Prevalence of Paget's disease of bone in Spain

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ABSTRACT

Introduction: Epidemiological studies in Europe have revealed that the prevalence of Paget's disease of bone (PDB) has marked geographic variations. At present, the prevalence of PDB in Spain is unknown, limited to data from isolated towns or centers. We conducted a radiological national-based survey, to estimate the age and sex prevalence of PDB and its geographic variation within the country. In addition, we tested the patients' awareness of their disease.

Methods: Stratified samples throughout Spain of abdominal radiographs, of subjects aged ≥55 years, from stored consecutive digitalized films in selected hospitals were obtained, over the period of 2006–2007. Radiographs including all lumbar vertebrae, pelvis, sacrum and femoral heads were examined for the diagnosis of PDB, according to standardized criteria. Age, sex and information regarding patient's awareness of the illness were obtained from the hospital files.

Results: A total of 4528 radiographs from 13 centers were evaluated. The crude prevalence of PDB was 1% (95%CI: 0.7–1.3) in individuals older than 55, and the estimated prevalence ranged from 1.1% (95%CI: 0.8–1.4) to 1.6% (95%CI: 1.1–2.1) when a reported pelvic involvement in 60–90% of PDB patients was considered. The prevalence was slightly higher in men than in women, and significantly higher in individuals older than 75. A significant geographic variation in prevalence was observed within the country (p=0.004). 73% of PDB patients were unaware of their illness at the time of the radiological survey.

Conclusions: Prevalence of PDB in Spain is at least 1% in individuals older than 55, with remarkable geographical variations and age related differences. Most patients were unaware of their disease.

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Introduction

Paget's disease of bone (PDB) is the second most frequent metabolic bone disease, which usually occurs in elderly patients and has a strong genetic component [1]. It is known that PDB prevalence in Europe has remarkable geographic variations. The highest prevalence (3–5% in population over the age of 55) has been reported in Britain whilst the lowest indices have been found in the Scandinavian population (0.4%) [2,3]. Also, a low prevalence of PDB in Southern Europe has been described [4]. A recent survey in Italy estimated that the overall prevalence of PDB, by radiological assessment, ranges from 0.7 to 1.5% in subjects older than 60, increasing to 2.4% when a scintigraphic survey in an over 43-year old population from Siena, was performed [5]. At present, there is little information regarding the prevalence of PDB in other Southern European countries, and reports are limited to studies providing data from local surveys [4,6–8].

The reported decrease in frequency of PDB in the last two decades in a number of European centers and in New Zealand [6,9,10], and the
lower number of symptomatic patients at diagnosis in the late periods of long surveys may modify the previous reported prevalences of PDB [9]. Furthermore, since this is frequently an asymptomatic condition [11,12], it is interesting to assess whether patients are aware of their disorder in order to seek medical care.

To estimate the total and the sex and age prevalence of PDB in Spain, as well as the patients’ awareness of the disorder, we conducted a radiographic survey using abdominal radiographs in a national-based study.

**Methods**

We selected 18 geographic areas of the country according to the distribution in Autonomous Communities of Spain and stratified them, taking into account their population. A total of 25 centers from these areas were selected at random using the National Hospital Catalog. The number of centers per stratum was proportional to the population aged 55 in any given stratum.

Abdominal radiographs of consecutive subjects aged ≥55 years were obtained from the stored digitalized films in the radiology departments of the selected centers over the period of 2006–2007. The radiographs had to include the entire pelvis and sacrum, all lumbar vertebrae and both femoral heads.

At each center, the radiographs were classified with the help of a standard atlas by a trained observer into three categories: positive (PDB present), doubtful, and negative (no PDB present). All positive and doubtful radiographs were reviewed by a consultant radiologist, as well as 2% of the negative radiographs selected at random. The radiologist was unaware in any case of the classification conclusion of the trained observer. Discordant results were assessed centrally by an experienced radiologist.

The radiographic diagnosis of PDB was based on standardized criteria including: localized enlargement of bone, cortical thickening, enhancement of the trabecular pattern, sclerotic changes and osteolytic areas. Additional features in the pelvis, including thickening of the ilipectineal line and protusio acetabuli, were also evaluated [13].

Data from all subjects included in the radiographic survey were recorded through the hospital files. Information included: age and gender as well as the date of the radiographic examination. In addition, in individuals with PDB, information regarding their awareness of the illness was collected; this is whether a diagnosis of PDB was recorded in the clinical history.

A total sample size of 4000 evaluable digitalized radiographs was required to establish the prevalence of PDB with a 15% relative error. In addition, at least 425 abdominal radiographs were required in each center to detect a prevalence of 3-fold the theoretical prevalence, accepting an α error of 0.05 and a β error of 0.2.

Concordance in the radiological diagnosis between trained observers and consultant radiologists was assessed by the kappa index. The estimation of prevalence of PDB by age was performed in 10-year age bands from 55 to 85+ years of age, and age and sex prevalence rates of PDB were calculated with 95% confidence intervals (95%CI). The differences in prevalence by age and sex as well as by geographical location were statistically tested by logistic regression.

The study was approved by the Ethics Committee of the Hospital Clinic, Barcelona.

**Results**

In total, 4528 abdominal radiographs were evaluated. For reasons related to the standardized criteria for the radiological survey that required digitalized radiographs, only 13 centers could finally take part in the study from the initially 25 selected. The geographic distribution throughout the country and the number of films recruited per geographical stratum is shown in Table 1. The average number of radiographs examined per center was 350 (range 148–700). The reason for having assessed less than the average number of radiographs was that in some centers there were space and time constraints for storing images. There were 2363 (52%) radiographs from women and 2165 (48%) from men with a mean age of 73±10 and 72±10 years, respectively. According to the age groups, 42% were older than 75 years of age. There was a high concordance between the radiological diagnosis performed by trained observers and consultant radiologists, measured by the kappa index which was 0.92 (95%CI: 0.86–0.98).

Forty-four radiographs showed PDB. Thus, the crude prevalence of the disease was 1% (95% CI, 0.7–1.3) in individuals older than 55. Since it is considered that pelvic involvement is present in 60–90% of patients with PDB, the overall estimated prevalence in the Spanish population over 55, might range from 1.1% (95%CI: 0.8–1.4) to 1.6% (95%CI:1.1–2.1).

The prevalence was slightly higher in men than in women (1.16% (95% IC: 0.71–1.61) vs. 0.80% (95%IC: 0.44–1.16), p=0.2) and significantly higher in individuals older than 75 when compared with the age group of 55 to 74 years (1.6% (95%IC: 1.02–2.14) vs. 0.5% (0.25–0.81) p=0.0001). Indeed, a gradual increase in prevalence was observed along with the age groups, from 0.08% (95%IC: 0.00–0.25) in individuals below 65 years to 2.43% (95%IC: 1.07–3.79) in those over 85 years (Fig. 1).

The prevalence of PDB showed a significant geographic variation within Spain (p=0.004) (Table 1), even after adjusting by age (p=0.03). Slightly lower prevalence rates on the coast, particularly the Mediterranean coast, were observed when compared with the Inland regions. Fig. 2 shows the geographic prevalence of PDB in the areas of the survey.

### Table 1

Geographical distribution of assessed radiographs and prevalence of Paget’s disease throughout Spain

<table>
<thead>
<tr>
<th>Geographical stratum</th>
<th>Number of X-rays</th>
<th>X-rays (%)</th>
<th>Prevalence (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andalusia</td>
<td>714</td>
<td>15.8</td>
<td>0.14</td>
<td>(0.00–0.41)</td>
</tr>
<tr>
<td>Canary Islands</td>
<td>433</td>
<td>9.6</td>
<td>1.62</td>
<td>(0.43–2.81)</td>
</tr>
<tr>
<td>Castille La Mancha/Castille León</td>
<td>422</td>
<td>9.4</td>
<td>2.37</td>
<td>(0.92–3.82)</td>
</tr>
<tr>
<td>Catalonia</td>
<td>855</td>
<td>18.8</td>
<td>0.47</td>
<td>(0.01–0.93)</td>
</tr>
<tr>
<td>The Valencian Community</td>
<td>721</td>
<td>16</td>
<td>0.83</td>
<td>(0.17–1.50)</td>
</tr>
<tr>
<td>Galicia</td>
<td>700</td>
<td>15.5</td>
<td>1.00</td>
<td>(0.26–1.74)</td>
</tr>
<tr>
<td>Madrid</td>
<td>683</td>
<td>15.1</td>
<td>1.32</td>
<td>(0.46–2.17)</td>
</tr>
</tbody>
</table>
Discussion

The results of this national-based radiological survey contribute to the knowledge of the epidemiology of PDB, providing new information on the prevalence and the geographic distribution of this disorder in Spain. The methodology of this survey, evaluating abdominal radiographs, has been previously used in epidemiological studies in Britain, Italy, the United States and New Zealand, as well as in one study assessing six European towns [4,5,14–16]. When we compare our data with those observed in studies from Europe, the disease was present in up to 1% of Spanish radiographs, a slightly higher figure than that reported in another Southern European country such as Italy, in which the frequency ranged from 0.60% to 0.89%, when the survey was conducted from 1999–2000 [5,17]. In fact, available data from France, Scandinavia, Greece and Britain show marked variations in prevalence according to the country, the individual towns within the country, and the period of the survey. It is well known that Britain has the highest prevalence of the disease, up to 5% in subjects older then 55, in surveys performed in the seventies and eighties; and 2.5% among men and 1.6% among women, when the survey was performed in the nineties [1,6,14]. The lowest prevalence was found in southern Europe pointing to Sicily and Greece (0.5%) and also in Sweden (0.4%) in a radiological survey throughout Europe, performed 25 years ago [4]. In this study, the prevalence in two Spanish towns ranged from 0.9% in La Coruña to 1.3% in Valencia. Interestingly, a second European survey using identical methods conducted from 2000–2001, showed lower rates in both Spanish towns being 0.4% and 0.5%, respectively [6]. In our study, pelvic PDB was observed in 1% and 0.83% of radiographs from the same geographical strata, suggesting no secular trend for a decreasing prevalence of PDB in Spain. In fact, both surveys were hospital-based studies, and included a similar number of abdominal radiographs. The sample size of the selected towns in the surveys, however, may be underpowered to detect a true significant difference in prevalence of PDB in Spain over recent years.

When we compared our data with the reported prevalence of PDB in the United States, the rates were comparable, 0.79% and 1%, although the largest study in the United States was community-based [15] and our study was a large hospital-based survey. An interesting observation is the geographical variation of PDB within the United States, with the highest prevalence in the Northeast and the lowest prevalence in the South [15]. Probably, ethnic susceptibility and ancestry has a marked role on this regional distribution. Indeed, Spanish ancestry may have a similar influence to that reported in Australia in subjects of British origin [3]. This point deserves further demographic study.

In our survey we found remarkable geographic variations within Spain, with higher rates in the Inland regions and lower prevalence on the coast, particularly the Mediterranean coast. Although this is the first nation-wide survey, some previous reports pointed to a large number of areas of high prevalence of PDB in Spain, up to 13 possible clusters in some delineated territories of Central and Western Spain [7,8,18]. However, the influence of these areas of high prevalence in their geographical stratum is unknown, since in the British survey the bordering towns of the Lancashire cluster had rates of around the average for all other British towns [2,3]. Interestingly, the geographical stratum of Castille La Mancha and Castille Leon, in the center of Spain, has the highest prevalence rate among all the strata.

Another point that needs to be taken into account is the estimated prevalence of PDB according to its anatomical distribution, since abdominal radiographs only capture a proportion of the pagetic skeletal involvement. Thus, from 40 to 95% of patients have pagetic lesions in pelvic radiographs, according to different studies and assumptions [19,20], with a more realistic figure of 60–90%. These percentages of skeletal involvement have been chosen in our study for the extrapolation of the crude prevalence to the estimated prevalence of PDB in Spain. However, any of these assumptions may overestimate or underestimate the true prevalence of PDB in our country.

The influence of age and sex distribution in PDB frequency observed in our study is in agreement with prior surveys [2,3,21]. Thus, Spanish subjects older than 75 have a higher frequency of radiological evidence of PDB than younger subjects, and the rates rose steeply with age. In addition, PDB was slightly more prevalent among men than among women.
An interesting finding was that most patients with PDB were unaware of their disease at the time of the survey. Only in 27% of cases was the diagnosis of PDB recorded in the hospital’s files. This observation supports an underestimation of the diagnosis of PDB in clinical practice, and the most plausible explanation for this is the high frequency of asymptomatic lesions [11,22], in addition to the decline in severity of PDB in recent years [23,24].

There are some methodological limitations that must be considered. The total number of the participating centers in the study and the number of geographical strata throughout Spain were lower than initially designed. Both facts were due to the limited availability of digitalized radiographs in the selected centers of the geographical strata. However, after examining closely the centers that participated and those who did not, there is no clear bias associated to centers having X-rays digitalized. Another limitation is that not all centers recruited the target number of radiographs. Although it is possible that some of the variation in prevalence may be in part related to these limitations, the influence on the data is probably insignificant, since the total number of radiographs is relatively high and exceeded the required total sample size. In addition, although there were some centers that recruited fewer radiographs than the target numbers, the total amount of radiographs per geographical stratum was around or higher than 425, which is the number required to detect differences in prevalence between strata.

In summary, our radiological survey reveals that the crude prevalence of PDB in the Spanish population over 55 years of age is 1%, with an overall estimated prevalence that ranges from 1.1 to 1.6%. These data do not support a negligible prevalence of the disease in Southern Europe. Our study also provides information on the underdiagnosis of PDB.

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Appendix. PAGET Study Group

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