model assessed the predictive role of each disease localization on the probability of being symptomatic and clinically diagnosed. The evaluated localizations were skull, face, clavicle, sternum, ribs, thoracic spine, lumbar spine, sacrum, pelvis, scapula, humerus, radius, femur, tibia, and foot. Adjusted OR and the corresponding 95% confidence intervals (CI) were calculated in relation to the variables entered into each model. All the statistical tests were 2-sided at the 5% level and performed using SAS Software (release 8.2; SAS Institute).

## RESULTS

Demographic and clinical features are reported in Table 1. Among the 224 patients recruited, 124 (55.4%) were male with a male/female ratio of 1.24. The median age at diagnosis was 62 years (range: 53-70 yrs), with women significantly older (women: 64, 56-72; men: 58, 51-68;  $p = 0.007$ ), while the number of affected bones and the disease extent did not differ between men and women.

Overall, there were 652 skeletal sites affected by the disease, with a median value of 2 sites for each patient (1-3, mean  $\pm$  standard deviation:  $2.9 \pm 4.6$ ). Monostotic disease was recognized in 97 patients (43.3%). The most common affected sites were pelvis (126 patients, 56.3%), lumbar spine (67 patients, 29.9%), femur (61 patients, 27.2%), skull (46 patients, 20.5%), sacrum (42 patients, 18.7%), and tibia (38 patients, 17.0%). In the sample as a whole, there were 100 (44.6%) asymptomatic patients referred following an incidental diagnosis. In 79 cases (35.3%) the patients came to our observation as a result of suspected PDB because of biochemical investigations showing an increased SAP, with other liver enzymes in the normal range. In 16 cases (7.1%) the diagnosis was made when a radiograph was obtained for another reason, and in 5 cases (2.2%) the disease was diagnosed by a bone scintigraphy performed for other indications. Among the 124 patients (55.4%) diagnosed through investigations requested for specific clinical manifestations, 36 subjects (16% of the sample, 29% of the symptomatic group) complained of bone pain; 32 patients (14.3% of the sample, 25.8% of the symptomatic group) complained of articular pain; 42 patients (18.7% of the sample, 33.9% of the symptomatic group) were diagnosed as a consequence of back pain, and in 2 cases (0.9% of the sample, 1.6% of the symptomatic group) the symptom at the onset was headache. Finally, 9 patients (4% of the sample, 7.2% of the symptomatic group) were diagnosed because of fractures of Paget bone (3 vertebral, 4 fissure fractures of the femur, 1 fissure fracture of the tibia, and 1 complete fracture of the femur), and in 3 cases (1.3% of the sample, 2.4% of the symptomatic group) the diagnosis was made by radiological investigations requested for bone deformity (1 femur, 2 tibia).

Comparing patients diagnosed clinically with those diagnosed by chance (Table 1), there was no difference in age at diagnosis, gender, place of birth, educational level, familial history for Paget's disease, prevalence of monostotic disease, SAP mean values, the number of involved bones, and the extent of the disease as calculated by Coutris index ( $p = 0.892$ ). No linear trend was found between the age at diagnosis (grouped into 10-year intervals) and the presence of a symptomatic disease ( $\leq 50$  years: 67%; 51-60 years: 57%; 61-70 years: 51%; 71-80 years: 51%;  $> 80$  years: 40%;  $p = 0.075$ ). Symptomatic patients showed less frequent involvement of the skull (18 patients vs 28;  $p = 0.02$ ); but more frequent (but not significant) involvement was observed for lumbar spine (44 vs 23;  $p = 0.056$ ) and pelvis (78 vs 48;  $p = 0.082$ ; Table 2). No significant differences were found for other sites of disease.

The number of involved vertebrae showed a significant correlation with the presence of back pain both at lumbar level (pain: mean = 0.607; no pain: mean = 0.346;  $p = 0.028$ ) and (although not statistically significant) at dorsal level (pain: mean = 0.444; no pain: mean = 0.234;  $p = 0.057$ ). The

**Table 1.** Demographic and clinical characteristics [median (interquartile range) or number of patients (percentage)] in 224 patients with Paget's disease of bone diagnosed by symptoms, or incidentally.

| Characteristic                     | All Patients,<br>n = 224 | Symptomatic Patients<br>Diagnosed Clinically,<br>n = 124 | Asymptomatic Patients<br>Diagnosed Incidentally,<br>n = 100 | p     |
|------------------------------------|--------------------------|--|---|-------|
| Age at diagnosis                   | 62 (53–70)               | 61 (52–69)   | 64 (55–71)  | 0.071 |
| Male/female                        | 124 (55.4)/100 (44.6)    | 67 (54.0)/57 (57.0)                                      | 57 (46.0)/43 (43.0)   | 0.687 |
| Age at symptoms onset              | —                        | 59 (51–68)   | —   | —     |
| Mono/polyostotic                   | 97 (43.3)/127 (56.7)     | 58 (46.8)/66 (53.2)                                      | 39 (39.0)/61 (61.0)   | 0.279 |
| Family history of<br>Paget disease | 14 (6.2)                 | 9 (7.3)  | 5 (5.0)   | 0.585 |
| No. of affected sites              | 2 (1–3)                  | 2 (1–3)  | 2 (1–3)   | 0.402 |
| SAP                                | 168 (123–281)            | 159 (113–278)  | 195 (136–326)   | 0.097 |
| Coutiris index                     | 9 (5–13)                 | 7 (5–12)   | 10 (5–14)   | 0.892 |
| Place of birth                     |                          |  |   |       |
| Milan                              | 53 (24.0)                | 22 (18.0)  | 31 (31.3)   | 0.067 |
| Northern Italy                     | 121 (54.8)               | 73 (59.8)  | 48 (48.5)   |       |
| Central/southern Italy             | 47 (21.3)                | 27 (22.1)  | 20 (20.2)   |       |
| Residence                          |                          |  |   |       |
| Milan                              | 117 (52.2)               | 56 (45.2)  | 61 (61.0)   | 0.041 |
| Northern Italy                     | 98 (43.7)                | 61 (49.2)  | 37 (37.0)   |       |
| Central/southern Italy             | 9 (4.0)                  | 7 (5.6)  | 2 (2.0)   |       |
| Level of education                 |                          |  |   |       |
| Primary school                     | 106 (47.5)               | 62 (50.4)  | 44 (44.0)   | 0.727 |
| Middle school                      | 53 (23.8)                | 26 (21.1)  | 27 (27.0)   |       |
| High school                        | 47 (21.1)                | 26 (21.1)  | 21 (21.0)   |       |
| University                         | 17 (7.6)                 | 9 (7.3)  | 8 (8.0)   |       |

SAP: serum alkaline phosphatase (percentage increase with respect to maximum normal value).

**Table 2.** Description of skeletal localization in patients with Paget's disease of bone diagnosed by symptoms or incidentally. Values are expressed as number (%).

| Involved Site  | All Patients,<br>n = 224 | Symptomatic Patients<br>Diagnosed Clinically,<br>n = 124 | Asymptomatic Patients<br>Diagnosed Incidentally,<br>n = 100 | p     |
|----------------|--------------------------|--|---|-------|
| Skull          | 46 (20.5)                | 18 (14.5)  | 28 (28.0)   | 0.019 |
| Face           | 5 (2.2)                  | 4 (3.2)  | 1 (1.0)   | 0.384 |
| Clavicle       | 9 (4.0)                  | 6 (4.8)  | 3 (3.0)   | 0.734 |
| Sternum        | 4 (1.8)                  | 2 (1.6)  | 2 (2.0)   | 0.999 |
| Ribs           | 7 (3.1)                  | 5 (4.0)  | 2 (2.0)   | 0.465 |
| Thoracic spine | 31 (13.8)                | 21 (16.9)  | 10 (10.0)   | 0.173 |
| Lumbar spine   | 67 (29.9)                | 44 (35.5)  | 23 (23.0)   | 0.056 |
| Sacrum         | 42 (18.7)                | 24 (19.3)  | 18 (18.0)   | 0.864 |
| Pelvis         | 126 (56.3)               | 78 (62.9)  | 48 (48.0)   | 0.082 |
| Scapula        | 8 (3.6)                  | 2 (1.6)  | 6 (6.0)   | 0.144 |
| Humerus        | 21 (9.4)                 | 10 (8.1)   | 11 (11.0)   | 0.495 |
| Radius         | 3 (1.3)                  | 2 (1.6)  | 1 (1.0)   | 0.999 |
| Femur          | 61 (27.2)                | 37 (29.8)  | 24 (24.0)   | 0.999 |
| Tibia          | 38 (17.0)                | 26 (21.0)  | 12 (12.0)   | 0.210 |
| Foot           | 4 (1.8)                  | 2 (1.6)  | 2 (2.0)   | 0.998 |

number of involved bones was also significantly correlated with SAP values ( $r = 0.461$ ;  $p < 0.0001$ ). Consistently, the majority of patients with normal SAP values (33 cases) had a monostotic disease (22 patients). In these patients, diagnosis was achieved by a radiological assessment requested for clinical symptoms in 28 cases.

Finally, in symptomatic patients no correlations were found in the time between age at symptom onset and age at

diagnosis and the level of education or the residence (data not shown).

Table 3 shows the results of the multivariable analysis (logistic regression) applied to evaluate the predictors of symptomatic disease. Age at diagnosis, gender, place of birth, residence, level of education, polyostotic disease, SAP values, and family history for PDB were not associated with increased odds of having a symptomatic disease, while the

**Table 3.** Multiple logistic regression analysis of the risk of being clinically diagnosed as having Paget's disease of bone, according to demographic and clinical characteristics (n = 224).

|   | OR    | 95% CI      | p      |
|---|-------|-------------|--------|
| Age at diagnosis<br>(1-year increment)      | 0.978 | 0.948–1.008 | 0.1516 |
| Gender                                      |       |             |        |
| Female                                      | 1.212 | 0.679–2.163 | 0.5157 |
| Male  | 1     | —           |        |
| Level of education                          |       |             |        |
| Primary school                              | 1.112 | 0.336–3.683 |        |
| Middle school                               | 0.593 | 0.167–2.106 | 0.4210 |
| High school                                 | 0.814 | 0.227–2.924 |        |
| University                                  | 1     | —           |        |
| Residence                                   |       |             |        |
| Milan                                       | 0.392 | 0.069–2.211 | 0.3271 |
| Northern Italy                              | 0.587 | 0.105–3.275 |        |
| Central/southern Italy                      | 1     | —           |        |
| Family history of Paget's disease           |       |             |        |
| Yes   | 1     | —           | 0.5698 |
| No  | 0.695 | 0.199–2.434 |        |
| No. of affected sites<br>(1-site increment) | 1.188 | 1.007–1.402 | 0.0407 |
| Disease extent                              |       |             |        |
| Mono  | 2.002 | 0.984–4.074 | 0.0556 |
| Polyostotic                                 | 1     | —           |        |
| SAP value (1 unit increment)                | 0.998 | 0.996–1.000 | 0.1216 |

SAP: serum alkaline phosphatase (percentage increase with respect to maximum normal value).

number of bones involved (OR = 1.18, 95% CI: 1.007–1.402;  $p = 0.04$ ) was the only variable that acted as an independent predictor for a clinical diagnosis.

When the same analysis was performed to investigate whether specific skeletal localizations were associated with a clinical diagnosis (Table 4), it was found that symptomatic patients were more likely to have an involvement of lumbar

**Table 4.** Multiple logistic regression analysis of the risk of being clinically diagnosed as having Paget's disease of bone, according to skeletal localization (n = 224).

| Involved Site          | OR      | 95% CI       | p     |
|------------------------|---------|--------------|-------|
| Skull, yes/no          | 0.304/1 | 0.139–0.665  | 0.003 |
| Face, yes/no           | 6.425/1 | 0.523–78.967 | 0.146 |
| Clavicle, yes/no       | 1.376/1 | 0.276–6.865  | 0.697 |
| Sternum, yes/no        | 0.640/1 | 0.069–5.975  | 0.696 |
| Ribs, yes/no           | 2.487/1 | 0.225–27.542 | 0.458 |
| Thoracic spine, yes/no | 1.339/1 | 0.502–3.572  | 0.560 |
| Lumbar spine, yes/no   | 2.085/1 | 1.024–4.244  | 0.043 |
| Sacrum, yes/no         | 1.370/1 | 0.617–3.041  | 0.439 |
| Pelvis, yes/no         | 1.753/1 | 0.982–3.129  | 0.058 |
| Scapula, yes/no        | 0.149/1 | 0.021–1.044  | 0.055 |
| Humerus, yes/no        | 0.667/1 | 0.237–1.874  | 0.442 |
| Radius, yes/no         | 1.441/1 | 0.120–17.361 | 0.774 |
| Femur, yes/no          | 1.356/1 | 0.695–2.647  | 0.371 |
| Tibia, yes/no          | 2.075/1 | 0.940–4.579  | 0.071 |
| Foot, yes/no           | 0.748/1 | 0.088–6.375  | 0.791 |

spine (OR = 2.085, 95% CI: 1.024–4.244;  $p = 0.043$ ). Instead, the involvement of the skull was more unlikely in symptomatic patients (OR = 0.304, 95% CI: 0.139–0.665;  $p = 0.003$ ). Pelvis and tibia involvement showed a borderline statistical significance for symptomatic disease (pelvis: OR = 1.753, 95% CI 0.982–3.129;  $p = 0.058$ ; tibia: OR = 2.075, 95% CI 0.940–4.579;  $p = 0.071$ ), while scapula involvement showed a borderline statistical significance for asymptomatic disease (OR = 0.149, 95% CI 0.021–1.044;  $p = 0.055$ ).

## DISCUSSION

Our aim was to assess whether demographic and clinical characteristics can influence the probability that a patient would be symptomatic and then diagnosed as having PDB. The results confirm that the number of affected bones is the only variable that generates symptoms that may enable the diagnosis<sup>7,12</sup>. It is generally accepted that most of the patients are asymptomatic, but the prevalence of subjects who develop symptoms and reach a clinical diagnosis varies considerably among studies, ranging from 1% to 94%, depending on the study design and the referral pattern<sup>12,13</sup>. A widely accepted figure estimates that symptomatic disease could account for 5% of the total population of patients with PDB<sup>7</sup>. As reported by others, the age at diagnosis was not different between asymptomatic patients diagnosed by chance and patients with a clinical diagnosis, suggesting that the disease does not become symptomatic with age<sup>14</sup>. Even if the disease extent were not greater in men than in women, a significantly older age at diagnosis was found in women, in keeping with other series<sup>4,15</sup>. The hypotheses to account for this difference are a more intense mechanical stress in the male skeleton that increases the probability of an earlier onset of symptoms<sup>4</sup> or a less-active disease in women before menopause due to an estrogen-mediated inhibition of osteoclastic activity<sup>16</sup>.

Although the number of affected bones was a predictive variable for a symptomatic disease, in our sample monostotic PDB was not more frequent in incidentally diagnosed patients than in clinically diagnosed ones, nor was polyostotic disease predictive for a symptomatic disease in comparison with monostotic disease. Generally, polyostotic disease has been found to be more symptomatic<sup>17</sup>, but in 197 consecutive patients referred to Sheffield University, the clinical presentation was not different in patients with monostotic or polyostotic disease<sup>7</sup>. Another possibility could be an underrepresentation of monostotic disease in patients diagnosed by chance.

As in other studies<sup>7</sup>, there was a significant correlation between SAP values and the number of involved bones. Consistently, we found a high prevalence of monostotic disease in patients with SAP values within the normal range. In these patients, diagnosis of PDB can be achieved only by radiological assessment. Even if bone pain were the most evocative symptom for PDB, in our sample the great major-



ity of symptomatic patients with normal SAP values (25 of 28) complained of nonspecific symptoms, such as joint or back pain.

Age at diagnosis was not significantly different among patients recognized clinically or by chance according to place of birth, residence, and the educational level. In the same way, the results of the logistic analysis showed that these variables were not predictive for a clinical diagnosis. These results, together with the lack of any correlation between the time from the onset of symptoms and diagnosis, seem to exclude inequalities in the awareness of the health system of the disease and suggest that all patients share the same opportunity to be diagnosed.

Consistent with most of the other series, pain was the main reason for referral in symptomatic patients (90% of cases clinically diagnosed). We tried to distinguish pain arising from bone and pain due to joint involvement, even if a distinction based only on clinical signs or symptoms is frequently difficult and often unreliable<sup>11</sup>. The presence and an increased severity of osteoarthritis in joints affected by PDB have been found in studies that look at this issue from different approaches. However, in a number of series, secondary osteoarthritis is the most common complication of PDB<sup>4,18</sup>. Back pain was the most frequent complaint in more than one-third of symptomatic patients. This result is in agreement with studies showing that this symptom is the most common one among patients with PDB<sup>4,19-21</sup>. Degenerative changes, with a high prevalence of facet joint arthropathy as assessed by computed tomography<sup>22</sup>, spinal stenosis, microfractures, vascular insufficiency, and root compression are the possible causes of back pain in PDB<sup>3</sup>. It is noteworthy that, in agreement with Harinck, *et al*<sup>12</sup>, we found an increased prevalence of back pain along with an increased number of involved vertebrae. This feature is not shared by other samples in which no difference in pain has been seen in multilevel involvement compared with single level involvement<sup>23</sup>.

As demonstrated by logistic analysis, the disease localizations that increase the likelihood of symptomatic disease were the lumbar spine, pelvis, and tibia, while skull involvement was significantly predictive for asymptomatic PDB diagnosed incidentally. Although the pathogenesis of bone pain is not fully elucidated, it is likely that the mechanical load on weight-bearing bones may cause pain due to microfractures. Modeling of Paget bone is impaired, and changes in size and shape of the affected bones impair their mechanical competence. Moreover, the increase in disorganized bone remodeling causes bone expansion and deformity and disrupts normal bone architecture, leading to mechanical weakening by a number of mechanisms. These abnormalities can increase the risk of symptomatic microfractures through the widening of remodeling space<sup>7,24,25</sup>, the loss of targeted remodeling with a defective damage repair<sup>26</sup>, the woven pattern of collagen deposition<sup>27</sup>,

and the impaired mineralization of woven bone<sup>28</sup>. Besides microfractures, it has been proposed that pain in Paget bones can be due to hypervascularity with a raised intramedullary pressure and periosteal stretching<sup>29</sup>.

The main limitation of this study is a possible referral bias. Because all patients were seen in a single tertiary care center focused only on musculoskeletal diseases, it is possible that patients with other clinical symptoms at the onset (for example, headache or neurological complications) were referred to other hospitals. In the same way, we cannot exclude overrepresentation of patients who were diagnosed for a fracture or complained joint pain. Nevertheless, the similarities in clinical features with a recently described Italian sample recruited by a national registry would minimize these possible biases<sup>30</sup>.

A further limitation is the cross-sectional design of the study. Only longitudinal investigations will determine how many asymptomatic patients become symptomatic with increased age and disease duration. Lastly, some variables with a potential influence on clinical features were not assessed, such as the genetic arrangement and parathyroid hormone and vitamin D levels.

Our study showed that the extent of PDB and the involvement of some frequently affected skeletal sites such as the lumbar spine, pelvis, and tibia are the only features related to a symptomatic onset allowing a clinical diagnosis. Because pain is the most common symptom, and a systematic radiological evaluation of any older subject complaining of bone pain, joint pain, or back pain could be unwarranted, a routine laboratory screening including a single and inexpensive test such as SAP could be the sole strategy to improve the diagnostic sensitivity for PDB at the population level.

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