Clinical and demographic aspects of Paget disease of bone: A multicentric study from Turkey

Dilek Gogas Yavuz1, Semra Aytürk2, Şevki Çetinkalp3, Fırat Bayraktar4, Mustafa Kulaksızoğlu5, Zeliha Hekimsoy6, Hasan Aydın7, Melin Uygur8, Ferhat Deniz9, Süleyman İpekçi10, Ayşegül Atmaca11, Fullen Saraç12, Nilüfer Özdemir13, Zeynep Cantürk13, Meral Mert14, Seda Sancak15, Eda Ertörer16, Cevdet Duran17, Ersin Akarsu18, Oğuzhan Deyneli19, Alev Selek20, Alper Gürlek20

Abstract

Objective: Paget disease of bone (PDB) is a metabolic bone disease that has been rarely reported in the Eastern countries. This study aimed to evaluate the clinical and demographic characteristics of patients with PDB followed up at endocrinology clinics in Turkey.

Methods: An invitation was sent to tertiary endocrinology clinics to complete a survey on the demographic, clinical, radiological, and laboratory parameters, as well as treatment modalities of patients with PDB. This study enrolled clinically and radiologically proven 185 patients with PDB from 18 endocrinology centers based in 10 cities of Turkey.

Results: This cohort of PDB had female preponderance (women/men: 105/80) with a mean age, during diagnosis, of 57±10 years. Most of the patients (59.6%) were symptomatic at diagnosis. Bone pain and headache were the predominant clinical symptoms. Polyostotic disease was observed in 67.5% (n=125) of patients. Frequently affected bones were skull (41.6%), pelvis (53.5%), spine (41%), and femur (25.4%). Moreover, 17 patients with skull involvement had hearing loss. Mean serum alkaline phosphatase (ALP) level (552±652 IU/L; range: 280-5762 IU/L) was over the normal reference cutoff with normal serum calcium levels. Intravenous bisphosphonates (zoledronic acid, 5 mg; pamidronate, 60-90 mg) were the most used drugs (75%) for the treatment of PDB. Most of the patients (87.1%) treated with intravenous bisphosphonates responded well, with a decrease in serum ALP level (117±114 IU/L) in the 12th month of therapy. Furthermore, 16 patients relapsed after the second year of therapy; 3 patients did not respond to the initial intravenous bisphosphonate treatment.

Conclusion: The patients with PDB followed up by endocrinology clinics of Turkey exhibited polyostotic disease with classical clinical, radiological, and biochemical features and women’s predominance with good response to intravenous bisphosphonate therapy.

Keywords: Paget disease of bone, polyostotic disease, serum alkaline phosphatase, bisphosphonate therapy

Introduction

Paget disease of bone (PDB) or osteitis deformans is a chronic, nonmalignant disorder of the bone that generally affects 1 or several bones (1, 2). Common presentation of PDB is incidental finding of abnormal radiograph or elevated serum alkaline phosphatase (ALP) on a multiphasic screening chemistry panel in patients who are under investigation of other diseases (1, 3).

The prevalence of PDB differs among the populations. Considerable regional differences have been reported regarding PDB prevalence. Notably, the highest prevalence is observed in the European countries, especially in the United Kingdom (4). Clinical and epidemiological studies indicate that PDB affects Caucasians from North-western Europe but can occur in other ethnic groups too (5). However, PDB has rarely been reported in Southern Europe, Africa, and Asia, including China, India, and the Middle East (4).

Although recent studies have suggested a decline in the frequency and severity of PDB in New Zealand and Great Britain (6, 7), the number of PDB cases seem to have increased since 2005 in the Asian population (8).
Patients with Paget disease of bone followed up at the endocrinology clinics in Turkey exhibited polyostotic disease. Cranial involvement was frequent in this cohort than in European cohorts. Patients with Paget disease of bone show excellent response to bisphosphonate therapy.
According to the DXA measurements, 16 patients had osteoporosis (mean age: 71±9.87 years; 9 men and 8 women), and 33 patients had osteopenia (mean age: 65.72±11.98 years; 16 men and 17 women).

### Table 1. Demographic, clinical, and skeletal involvement data according to sex of patients with Paget disease of bone.

|                     | Women, n=105 (%) | Men, n=80 (%) | Total, (N=185) |
|---------------------|-----------------|--------------|--------------|
| Age at diagnosis (years) | 56.9±10 | 57.1±10 | 57.0±10.5 |
| Age at inclusion (year) | 64.3±10 | 64.1±10 | 64.4±10.5 |
| Number of affected bones | 3.22 | 2.11 | 2.66 |
| Bone biopsy for diagnosis | 13 | 15 | 28 |

### Clinical features

- **Skeletal deformity, n (%):** 7 (6.6) | 10 (12.5) | 17 (9.1)
- **Fractures, n (%):** 3 (2.8) | 2 (2.5) | 5 (2.7)
- **Deafness, n (%):** 9 (8.5) | 13 (16.2) | 22 (11.8)
- **Bone pain, n (%):** 48 (45.7) | 29 (36.2) | 77 (41.6)
- **Headache, n (%):** 23 (21.9) | 15 (18.7) | 38 (20.5)
- **Radicular compression, n (%):** 1 (0.9) | 1 (1.2) | 2 (1)
- **Sweating, n (%):** 1 (0.9) | - | 1 (0.5)

### Site of skeletal involvement (frequency)

| Site of Skeletal Involvement | Women, n (%) | Men, n (%) | Total, (N=185) |
|-----------------------------|-------------|-----------|--------------|
| Cranium | 53 (50.4) | 29 (36.2) | 82 (44.3) |
| Pelvis | 41 (39) | 40 (50) | 81 (43.7) |
| Spine | 42 (40) | 33 (41.2) | 75 (40.5) |
| Femur | 27 (25.7) | 24 (30) | 51 (27.5) |
| Tibia | 12 (11.4) | 16 (20) | 28 (15.1) |
| Scapula | 11 (10.4) | 5 (6.2) | 16 (8.6) |
| Sacrum | 17 (16.1) | 20 (26.5) | 37 (20) |
| Humerus | 10 (9.5) | 5 (6.2) | 15 (8.1) |
| Clavicle | 11 (10.4) | 4 (5) | 15 (8.1) |
| Ulna | 1 (0.9) | 2 (2.5) | 3 (1.6) |
| Calcaneus | 1 (0.9) | 1 (1.2) | 2 (1) |
| Mandible | 1 (0.9) | - | 1 (0.54) |
| Costa | 2 (1.8) | - | 2 (1) |
| Sternum | 1 (0.9) | 1 (1.2) | 2 (1) |
| Radius | 1 (0.9) | - | 1 (0.54) |

Data about symptomatic relief after treatment were unavailable.

### Discussion

This study involved a PDB cohort including 185 patients from 18 tertiary endocrinology centers from Turkey. The mean age at diagnosis was 57 years. Polyostotic involvement was observed in 63.7% of patients. The most common skeletal involvement areas were the cranium (44.3%), pelvis (43.7%), vertebrae (40.5%), and femur (27.5%) in this cohort of patients from Turkey.
Although this cohort might not represent the overall number of patients cared in the clinics, this study reported the largest case series from an area where there is relatively little information in the literature.

PDB occurs most commonly in people of British descent and European countries aged 55 years and above and exhibits a slight male predominance (4). In the Eastern countries, where PDB is thought to be rare, the number of cases has increased in the last decade, as reported from China (14), Japan (15), and India (16). PDB prevalence was estimated to be 1% in the Middle East populations (17). A Chinese PDB cohort (n=256) exhibited male dominance with a mean age of 55 years. A Japanese survey of 181 patients with PDB revealed a men:women ratio to be 0.86:1, with a slight female predominance and a mean age of 64.7 years. A PDB cohort of 48 patients from India exhibited a men:women ratio of 1.8 and a mean age at presentation of 60 years (14, 16).

Contrary to several reports from the Eastern and Western populations, female predominance was observed in our PDB cohort (women/men ratio was 1.31). Sex-related differences in our Turkish cohort cannot be explained based on the greater life expectancy in women because of the similar age of both sexes in the cohort or ascertainment bias. Nevertheless, the age of our PDB cohort was in the expected range, as noted in previous clinical studies.

This study had 59.4% of symptomatic patients, whereas up to 30%-40% of patients with PDB in the European countries exhibited symptoms (17). The ratio of symptomatic patients was 75.1% in the Japanese cohort (15), 89% in the Indian cohort (16), and 88.3% in the Chinese cohort (14).

The most frequent clinical symptoms observed in our group of patients with PDB were bone pain, headache, deafness, and skeletal deformity, which were similar to those observed in the high- and low-prevalence countries, except for headache and hearing loss (15, 18). Symptoms, such as headache and deafness, observed in this group of patients could be associated with the high frequency of skull involvement in our group. Monostotic involvement was observed in 36.2% of patients, which is a similar range observed in the high-prevalence countries (9, 19, 20). Monostotic involvement was reported in 10%-35% of cases in the European countries (21). Monostotic involvement was reported as 48.5%, 54.4%, and 94% in the Japanese, Chinese, and Indian studies, respectively (14-16).

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Table 2. Demographic, clinical, and pharmacological data according to skeletal involvement in patients with Paget disease of bone.

|                               | Monostatic (n=67) | Polyostotic (n=118) | p     |
|-------------------------------|------------------|---------------------|-------|
| **Sex (women/men)**          | 45/22            | 60/58               | n.s.  |
| **Age at diagnosis (years)** | 57.5±10.5        | 56.7±10.6           | n.s.  |
| **Age at inclusion (years)** | 63.8±10.6        | 64.8±10.2           | n.s.  |
| **Number of affected bones** | 1                | 3.1±1.3             | 0.04  |
| **Bone bx for diagnosis**    | 13               | 15                  | -     |

**Clinical features**

|                                | Monostatic (n=67) | Polyostotic (n=118) | p     |
|--------------------------------|------------------|---------------------|-------|
| **Skeletal deformity, n (%)**  | 5 (7.4)          | 12 (10.6)           | n.s.  |
| **Fractures, n (%)**           | 1 (1.49)         | 4 (3.8)             | -     |
| **Deafness, n (%)**            | 10 (14.9)        | 12 (10.6)           | n.s.  |
| **Bone pain, n (%)**           | 30 (44.7)        | 47 (39.8)           | n.s.  |
| **Headache, n (%)**            | 16 (23.8)        | 22 (18.6)           | 0.49  |
| **Radicular compression, n (%)**|                   | 2 (1.69)            | -     |
| **Arthropathy, n (%)**         | 20 (29.8)        | 29 (24.5)           | n.s.  |
| **Sweating, n (%)**            | 1 (1.49)         | -                   | -     |

**Site of skeletal involvement (frequency)**

| Location         | Monostatic (n=67) | Polyostotic (n=118) | p     |
|------------------|------------------|---------------------|-------|
| Cranium          | 21 (31.3)        | 61 (51.6)           | 0.0041|
| Pelvis           | 15 (22.3)        | 66 (55.9)           | <0.0001|
| Spine            | 10 (14.9)        | 65 (55)             | <0.0001|
| Femur            | 6 (8.9)          | 45 (38.1)           | <0.0001|
| Tibia            | 6 (8.9)          | 22 (18.6)           | 0.06  |
| Scapula          | 2 (2.9)          | 14 (11.8)           | 0.031 |
| Sacrum           | 3 (4.47)         | 34 (28.8)           | <0.0001|
| Humerus          | 3 (4.47)         | 12 (10.1)           | 0.16  |
| Ulna             | -                | 3 (2.5)             | -     |
| Calcaneus        | -                | 2 (1.6)             | -     |
| Mandible         | -                | 2 (1.6)             | -     |
| Costa            | -                | 2 (1.6)             | -     |
| Sternum          | -                | 2 (1.6)             | -     |
| Radius           | -                | 1 (0.8)             | -     |
| Clavicle         | -                | 11                  | -     |
| Metatarsus        | -                | 1                   | -     |

**Pharmacological treatment**

| Treatment         | Monostatic (n=67) | Polyostotic (n=118) | p     |
|-------------------|------------------|---------------------|-------|
| Calcitonin        | 1 (1.49)         | 2 (1.69)            | -     |
| Alendronate       | 14 (20.8)        | 19 (16.1)           | -     |
| Risedronate       | 6 (8.9)          | 5 (4.2)             | -     |
| Pamidronate       | 14 (20.8)        | 35 (29.6)           | -     |
| Zoledronate       | 24 (35.8)        | 49 (41.5)           | -     |
| Never treated     | 7 (10.4)         | 7 (5.9)             | 0.4343|

n.s: not significant.
The most common radiological finding was asymmetric polyostotic involvement, as observed in 65%-90% of cases in the European population. Nonetheless, a study from New Zealand reported an increased proportion of monostotic disease from 24%-36% since the beginning of the millennium (22).

Notably, European studies have reported that PDB preferentially targets the axial skeleton, frequently affecting the pelvis, femur, lumbar spine, skull, and tibia (1, 2, 23, 24). In contrast, the common sites of PDB were the cranial, pelvis, spine, femur, and tibia in our PDB cohort. Cranium involvement was seen in 31.1% patients with monostotic involvement. In contrast, pelvis and spine were the frequently involved sites in patients with polyostotic involvement.

Like the observation in high-prevalence countries, the serum ALP levels at the first visit were elevated beyond the upper limits of normal in 83.7% of patients in our PDB cohort (1, 2, 25).

Although guidelines do not recommend bone biopsy for the diagnosis of PDB, a diagnostic bone biopsy was performed in 15.1% of our group of patients (1).

Only 2 patients of our cohort had reported family history of PDB, but detailed and genetic data were not available; consequently, familial aggregation needs to be clarified with further examination of the family members and genetic studies.

This study revealed that the medical management of patients with PDB was performed according to the suggested clinical guidelines at the endocrinology clinics in Turkey. Most patients (91.3%) were provided with medical treatment. Oral or IV bisphosphonates were the treatment of choice, except for 2 patients who received nasal calcitonin. Biochemical response to bisphosphonate was observed in 89.3% of patients with a decrease in ALP levels during the first year of treatment. Relapse was observed in 16.1% of patients (men/women: 13/3, no reported family history) within the second year of bisphosphonate therapy. However, data regarding the symptomatic relief or quality of life after treatment were unavailable.

There is a lack of data that investigate bone density in Paget disease. Patients with PDB patients who carry high risk for osteoporosis need to be screened with DXA measurements for osteoporosis. Coexistence of osteoporosis also needs to be treated and followed up. In our group, DXA measurements revealed that 16 patients had osteoporosis and 33 patients had osteopenia.

This study had limitations. Ascertainment bias is a crucial issue in our study, which reflects the patients with PDB referred to endocrinology clinics for evaluation and treatment but not the actual number of symptomatic or asymptomatic patients with PDB in Turkey. Retrospective data were collected from patients’ records at the endocrinology and metabolism clinics. Genetic data and detailed family history were not available. Data of asymptomatic patients and patients treated at other clinics (rheumatology, physical rehabilitation, and orthopedics) were not obtained.

In conclusion, this retrospective epidemiological study revealed that a substantial number of patients with PDB are referred and treated at the endocrinology clinics in Turkey. We observed differences related to clinical features compared with the patients of Asia and other high-prevalence countries. These patients with PDB have polyostotic disease with female predominance, frequent cranial involvement, and a good response to bisphosphonate therapy.

Further studies are required to clarify the prevalence, clinical and genetic phenotype, and consequences of PDB in Turkey and the Middle East area.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Marmara University School of Medicine (Approval Date: September 21, 2015; Approval Number: 09.2015.152).

Informed Consent: Informed consent was not obtained due to the nature of this study.

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References
1. Singer FR, Bone HG III, Hosking DJ, Lyles KW, Murad MH, Reid IR, et al. Paget's disease of bone: An Endocrine Society clinical practice guideline. Clin Endocrinol Metab 2014; 99: 4408-22. [Crossref]
2. Ralston SH, Conal-Gudino L, Cooper C, Francis RM, Fraser WD, Gennari L, et al. Diagnosis and management of Paget's disease of bone in adults: A clinical guideline. J Bone Miner Res 2019; 34: 579-604. [Crossref]
3. Lyles KW, Siris ES, Singer FR, Meunier PJ. A clinical approach to diagnosis and management of Paget’s disease of bone. J Bone Miner Res 2001; 16: 1379-87. [Crossref]
4. Michou L, Philippe O. The changing countenance of Paget’s disease of bone. Joint Bone Spine 2016; 83: 650-5. [Crossref]
5. Guyer PB, Chamberlain AT. Paget’s disease of bone in two American cities. BMJ 1980; 280: 985. [Crossref]
6. Cundy T, McNulty K, Wattie D, Gamble G, Rutland M, Ibbertson HK. Evidence for secular change in Paget’s disease. Bone 1997; 20: 69-71. [Crossref]
7. Cooper C, Schafheutle K, Dennison E, Kellingray S, Guyer P, Barker D. The epidemiology of Paget’s disease in Britain: Is the prevalence decreasing? J Bone Miner Res 1999; 14: 192-7. [Crossref]
8. Sankaran S, Naot D, Grey A, Cundy T. Paget’s disease in patients of Asian descent in New Zealand. J Bone Miner Res 2012; 27: 223-6. [Crossref]
9. Tan A, Ralston SH. Clinical presentation of Paget’s disease: Evaluation of a contemporary cohort and systematic review. Calcif Tissue Int 2014; 95: 385-92. [Crossref]
10. Eray E, San R. Isolated MKB Paget’s disease of frontal bone: A case report. Turk J Endocrinol Metab 2004; 3: 121.
11. Kiskal G, Ozgen AG, Guney E, Kabalak T. HLA Typing in Turkish patients with Paget’s disease of bone. Turk J Endocrinol Metab 2000; 4: 143-6.
12. Baykan EK, Cetinkalp S, Ozgen G, Yilmaz C. Efficacy of zolodronic acid treatment in Paget disease of bone. J Osteopor Phys Act 2014; 2: 1-2. [Crossref]
13. Kanis JA, McCloskey EV, Johansson H, Cooper C, Rizzoli R, Reginster J-Y, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int 2013; 24: 23-57. [Crossref]
14. Wang QY, Fu SJ, Ding N, Liu SY, Chen R, When ZX, et al. Clinical features, diagnosis and treatment of Paget’s disease of bone in mainland China: A systematic review. Rev Endocr Metab Disord 2020; 21: 645-55. [Crossref]
15. Hashimoto J, Ohno I, Nakatsuoka K, Yoshimura N, Takata S, Zamma M, et al. Prevalence and clinical features of Paget’s disease of bone in Japan. J Bone Miner Metab 2006; 24: 186-90. [Crossref]
16. Cherian KE, Kapoor N, Shetty S, Jebasingh FK, Asha HS, Hepzhiba S, et al. Paget’s disease of bone in Turkey.
bone: An entity still exists in India. Indian J Endocrinol Metab 2018; 22: 368-72. [Crossref]
17. Merashli M, Jawad A. Paget’s disease of bone among various ethnic groups. Sultan Qaboos Univ Med J 2015; 15: e22-6.
18. 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 2002; 17: 465-71. [Crossref]
19. White G, Rushbrook J. Paget’s disease of bone. Orthop Trauma 2013; 27: 254-65. [Crossref]
20. Joshi SR, Ambhore S, Butala N, Patwardhan M, Kulkarni M, Pai B, et al. Paget’s Disease from Western India. J Assoc Physicians India 2006; 54: 535-8.
21. Cortis K, Micallef K, Mizzi A. Imaging Paget’s disease of bone—From head to toe. Clin Radiol 2011; 66: 662-72. [Crossref]
22. Cundy T. Is the prevalence of Paget’s disease of bone decreasing? J Bone Miner Res 2006; 21 Suppl 2: P9-13. [Crossref]
23. Davie M, Davies M, Francis R, Fraser W, Hosking D, Tansley R. Paget’s disease of bone: A review of 889 patients. Bone 1999; 24: 115-25. [Crossref]
24. Tiegs RD, Lohse CM, Wollan PC, Melton LJ. Long-term trends in the incidence of Paget’s disease of bone. Bone 2000; 27: 423-7. [Crossref]
25. Eastell R. Biochemical markers of bone turnover in Paget’s disease of bone. Bone 1999; 24: 495-505. [Crossref]