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# Paget's Disease of Bone: A Single Center Experience

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## Abstract

**Introduction:** Paget's disease of bone, osteitis deformans is a benign disease of bone that affects one or more bones. Its prevalence and clinical features show geographical region differences. In this study, it was aimed to investigate the treatment responses and follow-up results as a single center experience by using the demographic, clinical, laboratory and radiological characteristics of patients with Paget's Disease of the Bone.

**Method:** Fifty-one patients who were diagnosed and followed up in Aydın Adnan Menderes University Endocrinology clinic between September 2004 and December 2021 were included in the study retrospectively.

**Results:** The mean age of onset of the disease was 61.8±12.5 years and the mean follow-up period was 9.3±8.2 years. It was observed that 68.63% of the patients were asymptomatic. Polyostotic involvement is present in 62.7% of the patients. It was observed that the disease most commonly involved the pelvis. It was determined that alkaline phosphatase value was above the upper reference limit in all patients at the time of diagnosis. All patients have increased activity in whole body bone scintigraphy. Except for one patient, all patients received bisphosphonate therapy. Remission was achieved in all patients who received zolendronic acid treatment as the first treatment.

Since there was no response in the treatment of 8 patients receiving oral bisphosphonate and 2 patients receiving pamidronate, IV zolendronic acid treatment was started. Treatment response was achieved in 6 (75%) of 8 patients who did not go into remission with oral bisphosphonate, and in 1 (50%) of 2 patients who received pamidronate and did not go into remission, after switching to zolendronic acid, and serum alkaline phosphatase values were found to regress to the normal range.

**Conclusion:** In this study, it was determined that patients with asymptomatic alkaline phosphatase elevation should also be examined for Paget's disease of the bone and that zolendronic acid provides an effective treatment in Paget's disease of the bone.

**Keywords:** Paget's Disease of Bone, Zolendronic Acid, Isolated Alkaline Phosphatase Elevation

## Introduction

Paget's disease of bone, also known as osteoitis deformans, is a benign bone disease that affects one or more bones [1]. The prevalence of Paget's disease of bone varies between different populations. The overall prevalence of this disease has been reported to be approximately 0.3% worldwide. While it is common in Europe, it is rare in Africa, Asia and the Middle East [2]. The initial presentation in Paget's disease of the bone is very variable, with most patients having few symptoms or asymptomatic. Most of the time, this disease is detected incidentally during the inves-

tigation of isolated alkaline phosphatase (ALP) elevation or in radiological examinations performed for other indications [3]. In this study, it was aimed to investigate the treatment response and follow-up results as a single center experience by using the demographic, clinical, laboratory and radiological characteristics of patients with Paget's Disease of Bone.

## Material and Method

The study included 51 patients who were diagnosed and followed up in Aydın Adnan Menderes University Endocrinology clinic between September 2004 and December 2021. The data of the patients included in the study were reviewed retrospectively from the hospital system with the approval of the ethics committee. Approval was obtained from the Ethics Committee of the Faculty of Medicine of Aydin Adnan Menderes University (2021/84).

### Statistical Analysis

R software, version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analyses). A normal distribution of the quantitative data was checked using the Kolmogorov-Smirnov test. Chi-square was performed to compare categorical variables. Descriptive statistics were presented as mean ± standard deviation and percentage. A P value of less than 0.05 was considered statistically significant.

## Results

The mean age of onset of the disease was 61.8±12.5 years and the mean follow-up period was 9.3±8.2 years. While 54.9% of the patients were male, 45.1% of them were female, and only one patient had a family history. Polyostotic involvement is present in 62.7% of the patients. The sites of involvement are pelvis, spine, skull, femur, pubis, and sacrum, in order of frequency (Table).

**Table: Skeletal sites involved in patients with Paget's of bone disease**

| Skeletal sites | Frequency (%) |
|---|---|
| Pelvis | 56.9 |
| Spine | 35.3 |
| Cranium | 27.5 |
| Femur | 25.5 |
| ileopubis | 21.6 |
| Sacrum | 11.8 |

Four of the patients were old-diagnosed and the first presentation symptom of these patients was unknown. At the time of diagnosis, 5 patients reported hip pain, 4 patients reported low back pain, and 1 patient with hip pain had a pathological fracture of the ileopubis. While deformity of the skull bone was seen in 2 patients, there was hearing loss in 1 patient. Thirty-one of 35 (68.63%) asymptomatic patients were examined and diagnosed because of isolated ALP elevation and 4 patients due to incidental radiological appearance. At the time of diagnosis, ALP value was 459.5±414.2 IU/I (range 170-187) and it was above the normal reference range in all patients. Serum 25-OH, vitamin D level was 17.2±9.8 ng/ml, calcium and parathormone (PTH) values were within the normal reference range.

All patients had involvement in whole body bone scintigraphy (increased activity) except for 1 patient, all other patients received bisphosphonate therapy. 39 (76.5%) of the patients were on intravenous zolendronic acid ,4 of the patients were on intravenous pamidronate ,16 of the patients were on oral bisphosphonate, 1 patient was on denosumab treatment. The final serum ALP value 6 months after the start of treatment was 136±108.6 IU/L, and the ALP value of 78.4% of the patients was within the normal range. Considering the response of the patients to treatment, 89.5% of monostotic and 71.9% of polyostotic patients were in remission. Nine of 11 patients who did not go into remission were patients with polyostotic (81.8%) involvement. When the patients who went into remission and those who did not were compared, it was seen that the age at onset and the first ALP value were similar (p>0.05).

Remission was achieved in all patients who received zolendronic acid as the first treatment. IV zolendronic acid treatment was commenced on 8 patients who received oral bisphosphonates and did not get respond to treatment, and 2 patients who received pamidronate and did not get respond to treatment. Six of the 8 patients (75%) who did not go into remission with oral bisphosphonate, and 1 of the 2 patients who received pamidronate were responded to IV zolendronic acid and the serum ALP value regressed to its normal range.

## Discussion

In our study, the mean age of 51 Paget patients was 61.8±12.5 years and the mean follow-up period was 9.3 ±8.2 years. Paget's disease of the bone, which is a disease of the aging bone, is usually seen after the age of 55 [4]. In the data of a multicenter study conducted in Turkey [5], the mean age at diagnosis was 57±10 years, while in another study [6]. in which 69 patients were included in Tunisia, the mean age was found to be 64.9±11.6 years. In a review of 118 articles from China, a total of 332 patients with a diagnosis of Paget's disease of the bone were evaluated and the minimum patient age was 2 months, while the maximum was 86 years, and the mean age was found to be 55.1±7.2 years [7].

Although the average age for this disease varies according to the countries, it was observed that the age of onset of the disease was generally compatible with our study, except for familial ones. In our study, 54.9% of the patients were male, while 45.1% were female. Male dominance was reported for this disease in China

and the United Kingdom, while female dominance was reported in the Japanese and Brazilian studies [7-10]. No significant gender difference was observed in our study. This difference in age distribution shows different results according to countries and even within the same country. In our study, the sites of involvement were pelvis, spine, skull, femur, ileopubis, and sacrum, in order of frequency.

In a multicenter study involving 185 patients in 12 centers in Turkey, 53.5% pelvis, 41.6% skull, 45% vertebra, and 25.4% femur involvement were reported [5]. The most common site of involvement in the United Kingdom and Japan was reported as the pelvis [9, 10]. In a review of 889 patients, the most frequently affected areas were the pelvis (58%), spine (55%), femur (32%), tibia (20%), skull (19%), and hip (12%). The most common site of involvement of the disease was found to be the pelvis in our study, as in the literature.

In our study, polyostotic disease was observed in 62.7% of the patients. In the only multicenter data of Turkey, polyostotic involvement was reported in 67.5% of the patients, similar to our study [5]. In a study in which data of 391 patients were compiled in Italy, it was reported that 58.7% of the patients had monostotic involvement [11]. In the Tunisian study, monostotic involvement was found in 55.1% of the patients [6]. While polyostotic involvement is common in our study, consistent with the data of our country, monostotic involvement is more common in other countries' data. With the help of these results, it is seen that there are geographical differences in the course of the disease.

In our study, it is known that only 1 patient had familial Paget. While the incidence of familial Paget is 12.3% in the USA, it is 13.8% in the United Kingdom, and this value has been reported to be high compared to the literature. Similar to our data, only 1 familial Paget's disease was reported in the Tunisian study [12, 13, 6].

In our study, 68.63% of the patients were found to be asymptomatic. In other multicenter Turkey data, 59.6% of the patients were symptomatic, and the most common symptoms were reported as bone pain and headache [5]. In another study, pain was the most common symptom, and 83.7% of the patients described pain and 12% of them had fractures [14]. In the Indian study, only 9.8% of the patients were found to be asymptomatic [15]. In the Tunisian study, the number of asymptomatic patients was also very low [6].

According to the data we obtained with our study, the number of asymptomatic patients was found to be higher than the results of all other studies, including other data from Turkey. In other studies, the number of symptomatic patients was higher. The reasons for which these different results may be related include difficulties in reaching the hospital in other countries, fewer hospital admissions for general control purposes, and as a result, the lack of further investigations due to coincidental elevation of ALP or Paget's suspicion on X-rays. In the multicenter Turkey data, the number of asymptomatic patients is higher than in other countries.

In our hospital, serum ALP and, if necessary, bone-specific ALP were used in the diagnosis and follow-up of patients. At the time of diagnosis, ALP value was found above the reference upper limit in all patients. Involvement was observed in whole body bone scintigraphy of all patients. In a Chinese meta-analysis, ALP elevation was found in 89.7% of the patients [7]. Although ALP is a sensitive marker, it may be normal in patients with monostotic involvement and should be evaluated carefully. Bone scintigraphy is the most sensitive examination method [16]. Bone-specific ALP and serum ALP are frequently elevated in Paget's patients. Although it is known that the degree of elevation generally reflects the extent and activity of the disease, this correlation is not always consistent. Serum ALP is usually sufficient for evaluation and monitoring of disease activity [17].

ALP measurement and bone scintigraphy are generally sufficient in the diagnosis of Paget's disease. Computed tomography (CT) or magnetic resonance imaging (MRI) are not routinely used, but they may be helpful in the evaluation of bone lesions if malignancy is considered to be the foreground. Bone biopsy is usually not necessary unless bone metastasis or primary bone tumor is considered in the diagnosis of Paget's disease [1]. There was no need for further investigations such as CT, MRI, PET and bone biopsy in the diagnosis and follow-up of the patients in our follow-up.

In our study, all patients except 1 patient received bisphosphonate treatment. At least 6 months after the first treatment, 78.4% of the patients had ALP values in the normal range and in remission. While 89.5% of monostotic patients were in remission, 71.9% of polyostotic patients were in remission. Nine of 11 patients who did not go into remission were patients with polyostotic (81.8%) involvement. The age at onset and the first ALP value were found to be similar ($p>0.05$) in patients who were in remission and those who did not, and no significant difference was found between them. Eight patients who did not respond to oral bisphosphonate and 2 patients who did not respond to pamidronate were given IV zolendronic acid. In 6 (75%) of 8 patients who did not go into remission with oral bisphosphonate, a response to zolendronic acid was obtained, and serum ALP value decreased to the normal range and did not rise again.

Bisphosphonates, one of the antiresorptive treatments, are the basis of the treatment of Paget's disease of bone. Although it is known that bisphosphonate is quite powerful in reducing metabolic activity and is beneficial in pain control, there is no strong evidence to prevent complications of the disease [18]. In a study comparing alendronate with placebo, it was observed that oral alendronate normalized ALP in 60-70% of patients, healed lytic radiological lesions, and provided normal lamellar bone histology [19]. In a study examining those who received zoledronate, it was observed that the therapeutic response was still sustained in 98% of patients after 2 years and in 87% after 5-6 years [20].

In a study including 182 patients with active Paget's disease, ALP returned to normal at a rate of 96 % after administration of zolendronic acid [21]. In a study comparing zoledronic acid and pamidronate, the biochemical response was found to be higher in those taking zoledronic acid (97% vs. 45%). When zolendronic acid was administered to patients who did not respond to pamidronate, a response rate of 94% was obtained [22, 23]. In Paget's disease, biochemical remission was observed in 96

percent of patients even after the administration of zolendronic acid alone [21], while biochemical relapse was observed in 14% of patients within 9 years [22].

Although it is thought that denosumab may be useful as an alternative treatment for Paget's disease of bone in selected patients, such as those with renal impairment, there is insufficient clinical experience. Published evidence for denosumab in Paget's disease is limited to case reports. Denosumab treatment was used in only 1 of our patients. This patient was suffering from end-stage renal disease and had no chance to receive bisphosphonate therapy. He had been examined for many years with back and low back pain and could not be diagnosed. Because the ALP level was high inconsistently with renal failure, bone synthraphy was performed and Paget's diagnosis was made. Although ALP value returned to normal after denosumab, pain response could not be obtained due to severe bone deformities.

In the latest guideline on Paget's disease of the bone published in 2019, intravenous zoledronate is recommended as first-line therapy [23]. A long-term remission can now be achieved in the majority of patients, a single dose of intravenous potent amino bisphosphonates such as zoledronic acid [24].Considering the literature results and our single center experience, we use and recommend IV zolendronic acid as the first-line treatment of Paget's disease of the bone.

In our study; Paget's disease was found to be more common in male patients and in advanced age. It was determined that the majority of the patients were asymptomatic. In the vast majority of patients, the diagnosis was made while investigating isolated ALP elevation. It has been determined that polyostotic disease is more common and most commonly involved in the pelvis. It was found that remission was higher in monostotic disease and most of those who did not go into remission were those with polyostotic involvement.

Remission was achieved in all patients who received IV zolendronic acid in the first treatment. Patients who did not go into remission with oral therapy had a high response to IV zolendronic acid therapy. The most common used, most effective and highest remission rate treatment method was IV zolendronic acid, which was also used in our study. With the help of the data we obtained in our study, it was determined that Paget's disease of bone should be examined in patients with asymptomatic ALP elevation and that IV zolendronic acid treatment was effective in Paget's disease of the bone.

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