EJR European Journal of Rheumatology

DOI: 10.5152/eurjrheum.2020.20139

Original Article

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

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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

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Cite this article as: Gogas Yavuz D, Aytürk S, Çetinkalp Ş, Bayraktar F, Kulaksızoğlu M, Hekimsoy Z, et al. Clinical and demographic aspects of Paget disease of bone: A multicentric study from Turkey. Eur J Rheumatol 2021; 8(3): 156-61.

A part of this study was presented as a poster in European Congress of Endocrinology, 2016.

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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).

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Submitted: July 09, 2020
Accepted: September 13, 2020
Available Online Date: December 01, 2020

Main Points

- 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.

The clinical presentation of PDB can vary, with most patients having few or no symptoms. Limited data suggest that the clinical phenotype of PDB could be changing. A comparison of clinical data of patients from the last decade to the one before revealed that patients who are newly diagnosed with PDB were older, had low ALP levels, and presented mainly with bone pain (4, 9).

Turkey is a country that geographically lies between Europe and Asia with a multiethnic population. Prevalence and incidence of PDB have not been established in the Turkish population. Previously, case reports and case series including less than 20 patients with PDB have been published from Turkey (10-12). Patients with PDB are treated and followed up with a multidisciplinary approach primarily with endocrinology, orthopedics, and physical rehabilitation clinics.

This study aimed to evaluate the clinical, biochemical, and radiological characteristics in addition to the response to the treatment of patients with PDB at endocrinology clinics in Turkey.

Methods

An invitation was sent to the tertiary endocrinology clinics that have metabolic bone disease polyclinics in Turkey to complete a survey regarding patients with PDB, who were either diagnosed or being followed up. Overall, 18 of 30 tertiary endocrinology clinics responded to the invitation, and 185 patients who were diagnosed with and treated for PDB were included in the study. All patients were diagnosed with PDB according to a skeletal radiological survey and elevated ALP levels. A radionuclide bone scan was used to confirm the diagnosis and evaluate the extent of the disease.

Demographic, clinical, and laboratory data were collected from patients' files retrospectively. Data were collected regarding the presenting signs and symptoms (duration of the disease, bone deformity, fracture, deafness, bone pain, arthropathy, headache, medications for the treatment of PDB, dosage, and response to the treatment).

Biochemistry results (calcium, phosphorus, ALP, 25-hydroxycholecalciferol [25OHD3], immunoreactive parathyroid hormone [iPTH], creatinine, protein electrophoresis, and complete blood count) and radiographs (direct radiograms and bone scans) at diagnosis and for the last visit were recorded. In addition, available bone mineral density measurements of the hip and lumbar spine using dual-energy X-ray absorptiometry (DXA) for osteoporosis evaluation were collected. The T or Z scores were used to diagnose osteoporosis or osteopenia according to World Health Organization diagnostic thresholds (13).

The study protocol was approved by the local Ethics Committee of the Marmara University School of Medicine (Approval Date: September 21, 2015; Approval Number: 09.2015.152). The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki. Because this study was retrospectively designed, there was no requirement of informed consent forms.

Statistical analysis

Continuous variables were summarized using descriptive statistics presented as mean and standard deviation. Categorical variables were summarized using counts and percentages. Categorical data were analyzed using the chi-square (χ^2) test. The Mann-Whitney U test was used for the parametric variables. A value of $p<0.05$ was considered statistically significant. All statistical analyses were performed using the software Statistical Package for the Social Sciences version 16.0 (SPSS Inc.; Chicago, IL, USA).

Results

All the enrolled patients were diagnosed with PDB based on direct radiographs of the affected bone (n=185), and a radionuclide bone scan was performed for confirmation or detection of the disease extension in 165 patients. Overall, 28 (15.1%) patients had histological confirmation of PDB through the bone biopsy on suspected bone area.

Demographics

Table 1 presents the clinical features and site of the skeletal involvement according to sex. Female preponderance was noted in our PDB cohort (105 women and 80 men). The mean age at presentation was 57.0±10.5 (max-min: 81-26; 95% confidence interval: 54.03-58.34) years. Most of the patients (59.6%; n=110) were symptomatic at diagnosis. Bone pain, arthropathy, and headache were the predominant clinical symptoms. Deafness or hearing loss was reported in 22 patients. Fracture was reported in 5 patients: 2 patients had femur, 2 patients had vertebra, and 1 patient had humerus fracture. In total, 17 bone deformities were identified; including 6 in femur, 7 in tibia, 1 in vertebra, 1 in cranium, 1 in humerus, and 1 in clavicula. Only 2 patients had a reported family history of PDB who were unrelated to each other; 1 patient's mother and another patient's sister had reported PDB.

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)			
Cranium, n (%)	53 (50.4)	29 (36.2)	82 (44.3)
Pelvis, n (%)	41 (39)	40 (50)	81 (43.7)
Spine, n (%)	42 (40)	33 (41.2)	75 (40.5)
Femur, n (%)	27 (25.7)	24 (30)	51 (27.5)
Tibia, n (%)	12 (11.4)	16 (20)	28 (15.1)
Scapula, n (%)	11 (10.4)	5 (6.2)	16 (8.6)
Sacrum, n (%)	17 (16.1)	20 (62.5)	37 (20)
Humerus, n (%)	10 (9.5)	5 (6.2)	15 (8.1)
Clavicle, n (%)	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)

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).

Skeletal distribution of disease

The demographic and clinical characteristics of patients according to skeletal involvement are presented in Table 2. The most common skeletal involvement areas were the cranium (44.3%), pelvis (43.7%), vertebrae (40.5%), and femur (27.5%). In our cohort, monostotic involvement was observed in 36.2% (n=67) patients, and polyostotic involvement was observed in 63.7% (n=118) patients, which was statistically significant (p=0.04). The mean number of bones affected in patients with polyostotic involvement was noted to be 3.1.

In monostotic involvement, the most frequently affected bones were the cranium (31.3%), pelvis (22.3%), and spine (14.9%). Ulnar, calcaneal, mandibular, costal, sternal, radial, clavicular, and metatarsal involvements were not observed among patients with monostotic involvement in our cohort. Notably, monostatic involvement was more frequent in women than in men (p=0.044).

Biochemistry

At diagnosis, the mean ALP level was 552±652 (range: 280-5762) IU/L, and normokalaemia was observed in all patients. Data regarding 25OHD3 were available in only 85 patients. The mean 25OHD3 was 28.82±21 (range: 3-92.4) ng/dL. Overall, 17 patients had serum 25OHD3 levels below 10 ng/dL. The mean iPTH level was 75.2±15 (range: 32-126) pg/dL. Notably, 13 patients had high iPTH levels and were diagnosed with secondary hyperparathyroidism (2 patients with chronic renal failure and 11 with very low 25OHD3 levels [<10 ng/dL]). None of these patients had evidence of primary hyperparathyroidism.

Therapy

The duration of follow-up was 7.5±6.5 years. The decision of treatment and the choice of therapy were individualized and made by the clinicians. In addition, 16 patients did not receive treatment for PDB. The remaining 169 patients were treated with either bisphosphonates (n=166; intravenous [IV] zoledronic acid 5 mg [n=73], IV pamidronate [n=49], oral daily or weekly alendronate or risedronate [n=44]) or calcitonin nasal spray (n=3). Most of the patients who received treatment (n=151) responded well with a decrease in the serum ALP level (117±114 IU/L) at the first year of the therapy. Moreover, 3 women who did not respond to the initial therapy (oral alendronate, IV zoledronic acid, and IV pamidronate) were retreated with IV zoledronic acid and achieved partial remission with reduced from basal but elevated ALP levels in the third year of follow-up. Relapse was reported at 16 patients within the second year of therapy (men/women: 13/3; 5 patients on oral alendronate 70 mg weekly, 3 on IV pamidronate 60 mg IV, and 8 on IV zoledronic acid 5 mg). There was no reported family history in these patients.

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.

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			
Skeletal deformity, n (%)	5 (7.4)	12 (10.6)	n.s
Fractures, n (%)	1 (1.49)	4 (3.38)	-
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)			
Cranium, n (%)	21 (31.3)	61 (51.6)	0.0041
Pelvis, n (%)	15 (22.3)	66 (55.9)	<0.0001
Spine, n (%)	10 (14.9)	65 (55)	<0.0001
Femur, n (%)	6 (8.9)	45 (38.1)	<0.0001
Tibia, n (%)	6 (8.9)	22 (18.6)	0.06
Scapula, n (%)	2 (2.9)	14 (11.8)	0.031
Sacrum, n (%)	3 (4.47)	34 (28.8)	<0.0001
Humerus, n (%)	3 (4.47)	12 (10.1)	0.16
Ulna, n (%)	-	3 (2.5)	-
Calcaneus, n (%)	-	2 (1.6)	-
Mandible, n (%)	-	2 (1.6)	-
Costa, n (%)	-	2 (1.6)	-
Sternum, n (%)	-	2 (1.6)	-
Radius, n (%)	-	1 (0.8)	-
Clavicle, n (%)	-	11	-
Metatarsus, n (%)	-	1	-
Pharmacological treatment			
Calcitonin, n (%)	1 (1.49)	2 (1.69)	-
Alendronate, n (%)	14 (20.8)	19 (16.1)	-
Risedronate, n (%)	6 (8.9)	5 (4.2)	-
Pamidronate, n (%)	14 (20.8)	35 (29.6)	-
Zoledronate, n (%)	24 (35.8)	49 (41.5)	-
Never treated, n (%)	7 (10.4)	7 (5.9)	0.4343

n.s: not significant.

Although this cohort might not represent the overall number of patents 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).

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 cranium, 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.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - F.B., F.S.; Design - D.G.Y.; Supervision - S.A., S.İ.; Resources - D.G.Y.; Materials - D.G.Y.; Data Collection and/or Processing - D.G.Y., S.A., Ş.Ç., F.B., M.K., Z.H., H.A., M.U., F.D., S.İ., A.A., F.S., N.Ö., Z.C., M.M., S.S., E.E., C.D., E.A., O.D., A.S., A.G.; Analysis and/or Interpretation - D.G.Y., S.A., Ş.Ç., F.B., F.D., S.İ., A.A., F.S., N.Ö., M.M., S.S., C.D.; Literature Search - D.G.Y.; Writing Manuscript - D.G.Y., Ş.Ç., F.B., Z.H., H.A., M.U., F.D., A.A., F.S., Z.C., M.M., E.E., E.A., A.S., O.D., A.G.; Critical Review - D.G.Y., M.K., Z.H., H.A., N.Ö.

Conflict of Interest: The authors have no conflict of interest to declare

Financial Disclosure: The authors declared that this study has received no financial support.

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