J Bone Miner Metab (2006) 24:186–190
DOI 10.1007/s00774-005-0670-z

SPECIAL REPORT

**Jun Hashimoto · Ikko Ohno · Kiyoshi Nakatsuka
Noriko Yoshimura · Shinjiro Takata · Masaaki Zamma
Hiroo Yabe · Satoshi Abe · Masaki Terada · Kousei Yoh
Masao Fukunaga · Cyrus Cooper · Hirotoshi Morii
Hideki Yoshikawa**

Prevalence and clinical features of Paget's disease of bone in Japan

Received: July 29, 2005 / Accepted: December 8, 2005

Abstract The present study aimed to evaluate the prevalence and clinical presentation of Paget's disease of bone (PDB) in Japan. As PDB is a very rare disease in Japan, a nationwide mail survey was conducted targeting doctors in the specialty most frequently diagnosing and treating PDB patients in Japan. First, the literature for all case reports in Japan published between January 1990 and December 2002 was reviewed to determine who was diagnosing and treating PDB in Japan. This literature review for all case reports in Japan revealed that 72.1% of cases in Japan were reported from departments of orthopedic surgery. A nationwide two-phase mail survey was conducted for the departments of orthopedic surgery of 2320 general hospitals accredited by the Japanese Orthopaedic Association. Phase 1 involved determining how many patients with PDB were followed at each hospital. If the answer was one or more, phase 2 of the survey gathered information on the clinical presentation of current patients. The mail survey yielded a final response rate of 75.4% for phase 1 and 87.6% for phase 2. Phase 1 indicated that the prevalence of PDB in Japan is about 2.8 cases per million capita. Phase 2 revealed a slight female predominance, lower frequency of familial clustering, higher frequency of femoral fracture in the affected femur, and a higher ratio of symptomatic PDB in Japan compared with findings in countries displaying a higher prevalence of PDB. The present epidemiological study revealed that the disorder is extremely rare in Japanese individuals, and that some differences exist with regard to the clinical features of PDB between Japanese patients and patients from high-prevalence countries.

Key words Paget's disease of bone · prevalence · clinical manifestation · nationwide mail survey · Japanese population

The Japanese Committee on Clinical Guidelines of Diagnosis and Treatment of Paget's Disease of Bone of the Japan Osteoporosis Society, Japan

J. Hashimoto (✉) · I. Ohno · H. Yoshikawa
Department of Orthopaedic Surgery, Osaka University Graduate School of Medicine, 2-2 Yamada-oka, Suita 565-0871, Japan
Tel. +81-6-6879-3552; Fax +81-6-6879-3559
e-mail: junha@ort.med.osaka-u.ac.jp

K. Nakatsuka
Department of Endocrinology, Metabolism and Molecular Medicine, Osaka City University Graduate School of Medicine, Osaka, Japan

N. Yoshimura
Department of Joint Disease Research, Graduate School of Medicine, The University of Tokyo, Tokoyo, Japan

S. Takata
Department of Orthopaedics, Institute of Health Biosciences, The University of Tokushima Graduate School, Tokushima, Japan

M. Zamma
Dainippon Sumitomo Pharma Co., Ltd., Osaka, Japan

H. Yabe
Department of Orthopaedic Surgery, School of Medicine, Keio University, Tokyo, Japan

S. Abe
Department of Orthopaedic Surgery, Teikyo University, School of Medicine, Tokyo, Japan

M. Terada
Department of Radiology, Wakayama Medical University, Wakayama, Japan

K. Yoh
Department of Orthopaedic Surgery, Sasayama Hospital, Hyogo College of Medicine, Hyogo, Japan

M. Fukunaga
Department of Nuclear Medicine, Kawasaki Medical School, Okayama, Japan

C. Cooper
MRC Environmental Epidemiology Unit, University of Southampton School of Medicine, Southampton General Hospital, Southampton, UK

H. Morii
Emeritus Professor, Osaka City University, Osaka, Japan

Introduction

Paget's disease of bone (PDB) is very common in elderly Caucasian populations in Europe, the United States, and Australia, and is well known to display distinct geographical variation. The prevalence of PDB varies from 0.1% to 5% in individuals, depending on the country [1–9]. While PDB

is highly prevalent in countries such as the United Kingdom, France, Germany, New Zealand, and Australia, prevalence is relatively low in Northern Europe [6], and the disease is extremely rare in Asia and Africa, where data are limited to a small number of published case reports [10–14] and no prevalence data are currently available.

Recent studies in Europe, North America, and New Zealand have suggested a decline in the prevalence and an attenuation of the clinical severity of PDB [15–18]. Although a wide range of clinical manifestations is reported among patients with PDB, including bone pain, fracture, secondary osteoarthritis, hearing loss, and secondary sarcoma, the precise clinical manifestations of PDB in Asia and Africa remain unknown. Because epidemiological research in countries with an extremely low prevalence of PDB would provide valuable insights into the etiology of PDB, by comparing patients' clinical manifestations among geographical areas with clearly different prevalences, the present study sought to conduct such research in the Japanese population.

Estimates of the prevalence of PDB have primarily been derived from autopsies, bone scans, or radiographic surveys of subjects investigated in hospitals, and population-based radiological and biochemical surveys [9,19,20]. In a preliminary study, lumbar and pelvic lesions were surveyed, using abdominal radiographs of 1000 Japanese population-based subjects in a limited area, but the study failed to identify any Pagetic lesion. The present study therefore selected a nationwide mail survey to estimate the prevalence of PDB in Japan. However, contacting all Japanese medical doctors was clearly impractical. The nationwide mail survey was therefore targeted at doctors in the specialty most frequently involved in diagnosing and treating PDB patients in Japan. In order to determine which kind of doctor most frequently diagnoses and treats PDB patients in Japan, a search of the literature for case reports in Japan was conducted.

The objectives of this study were to evaluate the prevalence and clinical presentation of PDB in Japan.

Materials and methods

Review of published case reports of PDB in Japan

The literature was reviewed for all case reports in Japan published between January 1990 and December 2002, to determine who was diagnosing and treating PDB patients. A systematic search was performed using the key words "Paget's disease in bone" in electronic databases (Japana Centra Revuo Medicina). Duplication of cases was avoided by referring to the key content of each report, and cases were classified by the reporting affiliation as Department of Orthopedic Surgery, Department of Internal Medicine, or Other.

Mail survey

A mail survey was conducted from September 2002 to May 2003, proceeding in two phases. Phase 1 involved determining how many patients with PDB were followed at each hospital at the time of the mail survey. If the answer was one or more, phase 2 of the survey gathered the following information on the clinical presentation of current patients: diagnostic procedure; age; sex; familial aggregates; types of clinical symptoms; complications; pattern of bone involvement; serum alkaline phosphatase levels; therapeutic agents used; and prognosis. Surveys were mailed on three occasions to nonresponders in order to maximize the response rate.

Table 1. Sources of referral (by specialty) of 154 cases of Paget's disease in Japan (1990–2002)

Department	Frequency listed (%)
Orthopedic surgery	111 (72.1%)
Others	43 (27.9%)
Total	154

Results

Review of published case reports of PDB in Japan

Use of the key words "Paget's disease in bone" in the published databases yielded 245 hits, representing 154 cases after meticulous exclusion of duplicated data. These final 154 cases were categorized as 111 cases reported by Departments of Orthopedic Surgery (72.1%) and 43 cases reported by Others (27.9%; Table 1).

Mail surveys

Becasuse PDB was diagnosed mainly at departments of orthopedic surgery in Japan, we conducted a mail survey of the departments of orthopedic surgery at 2320 general hospitals accredited by the Japanese Orthopaedic Association. The response rate for phase 1 of the survey was 75.4%, revealing a total of 194 patients, including 1 Indian patient, being followed at departments of orthopedic surgery at 162 general hospitals. The response rate for the phase 2 survey that gathered data on the 194 PDB patients was 87.6%. Of the 194 cases identified in phase 1, phase 2 responses were gained for 170 cases (169 Japanese patients, 1 Indian patient). No duplication of cases was found among the 170 cases according to the obtained clinical data, age, sex, and initials of the name, but duplication could not be excluded from the remaining 24 cases.

Estimated prevalence of PDB in Japan

Based on 72.1% of Japanese cases of PDB being diagnosed and the patients treated at departments of orthopedic surgery, the response rate of 75.4% in the phase 1 survey, and data from the Ministry of Public Management that the Japanese population was 126 008 000 in 2002, the prevalence of PDB in Japan was calculated as 2.8 per million capita, using

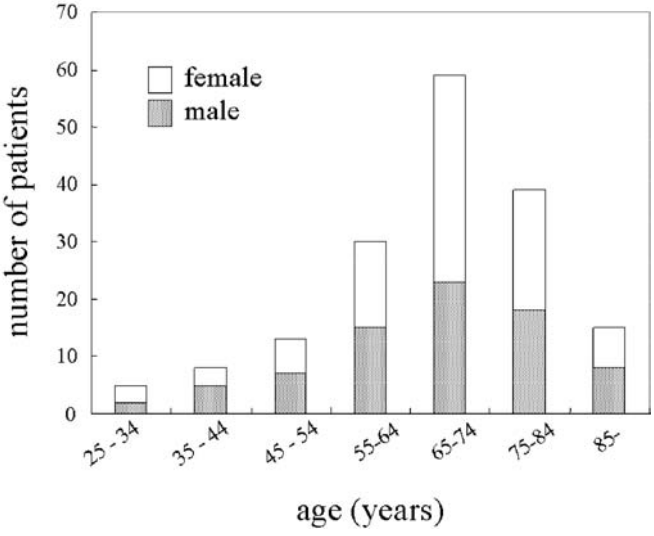

Fig. 1. Age distribution of patients with Paget's disease of bone in Japan

Table 2. The clinical features of 169 patients with PDB in Japan

Age (years) mean ± SD	64.7 ± 14.5
Sex, male/female (ratio)	78 : 91 (0.86 : 1)
Familial aggregation (n = 158)[a]	10 (6.3%)
Symptom	
Asymptomatic (%)	42 (24.9%)
Symptomatic (%)	127 (75.1%)
Monostotic/polyostotic (ratio)	87 : 82 (1.06 : 1)
Skeletal distribution (%)	
Pelvis	93 (55.0)
Spine	54 (32.0)
Femur	46 (27.2)
Skull	34 (20.1)
Tibia	25 (14.8)
Serum ALP levels (n = 164)[b]	
Normal range	17 (10.4)
≤3-fold above ULN	74 (45.1)
3- to 6-fold above ULN	49 (29.9)
≥6-folds above ULN	24 (14.6)

ULN, upper limit of normal range
[a] Data not available for 11 patients
[b] Data not available for 5 patients

the following equation: 193 cases × (100% / 72.1%) × (100% / 75.4%) × (1000000 / 126008000).

Analysis of clinical characteristics in Japanese PDB patients

Data for the 169 Japanese patients gathered in the phase 2 study were analyzed. Among these 169 patients (age range, 26 to 92 years; mean age ± SD, 64.7 ± 14.5 years; Table 2), PDB markedly increased in prevalence with increasing age up to age 74 (Fig. 1). The male/female ratio was 0.86 : 1, and only 6.3% of patients had familial clustering; 75.1% of patients were symptomatic, and the most frequent symptoms were pain (including lumbago, coxalgia, buttock pain, and gonalgia) followed by skeletal deformity (Tables 2 and 3). Data regarding skeletal distribution revealed that monostotic and polyostotic disease exhibited almost equal prevalence. Commonly involved skeletal sites were the pelvis, spine, and femur. Serum alkaline phosphatase levels were elevated beyond the upper limit of normal in 89.6% of patients (Table 2).

Table 3. Symptomatology of 127 patients with symptomatic PDB in Japan

Lumbago	30
Coxalgia	29
Skeletal deformity	24
Buttock pain	18
Gonalgia	11
Hearing loss	8
Dental problem	5
Others	9

The total number of patients listed is more than 127 because several patients had more than one symptom

In addition to the fundamental diagnostic procedures of radiology, bone scans, and biochemical parameters of bone metabolic activity, bone biopsy was performed for diagnosis in 55% of the patients. Medical management was limited almost exclusively to the use of calcitonin and etidronate, becaue these are the only two agents licensed for the management of PDB in Japan. However, some doctors have used other bisphosphonates, including alendronate, risedronate, and pamidronate, which are approved in countries advanced in the management of PDB. Despite the high frequency of medical management, more than half of the patients remained symptomatic. In regard to complications, 16 patients displayed fractures, 1 developed hip osteoarthritis requiring total hip replacement, 2 developed osteosarcomas, and 1 had malignant fibrohistiocytoma (MFH) in bone. The most frequent sites of fracture were the hip and pelvis (Table 4).

Discussion

PDB is known to be a very rare disease in Japan, although its prevalence and clinical features have not been clarified. Thus, the majority of cases of PDB in Japan tend to be reported in the literature as case reports. This permitted us to ascertain the sources of referral in Japanese patients with PDB through a review of published case reports. Between January 1990 and December 2002, 154 cases were reported of which 72.1% were reported from departments of orthopedic surgery in the country. We therefore performed a nationwide mail survey to the departments of orthopedic surgery of 2320 general hospitals accredited by the Japanese Orthopaedic Association; the final response rate in this mail survey was 75.4% for phase one and 87.6% for phase two. These response rates may be sufficient to delineate the prevalence of PDB in Japanese patients.

The study has revealed that the prevalence of PDB in Japan across all ages is 2.8 per million. The prevalence of PDB is reported to range from 0.1% to 5% in high-prevalence countries [1–9]; thus, the prevalence in Japan is

Table 4. Treatment, prognosis, and complications of PDB in 169 Japanese patients

	Frequency listed (%)
Diagnostic procedures	
Biopsy	93 (55.0)
Without biopsy	76 (45.0)
Treatment	
No drug	26 (15.4)
NSAID	65 (38.5)
Calcitonin	105 (62.1)
Etidronate	25 (14.8)
Alendronate	15 (8.9)
Risedronate	2 (1.2)
Other bisphosphonates	4 (2.4)
Prognosis ($n = 152$)[a]	
No symptoms	57 (37.5)
Pain decrease	50 (32.9)
Pain persistence	25 (16.4)
Complications	20 (13.2)
Complications	
Fractures	16 (9.5)
Femur	10
Pelvis	2
Lumbar spine	1
Tibia	1
Unreported	2
Total hip arthroplasty	1 (0.6)
Sarcoma	3 (1.8)

[a] Data not available for 17 patients

The sum of listed percentages for treatment is more than 100%, because this list includes drugs that were used formerly, as well as currently used drugs

extremely low. PDB increased markedly in prevalence with advancing age, and this age distribution is somewhat similar to that observed in high-prevalence countries. The male/female ratio in the Japanese population is 0.86:1, with slight female predominance, although most studies in high-prevalence countries have reported a slight male predominance, with male/female ratios ranging from 1.2 to 1.8 [15,16,21–22]. The frequency of familial clustering in the Japanese population (6.3%) was lower than that of 15%–40% in high-prevalence countries [23–25].

In the present study, 75.1% of patients were symptomatic, although up to 30% of PDB patients in the United Kingdom and the United States had symptoms related to the disease [16,22]. This study has several limitations. First, the data were analyzed for subjects followed only at departments of orthopedic surgery. Second, these data might not reflect the true proportion of patients with PDB in Japan, through selection bias (missing asymptomatic patients with PDB might result in underestimation of the overall prevalence of asymptomatic PDB). Despite potentially missing asymptomatic PDB cases in this study, we consider any such bias to be insufficient to dispel the findings of an extremely low prevalence of PDB in Japan.

The most frequent clinical symptoms in Japanese PDB patients were musculoskeletal pain and skeletal deformity, findings similar to those in high-prevalence countries. There was a slight difference in the monostotic/polyostotic ratio among Japanese and Caucasian populations, with the prevalence of polyostotic disease in Japan being 48.5%, contrasting with 66% in high-prevalence countries [26]. The common sites of involvement were pelvis, spine, and femur, and this distribution is similar to that seen in the Caucasian population [27]. Serum alkaline phosphatase levels were elevated beyond the upper limit of normal in 89.6% of Japanese patients, a finding similar to that in high-prevalence countries, where levels are elevated in 85% of patients with untreated Paget's disease [28].

Diagnostic bone biopsy was performed in 55% of patients in Japan. In high-prevalence countries, bone biopsy is not recommended for the diagnosis of Paget's disease [29,30]. This tendency in diagnostic procedures probably reflects the fact that Japanese physicians are unfamiliar with the disease and our principal concern in diagnosis is to exclude possible malignant bone tumor. The present study showed that more than half of patients remain symptomatic in Japan, possibly due to the limited number of agents licensed in Japan for PDB treatment. It remains unclear whether aggressive treatment of PDB to normalize disease activity would result in fewer long-term complications, as the only two licensed drugs, etidronate and calcitonin, did not sufficiently alleviate pain for the majority of PDB patients. However, despite insufficient medical management of PDB in Japan, the frequency of hip osteoarthritis and secondary sarcoma was not high compared with frequencies in high-prevalence countries. The ratio of arthroplasty performed to frequency of hip osteoarthritis in Paget's disease was 1.5% in high-prevalence countries [22], while it was 0.6% in Japan. The frequency of malignant bone tumor in PDB was between 0.1% and 5% in high-prevalence countries [22,31–33], while it was 1.8% in Japan. In contrast to the lower frequency of hip osteoarthritis and secondary sarcoma, that of fracture in the affected femur was much higher in Japan than in high-prevalence countries {21.7% (10 cases/46 cases), compared with 3% [27]}. The higher ratio of symptomatic PBD in Japan, which might be a result of insufficient therapeutic intervention in Japan compared to that in high-prevalence countries, might explain some part of this difference.

In conclusion, the present epidemiological study clarified the prevalence and clinical manifestations of PDB in Japan, revealing that the disorder is extremely rare in Japanese individuals and that there are some differences in the clinical features of PDB between Japanese and patients from high-prevalence countries. Familial aggregation (6.3%) and polyostotic PDB (48.5%) were less common in Japan than in high-prevalence countries. Based on the results of this study, we are currently developing a registration system for PDB patients in Japan in order to facilitate the dissemination of knowledge to physicians of this rare disease among Japanese.

Acknowledgments We thank Professor S. Ralston and Professor F. Singer in their roles as scientific advisors for the Japanese Committee of Paget's Disease for their helpful advice and cooperation during this study. We also thank the Japanese Orthopaedic Association for the opportunity to conduct the mail survey with licensed departments of orthopedic surgery at 2320 general hospitals in Japan. This study was supported by a Research Encouragement Award of the Japan Osteoporosis Society and Grants-in-Aid from the Research Society for Metabolic Bone Diseases.

References

1. Siris ES (1998) Paget's disease of bone. J Bone Miner Res 13: 1061–1065
2. Barker DJ, Clough PW, Guyer PB, Gardner MJ (1977) Paget's disease of bone in 14 British towns. BMJ 1:1181–1183
3. Barker DJ, Chamberlain AT, Guyer PB, Gardner MJ (1980) Paget's disease of bone: the Lancashire focus. BMJ 280:1105–1107
4. Gardner MJ, Guyer PB, Barker DJ (1978) Radiological prevalence of Paget's disease of bone in British migrants to Australia. BMJ 1:1655–1657
5. Guyer PB, Chamberlain AT (1980) Paget's disease of bone in two American cities. BMJ 280:985
6. Barker DJ, Chamberlain AT, Guyer PB, Gardner MJ, Clough PW (1984) The epidemiology of Paget's disease of bone: the Lancashire focus. Radiological prevalence of Paget's disease of bone in British migrants to Australia. Paget's disease of bone in 14 British towns. Br Med Bull 40:396–400
7. Renier JC, Fanello S, Rodriguez N, Audran M (1995) Current prevalence of Paget's disease of bone in a region of France (Anjou). Rev Rhum Engl Ed 62:571–575
8. Ziegler R, Holz G, Rotzler B, Minne H (1985) Paget's disease of bone in West Germany. Prevalence and distribution. Clin Orthop 194:199–204
9. Altman RD, Bloch DA, Hochberg MC, Murphy WA (2000) Prevalence of pelvic Paget's disease of bone in the United States. J Bone Miner Res 15:461–465
10. Koga K, Kawasaki K, Kohno S, Yamada K, Itoh T, Nonaka K (1998) A patient with Paget's disease of bone treated with etidronate disodium. Kurume Med J 45:345–349
11. Itoyama Y, Fukumura A, Ito Y, Matsukado Y (1986) Acute epidural hematoma complicating Paget's disease of the skull. Surg Neurol 25:137–141
12. Yip KM, Lee YL, Kumta SM, Lin J (1996) The second case of Paget's disease (osteitis deformans) in a Chinese lady. Singapore Med J 37:665–667
13. Kim GS, Kim SH, Cho JK, Park JY, Shin MJ, Shong YK, Lee KU, Han H, Kim TG, Teitelbaum SL, Reinus WR, Whyte MP (1997) Paget bone disease involving young adults in three generations of a Korean family. Medicine (Baltimore) 76:157–169
14. Wang CL, Wu CT, Chien CR, Hang YH, Koga K, Kawasaki K, Kohno S, Yamada K, Itoh T, Nonaka K (1999) Paget's disease of the tibia. A patient with Paget's disease of bone treated with etidronate disodium. J Formos Med Assoc 98:444–447
15. Cooper C, Schafheutle K, Dennison E, Kellingray S, Guyer P, Barker D (1999) The epidemiology of Paget's disease in Britain: is the prevalence decreasing? J Bone Miner Res 14:192–197
16. Tiegs RD, Lohse CM, Wollan PC, Melton LJ (2000) Long-term trends in the incidence of Paget's disease of bone. Bone 27:423–427
17. Cundy T, McAnulty K, Wattie D, Gamble G, Rutland M, Ibbertson HK (1997) Evidence for secular change in Paget's disease. Bone 20:69–71
18. Siris ES (1994) Epidemiological aspects of Paget's disease: family history and relationship to other medical conditions. Semin Arthritis Rheum 23:222–225
19. Lecuyer N, Grados F, Dargent-Molina P, Deramond H, Meunier PJ, Fardellone P (2000) Prevalence of Paget's disease of bone and spinal hemangioma in French women older than 75 years: data from the EPIDOS study. Joint Bone Spine 67:315–318
20. Eekhoff ME, van der Klift M, Kroon HM, Cooper C, Hofman A, Pols HA, Papapoulos SE (2004) Paget's disease of bone in The Netherlands: a population-based radiological and biochemical survey – the Rotterdam Study J Bone Miner Res 19:566–570. Epub 2004 Jan 26
21. Melton LJ 3rd, Tiegs RD, Atkinson EJ, O'Fallon WM (2000) Fracture risk among patients with Paget's disease: a population-based cohort study. J Bone Miner Res 15:2123–2128
22. van Staa TP, Selby P, Leufkens HG, Lyles K, Sprafka JM, Cooper C. Incidence and natural history of Paget's disease of bone in England and Wales. J Bone Miner Res 17:465–471
23. Morales-Piga AA, Rey-Rey JS, Corres-Gonzalez J, Garcia-Sagredo JM, Lopez-Abente G, Siris ES, Ottman R, Flaster E, Kelsey JL, Sofaer JA, Holloway SM, Emery AE (1995) Frequency and characteristics of familial aggregation of Paget's disease of bone. J Bone Miner Res 10:663–670
24. Siris ES, Ottman R, Flaster E, Kelsey JL (1991) Familial aggregation of Paget's disease of bone. J Bone Miner Res 6:495–500
25. Sofaer JA, Holloway SM, Emery AE (1983) A family study of Paget's disease of bone. J Epidemiol Community Health 37:226–231
26. Mirra JM, Brien EW, Tehranzadeh J (1995) Paget's disease of bone: review with emphasis on radiologic features, part I. Skeletal Radiol 24:163–171
27. Davie M, Davies M, Francis R, Fraser W, Hosking D, Tansley R (1999) Paget's disease of bone: a review of 889 patients. Bone 24(5 Suppl):11S–12S
28. Eastell R (1999) Biochemical markers of bone turnover in Paget's disease of bone. Bone 24(5 Suppl):49S–50S
29. Selby PL, Davie MW, Ralston SH, Stone MD (2002) Guidelines on the management of Paget's disease of bone. Bone 31:366–373
30. Whitehouse RW (2002) Paget's disease of bone. Semin Musculoskelet Radiol 6:313–322
31. Freydinger JE, Duhig JT, Mc DL (1963) Sarcoma complicating Paget's disease of bone. A study of seven cases with report of one long survival after surgery. Arch Pathol 75:496–500
32. Wick MR, Siegal GP, Unni KK, McLeod RA, Greditzer HG 3rd (1981) Sarcomas of bone complicating osteitis deformans (Paget's disease): 50 years' experience. Am J Surg Pathol 5:47–59
33. Greditzer HG 3rd, McLeod RA, Unni KK, Beabout JW (1983) Bone sarcomas in Paget disease. Radiology 146:327–333