

Implications of a New Radiological Approach for the Assessment of Paget Disease

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Abstract In the present study, we quantified the proportion of skeletal involvement of Paget disease of bone (PDB) not captured by an abdominal X-ray. We also analyzed extension and severity over time and tested the hypothesis that X-rays from selected areas could replace bone scans for mapping PDB. We examined whole skeletal ^{99m}Tc -MDP bone scans from 208 consecutive untreated patients. Pagetic bones included in an abdominal X-ray were delimited; disease extension and activity were calculated using Coutris's index as well as Renier's index and serum alkaline phosphatase (AP) values, respectively. The study period (1965–2007) was divided into quartiles according to the date of the diagnosis. The percentage of patients with PDB captured by an abdominal X-ray was 79 % (95 % CI 74–85 %). In the last quartile vs. the first quartile, PDB was diagnosed at a more advanced age (67 ± 11 vs. 57 ± 9 years, respectively), with a lower

median extension (4 vs. 7) and similar median activity (32 vs. 35) but less activity through median AP values (183 vs. 485 UI/L). The skeletal locations to X-ray in order to capture up to 93 % of PDB extension were the abdomen, skull with facial bones, and both tibias. In conclusion, one-fifth of patients are underdiagnosed when assessing prevalence of PDB by an X-ray of the abdomen, and there is a secular trend to presentation in older patients with a decreasing extension of the disease. A set of X-rays that includes abdomen, skull with facial bones, and both tibias provides a reliable alternative to bone scans.

Keywords Paget disease · Secular trend · Bone scintigraphy

Paget disease of bone (PDB) is a focal disorder which may affect one, a few, or many skeletal sites. In the last decades, the prevalence of PDB has been estimated in several countries by radiological assessment, using abdominal radiographs, including the entire pelvis and sacrum, all the

The study was conducted on behalf of the Paget Study Group. Investigators for the Paget Study Group are listed in the [Appendix](#). The authors have stated that they have no conflict of interest.

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lumbar vertebrae, and both femoral heads [1–6]. However, abdominal X-rays capture only a proportion of the skeletal involvement of PDB. Pelvic involvement in 60–90 % of PDB patients has been considered a conservative estimation, making extrapolation of the crude data necessary for assessing the true prevalence of this disease. In fact, the frequency of pelvic involvement ranges 40–91 %, being 71–76 % in the largest series [2, 5, 7, 8]. These discrepant numbers result in inaccurate data when assessing worldwide prevalence of PDB. Recently, PDB prevalence has been assessed in Spain as well as in other countries such as Great Britain, the United States, New Zealand, and Italy [1, 2, 5, 9]. The Spanish survey showed a crude prevalence of 1 % in individuals older than 55 years and an estimated prevalence range of 1.1–1.6 % [1]. Similarly, in Italy, the crude prevalence was 0.62–0.89, depending on the city, and the estimated overall prevalence ranged 1–1.5 % [2]. In both surveys, it was concluded that the estimated prevalence was at least 1 %, which is imprecise.

A decrease in the prevalence of PDB in the last two decades has been reported in a number of British communities and in New Zealand, among other populations [4, 10, 11]. By contrast, this decline has not been observed in other countries, such as Italy and two Spanish locations, according to a previous study of prevalence of PDB in our country [1, 2]. In addition, decreased clinical severity of PDB has been reported. Thus, in a hospital-based study Morales-Piga et al. [12] found a temporal tendency toward a decreasing extent of affected skeleton without significant differences in disease activity, assessed by bone markers.

Another important issue when analyzing characteristics of PDB, such as the extension of the disease in a single patient, is related to the use of radionuclide bone scanning. Guidelines and expert opinions recommend performing a whole-skeleton bone scan at the time of diagnosis, a reliable method for mapping the disease [13, 14]. However, the radiation dose of up to 3–5.36 mSv [14, 15] and the inaccessibility of the test in some geographical areas merit further search for alternative tests in clinical practice. In order to substitute the use of bone scans, it is important to identify a set of a reduced number of bones to X-ray that could give an appropriate assessment of the extension of the disease with lower radiation than bone scans. In this sense, the effective radiation dose of a single X-ray is much lower, being 0.5–1 mSv for an abdominal X-ray, 0.005–0.07 mSv for an X-ray of the skull, and 0.008 mSv when the bone is in the lower limbs [16, 17].

The aims of this study were both to quantify the proportion of the skeletal involvement of PDB not captured by an abdominal X-ray and to analyze trends in PDB extension and activity over years. In addition, we tested the hypothesis that X-rays from selected skeletal areas could replace bone scans in assessing PDB.

Methods

We conducted a study to address all of these issues from a national PDB register, running between 2006 and 2007, which included 602 patients and 25 centers in different areas of Spain [18]. Consecutive patients were included in each center if they had a whole skeletal ^{99m}Tc -MDP bone scan and serum alkaline phosphatase (AP) measurement in the year of diagnosis. If both tests were not available at this time point, cases were included at any time only if the patient had not been previously treated with bisphosphonates or calcitonin.

Paget bones included in an abdominal radiograph were delimited from the whole skeleton in the bone scan by means of a grid. Disease extension was calculated according to the percentage of the skeleton affected and expressed using the Coutris index [19]. This index represents the sum of the coefficients, conventionally given to each pagetic bone, according to its volume. In addition, the coefficient is adjusted according to the extent of the pagetic involvement of each bone (whole, two-thirds, or one-third). The theoretical index ranges from 0 (no bone affected) to 100 (whole skeleton affected). In order to analyze pagetic bone activity, we used the index of activity described by Renier et al. [20], which includes the Coutris index and the AP activity in the formula. The AP value was converted to international units when necessary.

A sample size of 239 evaluable bone scans was required to recognize a difference ≥ 5 %, assuming 90 % of PDB patients with pelvic involvement and accepting an α error of 0.05 and a β error of 0.20. Estimation of the true PDB prevalence in Spain, after extrapolating the data of the noncaptured locations by abdominal X-rays, with 95 % confidence intervals (CIs), was performed using previous published data from our group [1].

Trends in PDB extension and activity over years were represented graphically with smoothed plots and compared with a nonparametric test for trends throughout the years of diagnosis, categorized as quartiles [21]. As a measure of internal validity, correlation and distribution between the number of patients and the extent of the disease or index of activity were computed [8].

In order to maximize the percentage of PDB extension with the least number of included bones, cumulative probability and the 95 % bias-corrected confidence interval (BC) were obtained with 1,000 bootstrap replications. Bootstrap [22] is a method where new samples that are randomly selected from the original sample are used to test the prediction.

Bone scans were evaluated by two independent expert rheumatologists (D.R. and S.H.). Both readers assessed bone scans in order to calculate the interobserver variability, and 30 bone scans were selected at random and

assessed on two occasions by the same reader to estimate the intraobserver variability. Concordance was analyzed by means of the intraclass correlation coefficient (ICC) for continuous variables and the kappa index for qualitative data. Additionally, the minimum detectable change was calculated. Discrepancies were discussed, and an adjudicated reading was recorded.

Informed consent was obtained from all patients of the Spanish national PDB register, and the ethics committee of the Hospital Clinic of Barcelona approved the register protocol.

Results

In total, bone scans from 208 patients with PDB, 114 (55 %) males and 94 (45 %) females, aged 62 ± 11 years, were analyzed. Twenty-one cases were excluded because of previous treatment (six patients) or technical difficulties in the analysis of bone scans. There were no significant differences ($p > 0.2$) between the included patients and those from the register compared by age, gender, and time from symptoms (Table 1). Most bone scans (75 %) were obtained during the first year after diagnosis and the remainder (25 %), after a median of 4 years from diagnosis.

The percentage of patients with PDB at the end of the lumbar spine, pelvis, and/or proximal femur, which are the locations captured by an abdominal X-ray, was 79 % (95 % CI 74–85 %), which is of borderline significance when comparing differences by gender ($p = 0.055$). Thus, taking into account the results of our previous study on the prevalence of PDB in the Spanish population [1], the estimate of the true prevalence of PDB in Spain in individuals older than 55 is 1.2 % (0.95–1.6 %), being 1.5 % (1–2.1 %) in men and 1 % (0.7–1.5 %) in women. The proportion of patients with PDB in the abdominal X-ray over time did not change throughout the study. Thus, the percentage of pelvic involvement in patients diagnosed in each period of time was 87, 74, 79, and 79 %, respectively.

The median Renier index (p25, p75) was 35 (21, 70), 29 (14, 64), 42 (20, 91), and 32 (12, 72) in each quartile, respectively, throughout the years of diagnosis. No significant differences between groups were observed ($p = 0.873$), although the median serum AP activity was higher in the first quartile compared with the last period (485 vs. 183 UI/L, respectively) and a trend toward lower values over time was detected ($p < 0.001$). There was a significant trend in the mean age at diagnosis ($p < 0.001$), being 57 ± 9 years in the first quartile compared to 67 ± 11 years in the last period. In addition, the median Coutris index decreased over time ($p = 0.002$), with lower values in the most recently diagnosed patients compared with patients in the first quartile (7 vs. 4). Moreover, the decline in the Coutris index was associated with a lower number of involved bones throughout the study, being 2.8 ± 2.1 , 2.2 ± 2.0 , 2.2 ± 1.5 , and 2.1 ± 1.9 ($p < 0.004$) from the first to the fourth quartiles, respectively. Taken together, in recent years, PDB was diagnosed at a more advanced age and the skeletal extension was minor, without significant changes in disease activity as assessed by the Renier index, but with less activity when assessed by AP values. Figure 1 shows the evolution of the Coutris and Renier indexes over time.

Figure 2 shows the percentage of patients with pagetic involvement in each skeletal area. Abdominal PDB location accounts for 57 % of the Coutris index with a 95 % BC of 51–62%, abdominal plus skull and facial bones account for up to 89 % (95 % BC 87–91%), and the two previous locations, in addition to the tibias, capture 93 % (95 % BC 91–95 %) of the Coutris index. No trend was detected throughout the years of diagnosis ($p > 0.8$) in any of the three models.

In order to determine the possibility of elderly patients with a quiescent late phase of the disease, with normal radionuclide activity but PDB signs on radiology [8, 23], we compared patients older than 80 years ($n = 7$) and those younger. The Coutris index at the ilium was similar in the two groups (2.9 vs. 2.2, respectively), thus suggesting ($p = 0.3663$) that this possible source of error is unrealistic. In addition, to reinforce consistency of the data,

Table 1 Characteristics of patients included in the study and in the National Paget's Register

	Bone scans	National Paget's register	<i>p</i>
Number of patients	208	394	
Females, <i>n</i> (%)	94 (45)	179 (45)	0.955
Age, mean (SD)	62 (11)	63 (11)	0.5396
Time from symptoms (years), mean (SD)	1.8 (3.7)	2.1 (6.5)	0.5958
PDB at the lumbar spine, pelvis, and/or proximal femur, <i>n</i> (%)	165 (79)	–	
Renier index, median (p25, p75)	39 (19, 74)	–	
Coutris index, median (p25, p75)	5 (3, 9)	–	

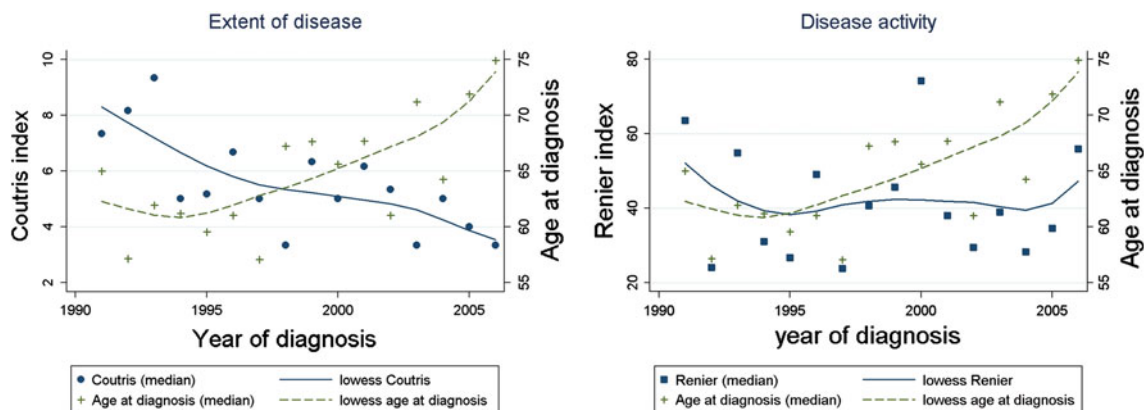


Fig. 1 Coutris and Renier index trends according to date and age at diagnosis. *LOWESS* locally weighted scatterplot smoothing

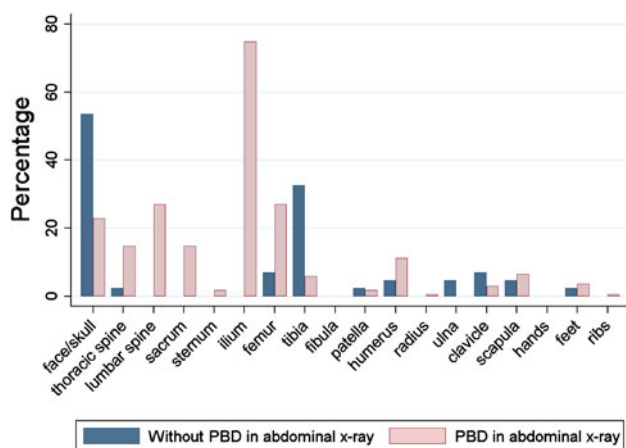


Fig. 2 Distribution of lesions in patients with and without Paget disease in abdominal radiographs

Fig. 3 shows the distribution between the number of patients and the extent and activity of PDB disease on a probability scale. Correlations were 0.889 and 0.7445, respectively.

There was a high concordance between the scintigraphic evaluations performed by the two trained observers, measured by the ICC, which was 0.995 (95 % CI 0.993–0.996). The intraobserver concordance was 0.988 (95 % CI 0.981–0.997). Concordance between the two observers for included bones in an abdominal X-ray, for a kappa statistic, was 1 (95 % CI 0.58–1). The minimum detectable change expressed as a measure error was 0.7 units.

Discussion

The results of this study show that abdominal X-rays underestimate the prevalence of PDB by one-fifth of patients and provide insights on the temporal trends in the characteristics of the disease. Thus, in our environment and

in recent years, PDB is diagnosed at a more advanced age and the skeletal extension is minor, when comparing patients diagnosed over time. The most interesting finding, however, is that we identified a set of skeletal locations to X-ray for mapping the disease with a reasonable probability. Thus, X-rays of the abdomen, skull with facial bones, and both tibias should capture up to 93 % of the locations of PDB.

To the best of our knowledge, this is the first report showing the usefulness of a combination of locations to X-ray for assessing the extent of PDB. Indeed, the proposed model (X-rays of abdomen, skull, and tibias) has an effective radiation dose up to 1.09 mSv, which is much lower than the radiation dose of a bone scan, 3–5.36 mSv. The effective radiation dose comes from the sum of the radiation of an X-ray of the abdomen, which accounts for 0.5–1 mSv, and the X-rays of the skull and both tibias, which account for 0.005–0.07 and 0.016 mSv, respectively [16, 17].

It must be pointed out, however, that as a general rule scintigraphy is more sensitive than plain X-rays in the identification of pagetic lesions [8]. Thus, Meunier et al. [24] found that bone scans identified 8.3 % more pagetic sites than X-rays when both methods were compared in a series of 170 untreated patients. Most authors, but not all, have found similar results. Indeed, some reports from the 1970 s and 1980 s found that X-rays underestimate pagetic sites by 5–32 % [24–26]. Other authors found a close correlation between X-rays and bone scans, while a higher proportion of abnormal X-rays compared to bone scans was reported in other series [27]. In the present study, we analyzed the possibility of scan-negative lesions with X-ray appearance due to a quiescent late (“burned-out”) phase of the disease. However, we did not find differences in the Coutris index at the ilium in the most elderly patients compared with younger patients, reinforcing the validity of our proposed model. However, we were unable to

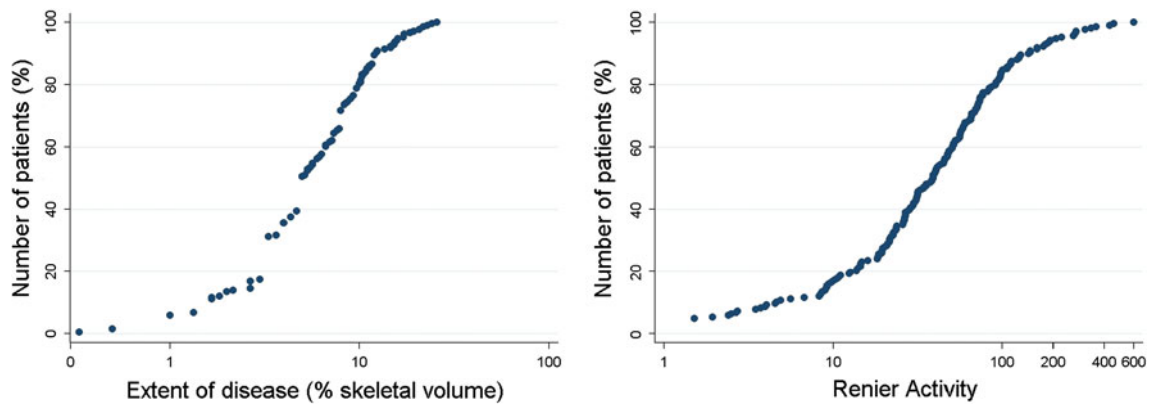


Fig. 3 Distribution of the extent and activity of the disease

determine the major cause of discrepancies between scan-positive and radiograph-negative lesions, such as particular locations of PDB, including clavicles, scapulae, ribs, and sternum [2, 28]. In fact, these locations were infrequent in our series, suggesting that their hypothetical influence in the skeletal assessment is low.

It is important to know the true prevalence of PDB in different countries. At present, it is usually roughly estimated from crude data obtained in radiological surveys. We have found that X-rays of the abdomen, the most common method for assessing the prevalence, capture 79 % of the skeletal locations of PDB. This percentage is within the range of 60–90 % reported in previous studies and close to the 71 % reported by Genari et al. in Italy [2]. Our data were obtained using strict methodology with a high concordance between bone scan readers, which adds value to the study. It may be argued that the numbers may change according to the possibility of a different skeletal extension of the disease over time. In fact, a secular trend for a decreasing extension was observed in our study when comparing bone scans over time; however, the percentages of the frequency of pelvic involvement were similar ($p < 0.467$), being 79 % in the whole series and 87 and 79 % in patients diagnosed in the first and last periods, respectively, suggesting that long-term trends in the extension of the disease did not influence our numbers on the frequency of pelvic involvement.

In the present study, based on a national register, we found data supporting changes over time in demographic and clinical severity of PDB. Several studies have reported that the mean age at diagnosis has increased in the last decades [10]. Thus, Cundy et al. [29] in a large series from one center in New Zealand found that the mean age at diagnosis had increased from 62 to 74 years when comparing periods 1973–1975 and 2000–2002. In agreement with this, we found that the mean age at diagnosis had increased from 57 to 67 years when comparing patients diagnosed in the first and last periods. Also, and in

accordance with previous surveys [9, 12, 29], we found less extensive disease in the later period. Indeed, the median Coutris index declined from 7 to 4. However, in our series, PDB activity assessed by the Renier index was similar in patients diagnosed in the first and last periods and no trend was detected. Importantly, our series included only untreated patients. Morales-Piga et al. [12], in a Spanish hospital-based study, showed that basal disease activity assessed by serum AP activity and urinary hydroxiproline excretion was similar in patients born before 1926 and those born after that year. By contrast, the study from New Zealand found a fall in mean AP activity over time and a reduction in the number of subjects with high values of this bone marker [29]. It is unlikely that the method used in our study could account for a bias in disease activity assessment since Renier's index is a reliable method, although when we compared serum AP activity over time, values were lower in patients diagnosed in the last period. In addition, a different frequency of skull involvement in the two periods could be suggested since it is known that skull location is associated with high AP values [30], which may interfere with disease activity assessment. However, this was not the case since skull involvement was similar in patients diagnosed over time. Taken together, our data suggest a similar activity of PDB over years, although some objections regarding this affirmation arise, based on serum AP values.

This study has several strengths and weaknesses. The strength of this study lies in its design and consistency of data. We included patients from a national register, and the concordance in the evaluation of bone scans was excellent. Only untreated patients were included in order to avoid changes in the uptake of bone scans induced by antiresorptive drugs. In addition, our proposed model was not influenced by secular trends in the extension of the disease. However, our study does have several caveats, such as concerns about whether the skeletal locations of the disease differ from country to country. However, when analyzing

the skeletal distribution of pagetic lesions based on series from different countries, these are quite similar [2, 8], suggesting that our findings may be extrapolated worldwide.

In conclusion, one-fifth of patients are underdiagnosed when assessing prevalence of PDB by an X-ray of the abdomen, and in recent years the disease has been diagnosed at a more advanced age and with less extension. In addition and importantly, we propose a new model for mapping the skeletal extension of PDB, based on a set of X-rays that includes the abdomen, skull with face, and both tibias. Our aim is not to substitute the bone scan, the gold standard, but to provide a reliable alternative test with a lower effective radiation dose and greater accessibility.

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Appendix: PAGET Study Group

Investigators for the above study was conducted on behalf of the Paget Study Group: Antonio Torrijos Eslava, Hospital Universitario La Paz, Madrid; Javier Aguilar del Rey, Hospital Clínico Virgen de la Victoria, Málaga; Javier Bachiller Corral, Hospital Ramon y Cajal, Madrid; Javier Del Pino Montes and Judit García, Hospital Universitario De Salamanca, Salamanca; Jesús Beltrán Audera, Hospital Universitario Miguel Servet, Zaragoza; Jesús Tornero, Hospital Universitario de Guadalajara, Guadalajara; Jorge Malouf Sierra, Hospital Sant Pau y Santa Creu, Barcelona; José Antonio Piqueras, Hospital Universitario de Guadalajara, Guadalajara; José Manuel Gorordo Olaizola, Hospital De Basurto, Vizcaya; José Miguel Ruiz Martín, Hospital de Viladecans, Barcelona; José Santos Rey Rey, Hospital Virgen de la Salud, Toledo; Juan Antonio Castellano Cuesta, Hospital Arnau de Vilanova, Valencia; Lucía Pantoja Zarza, Hospital del Bierzo, León; M. Angeles Martínez Ferrer, Hospital Clinic i Provincial, Barcelona; M. Asunción Salmoral Chamizo, Hospital Reina Sofía, Córdoba; Manuel Rodríguez Pérez, Hospital Universitario Carlos Haya, Málaga; Nicolás Chozas Candanedo, Hospital Universitario Puerta del Mar, Cádiz; Rosa Roselló Pardo, Hospital San Jorge, Huesca.

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