Original Article

Health-related quality of life following bisphosphonate therapy in individuals with Paget's disease of bone – A study from a teaching hospital in Southern India

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Abstract

Background: Paget's disease of bone (PDB) is associated with considerable morbidity because of bony pains, fractures, and deformities. Remission, as assessed by reduction in alkaline phosphatase levels, does not necessarily correlate with improvement in quality of life (QoL). Health-related quality of life (HR-QoL) in affected individuals is not well-studied in India. This study attempts to describe the QoL in individuals with PDB. **Methods:** In this prospective observational study spanning 6 years (Jan 2017–Dec 2022), we included 29 treatment-naïve patients diagnosed with PDB based on clinical, biochemical, and radiographic features. All patients received treatment with antiresorptive agents. SF-36 questionnaire was administered before treatment and at review. **Results:** A total of 29 patients with PDB (20 males), with a mean (SD) age of 68.1 (9.8) years, were included. Symptomatic disease was seen in 23/29 (79.3%) and polyostotic disease in 25/29 (86%) subjects. The median duration of symptoms was 6 months (0–24 months). The most frequently involved skeletal sites were the pelvis (69%), vertebrae and sacrum (68%), followed by the skull (48%) and lower limb (48%). The subjects were treated with parenteral zoledronate (65.5%), oral alendronate (24.1%), and denosumab (6.9%). There was a significant improvement in all eight domains of QoL ($P = 0.0001$) as assessed by the SF-36 questionnaire. The maximum improvement (27.2%) was observed in the physical functioning domain ($P = 0.0001$). **Conclusion:** This study assessed various domains in QoL by using the SF-36 questionnaire at baseline and post-treatment with antiresorptive agents, and it was noted that there was a significant improvement in all domains of QoL.

Keywords: Bisphosphonates, India, Paget's disease of bone, quality of life

Introduction

Paget's disease of bone (PDB), first described by Sir James Paget in 1877, is a chronic skeletal disorder characterized by abnormal bone remodeling processes, leading to structurally altered and weakened bones.[1] It is widely prevalent in Great Britain, with a prevalence of 4%–5%, and also in countries where there have been immigrants from Britain, such as the United States, Canada, Australia, and New Zealand.[2] It affects both men and women, with a slight male preponderance, and rarely manifests before the age of 40 years.[3] A high index of suspicion needs to be maintained in making a diagnosis of PDB as some affected individuals may be asymptomatic.[4]

While the exact etiology of PDB remains incompletely understood, it is believed to involve a complex interplay of genetic predisposition, environmental factors, and viral infections.[5] The hallmark of PDB is focal and disorganized bone

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remodeling, with increased osteoclastic bone resorption followed by excessive osteoblastic bone formation.[6,7] This dysregulated bone turnover results in structurally compromised bones with abnormal trabecular architecture and increased vascularity. These changes lead to a variety of skeletal manifestations, including bone pain, deformities, fractures, secondary osteoarthritis, and rarely neoplasms.[8] The complications of PDB occur due to overgrowth of the affected bone, rapid bone turnover, and deposition of structurally weakened bone.[9] In the Paget's Disease Randomized Trial of Intensive versus Symptomatic Management (PRISM) study, patients with sequestosome (*SQSTM1*) mutations had severe and extensive disease and a higher incidence of complications. However, these mutations did not predict quality of life (QoL).[10]

The diagnosis of PDB is based on clinical symptoms, elevated alkaline phosphatase, X-rays showing typical sclerotic-lytic patterns, and uniformly increased tracer uptake of involved regions on a $^{m}Tc^{99}$ methylene diphosphonate bone scan.[11] It can occur in any bone in the body but predominantly affects the femur, spine, skull, sternum, and pelvis in order of frequency.[12] PDB can be asymptomatic in approximately 10% of patients, often being incidentally diagnosed during the evaluation of elevated alkaline phosphatase levels done for unrelated reasons.[13]

Bisphosphonate therapy is the cornerstone of treatment of PDB.[14] They alleviate symptoms by inhibiting bone resorption, the main player in the pathogenesis of the disease.[6] Denosumab, a monoclonal antibody against RANKL, has been used in PDB in patients with contraindications to bisphosphonates such as chronic kidney disease (eGFR < 35 mL/min).[15] Response to treatment is ascertained by normalization of alkaline phosphatase levels or documentation of a reduction of at least 75% in the total alkaline phosphatase excess.[11] However, it is unclear whether remission in biochemical parameters translates to an improvement in the QoL.[16]

The diagnosis of PDB requires a high index of suspicion. Most patients present with bony pains to the primary care physician. It is thus imperative that basic bone biochemistry that includes calcium/phosphate, creatinine, and an alkaline phosphatase be done in these individuals. As stated, asymptomatic patients may present with an isolated elevation of alkaline phosphatase done for an unrelated purpose. The primary care physician may also obtain relevant X-rays in suspected cases prior to referral to a higher center. In addition, treated cases of PDB may be followed up at a primary healthcare facility. An inquiry into improvement of symptoms, occurrence of new symptoms, and monitoring of disease using alkaline phosphatase may be done at the level of primary care.

Understanding the impact of PDB on QoL is essential for holistic patient care. Individuals with PDB often experience physical discomfort, functional limitations, and psychological distress, all of which can significantly affect their overall well-being.[17] Chronic bone pain, a common symptom of PDB, can lead to decreased mobility and impairments in daily activities, thus diminishing QoL.[5] In addition, the risk of fractures and skeletal deformities associated with PDB can further exacerbate physical limitations and reduce QoL.[18] Health-related quality of life (HR-QoL) in patients with PDB is not well studied in India. We aimed to study the HR-QoL in patients affected with PDB following bisphosphonate therapy.

Methodology

This was an observational study spanning 6 years (Jan 2017–Dec 2022) in the Endocrinology department of a university-affiliated, 2500-bed private teaching hospital in semi-urban India. A diagnosis of PDB had been made based on clinical features, characteristic findings of sclerotic and mixed sclerotic lytic lesions on plain X-rays, the presence of elevated serum alkaline phosphatase, and bone scintigraphic images showing classical features of uniform increased uptake of tracer in involved sites as per the Guideline Development Group (GDG) led by the Paget's Association (UK).[6]

Blood biochemical data were collected, which included alkaline phosphatase (AlP; N: 40–125 IU/L), albumin-corrected calcium (N: 8.3–10.4 mg/dL), phosphate (N: 2.5–5 mg/dL), 25-hydroxy Vitamin D (Vitamin D) (N: 30–75 ng/mL), creatinine (N: 0.6–1.2 mg/dL), and bone turnover markers (namely the C-terminal telopeptide of type 1 collagen (CTx) and the N-terminal telopeptide of type 1 procollagen (P1NP)). Patients received treatment with either zoledronic acid (4 mg, intravenous), alendronate (70 mg twice weekly, oral), or denosumab (60 mg subcutaneous) when bisphosphonates were contraindicated. They were followed up every 6 months–1 year or earlier if required. AlP was assessed at every visit. When the bone turnover markers were made available, these were measured as well. HR-QoL was assessed using the SF-36 questionnaire at baseline and following bisphosphonate therapy at the last follow-up visit.[19] This tool was chosen as it has been used in other studies as well[16] SF-36 questionnaire was administered in the vernacular language by a single person. This has two main domains: the physical domain, which includes general health, physical function, physical role, and bodily pain; and the mental domain, which includes emotional role, social function, vitality, and mental health. This study was approved by the institutional review board and ethical committee of our institution, and patients provided informed consent.

Statistical analysis

Measurements of central tendency (mean) and dispersion (standard deviation, range) were used for continuous variables and distribution of frequencies for categorical variables. Differences in the variables of interest between comparison groups were made by the paired *t*-test for continuous variables when the data were normally distributed. The relationship between the quantitative variables was analyzed using the Pearson or Spearman bivariate correlations test. For all comparisons, a two-tailed *P* value of <0.05 was considered significant.

Results

Baseline demographic data: During the study period, 29 patients (males = 20) were included in the study. The mean (SD) age of the study cohort was 68.1 (9.8) years. The mean BMI (SD) was 25.7 (4.0) kg/m^2. The median (range) duration of symptoms was 6 (0–24) months. Among patients with PDB 23/29 (79.3%) were symptomatic and 25/29 (86%) had polyostotic disease. A family history of PDB was seen in 6.9%. A total of 19/29 (65%) had type 2 diabetes mellitus, and 8/29 (27.6%) had coronary artery disease. Further details are shown in Table 1. The median (IQR) duration of follow-up was 32 (25–46) months.

Physical manifestations of Paget's disease: The most frequent sites of involvement were the pelvis (69%), followed by vertebrae (62.1%), and skull and upper limbs (48.3%). The sites of involvement of PDB are depicted in Table 2. The median duration of symptoms was 6 (0–24) months. Other associated manifestations are shown in Table 3. Bony pain was the most common symptom in 58.6% of patients. Hearing loss was experienced by 9/29 (31%). PDB was not the only ailment in these patients as 6/29 (20.7%) had osteoarthritis and 3/29 (10.3%) patients had spinal canal stenosis. Five (17.2%) patients presented with headache and 3/29 (10.3%) had macrocephaly. Two patients had cranial nerve palsy. Multiple myeloma and carcinoma stomach were seen in one person each. Two patients required more than one dose of parenteral zoledronate due to persistent bony pains that eventually resolved.

Basic bone biochemistry: Biochemical measures available at the first visit and the last follow-up were used for comparison. Basic blood parameters revealed normal creatinine, calcium, phosphorous, and 25 (OH) vitamin D levels. There was a statistically significant reduction in the mean alkaline phosphatase (269 vs. 94 U/L; P = <0.001) and CTx levels (1131 vs. 348 pg/mL; P = <0.001) after treatment when compared to baseline [Table 4].

Quality of life in patients with Paget's disease: QoL in PDB was assessed using the SF-36 questionnaire. It has two main domains: the physical domain, which includes general health, physical function, physical role, and bodily pain; and the mental domain, which includes emotional role, social function, vitality, and mental health. The mean scores in the physical domain and mental domain were 56.44% and 61.38%, respectively. There was statistically significant improvement in all domains of QoL at review after treatment. The maximum percentage improvement (27.2%) from baseline was observed in the physical functioning domain (P = 0.0001). Improvements in various domains of QoL are depicted in Table 5 and Figure 1.

Discussion

In this prospective study among patients with PDB, we found that following treatment with antiresorptive agents, there was significant improvement in the HR-QoL. Over a median follow-up of 32 months, there was a significant reduction in the total alkaline phosphatase, the bone resorption marker CTx, and improvement in all domains of the QoL questionnaire.

PDB can be asymptomatic in up to 70% of affected individuals and may be discovered incidentally on evaluation of an elevated alkaline phosphatase.[17] In the other extreme, it can cause life-threatening complications such as heart failure, raised intracranial pressure, and rarely osteosarcoma.[18] Between these two extremes, patients experience various manifestations that could impair their QoL, such as bone pain, fractures, secondary

Table 1: Baseline characteristics of the patients

Parameter	*n*=29
Total (males)	29, (20)
Age [mean (SD)]	68.1 (9.8) years
BMI [mean (SD)]	25.7 (4.0) kg/m^2
Duration [median (range)]	6 (0–24) months
Symptomatic *n* (%)	23/29 (79.3%)
Polyostotic *n* (%)	25/29 (86%)
Family history of Paget's disease	2 (6.9%)
Comorbidities	
Type 2 diabetes mellitus	19 (65%)
Hypertension	13 (44.8%)
Coronary artery disease	8 (27.6%)
Hypothyroidism	3 (10.3%)
Treatment	Zoledronate – 65.5% Alendronate – 24.1% Denosumab – 6.9%

Table 2: Site of involvement of Paget's disease

Site	Number (%)
Pelvis	20 (69%)
Vertebrae and sacrum	18 (62.1%)
Skull	14 (48.3%)
Ribs and sternum	7 (24%)
Upper limbs	10 (34.5%)
Lower limbs	14 (48.3%)

Table 3: Clinical manifestations associated with Paget's disease

Symptoms	*n* (%)
Bony pain	17 (58.6%)
Fractures*	2 (6.9%)
Macrocephaly	3 (10.3%)
Headache	5 (17.2%)
Osteoarthritis	6 (20.7%)
Spinal stenosis	3 (10.3%)
Cranial nerve palsy	2 (6.9%)
Hearing loss	9 (31%)
Vision loss	1 (3.4%)
Nephrolithiasis	4 (13.8%)
Primary hyperparathyroidism	2 (6.9%)
Myeloma	1 (3.4%)
Carcinoma stomach	1 (3.4%)

*Both patients had fractures involving the right proximal femur and were conservatively managed. Malunion was noted in one patient

osteoarthritis, and hearing impairment.[16] PDB may impact psychological aspects of life, including emotional well-being and social functioning, ranging from symptoms of back pain, headache, bone pain, fractures, and hearing loss to conditions such as hydrocephalus and even recurrent paraparesis.[6,20] Chronic pain and physical disfigurement can lead to feelings of depression, anxiety, and social isolation.[6] Assessment of QoL in PDB is vital for tailoring treatment strategies and addressing patients' holistic needs. Tools such as the SF-36 QoL survey are useful to evaluate various domains of QoL in individuals with PDB.[17]

Table 4: Bone biochemistry of patients

Parameter, units Normal range	*n*=29 Baseline Mean (SD)	*n*=29 Follow-up Mean (SD)	*P*
Alkaline Phosphatase (U/L) (40–125)	269.8 (224.6)	94.7 (40.5)	<0.001
CTx (pg/mL) Males: (200–704) Females: (226–1088)	1131.4 (787.1)	348.1 (246.1)	<0.001
P1NP (ng/mL) Males: 16.9–42.4 Females: 16.0–73.9	112.0 (46.8–243.0)	32.8 (23.0–45.0)	0.05
Calcium (mg/dL) (8.3–10.4)	9.5 (0.5)	9.3 (0.4)	0.616
Phosphate (mg/dL) (2.5–4.5)	3.55 (0.6)	3.6 (0.5)	0.595
Creatinine (mg/dL) (0.7–1.2)	0.9 (0.3)	-	
PTH (pg/mL) (8–80) Median (IQR)	64.5 (44.5–89.5)	-	
25 (OH) Vitamin D (ng/mL) (30–75)	27.4 (16.4)	-	

CTx - C terminal telopeptide of type 1 collagen; P1NP - N-terminal telopeptide of type 1 procollagen

Table 5: HR-QoL in patients with Paget's disease

Domain	Baseline (% score)	Follow-up (% score)	*P*
General health	54.47	63.68	<0.001
Physical Function	54.74	68.95	<0.001
Physical role	64.21	80.53	<0.001
Bodily pain	52.37	64.47	<0.001
Emotional role	56.05	67.36	<0.001
Social function	55.26	63.42	<0.001
Vitality	65.79	77.37	<0.001
Mental Health	68.42	71.05	0.04

The mean scores for the physical and mental components in the present study were 56.44% and 61.38%, respectively, which were much higher than 36.3 ± 11.3 and 48.7 ± 11.8 in comparison to a study by Langston *et al.*[16] The majority of patients in our study had symptoms for a duration of 6 months and an earlier diagnosis, which could have led to better QoL scores. In the study by Langston *et al.*,[16] the SF summary scores were compared with normalized scores of the general population, and it showed that bone pain due to PDB ($P < 0.001$), increasing age ($P < 0.001$), and having previously received bisphosphonate therapy either in the last 12 months or more than 12 months ago ($P < 0.001$) were negative predictors of the physical component of SF-36. Further analyses were undertaken to explore the reason why bisphosphonate therapy was a negative predictor of QoL, and it was determined that they were likely to have suffered a complication of the disease such as bone deformity or prior orthopedic surgery. The mental summary score was also significantly lower when compared to that of the general population and was predicted by prior bisphosphonate treatment, being single, and bone pain.

In symptomatic patients, the most frequent symptom was bone pain in 73.8%.[21] The pain that arises from the affected bone can be lancinating and occurs throughout the day, which worsens on standing and at night.[12] Development of osteosarcoma or chondrosarcoma can also cause pain, and another 10%–30% of patients present with fractures.[22] The most common symptom (58%) in our study cohort was pain. A meta-analysis of placebo-controlled trials showed that bisphosphonates when compared to placebo reduced bone pain in 418 subjects (45% vs. 23%, with a relative risk [RR] = 1.97, 95% CI: 1.29–3.01; number needed to treat [NNT] = 5, 95% CI: 2–15).[23] Another meta-analysis showed reduction in bone pain almost three times in the treatment arm (31% vs. 9%) in comparison to

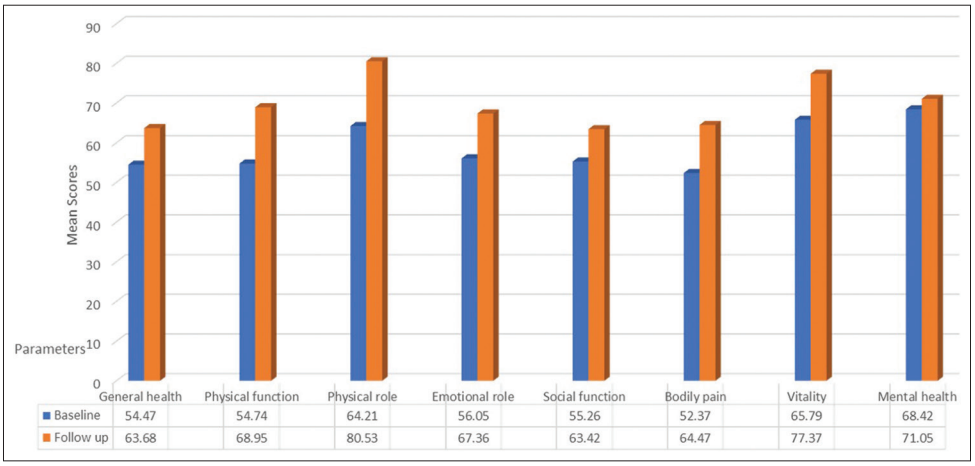

Figure 1: HR-QoL based on SF-36 questionnaire in patients at baseline and at follow up on treatment

the placebo (RR = 3.42, 95% CI: 1.31–8.9); two studies, 205 participants; NNT = 5, 95% CI: 1–31; with moderate-quality evidence).[23] Being the most frequent symptom in PDB, treatment with antiresorptive agents should be considered in all patients with bone pain.

Response assessment following therapy is primarily done by reduction in alkaline phosphatase levels and bone turnover markers.[12] Alendronate and risedronate were efficacious in reducing bone turnover markers in 60%–70% of patients with maintenance of biochemical remission for 18 months or longer.[24] In a study conducted in Western India, most patients showed a significant reduction in alkaline phosphatase levels after 6 months of treatment with alendronate.[25] In a study conducted in Southern India, patients receiving lower doses of alendronate (10–20 mg/day) experienced a 40% decline in serum alkaline phosphatase levels at 6 months of therapy, which further decreased by 64% after 1 year of treatment.[13] There was a statistically significant reduction in CTx and alkaline phosphatase in our study after treatment in comparison to baseline.

Langston *et al.*[16] in their study on 1324 patients with PDB showed that reduction in alkaline phosphatase does not always translate to improvements in QoL. This reiterates the need for addressing QoL in subjects with PDB. PRISM EZ study, which compared intensive versus symptomatic management of PDB for bone pain with zoledronic acid infusion showed that there were no clinically significant differences in QoL measures or bone pain between the two arms.[26] In our study, as the majority (79.3%) of the patients were symptomatic, there was a significant improvement in symptoms with antiresorptive agents. Treatment of PDB with potent bisphosphonates is efficient in controlling disease activity and is expected to prevent long-term complications of the disease.[18]

There was a significant reduction in scores in all domains of QoL in our study. Reid *et al.*[27] reported that improvements in all parameters in the SF-36 questionnaire continued during follow-up for up to 6.5 years. Gold *et al.*[4] showed that disease-related factors, including the number of complications, number of pagetic sites, and pain, became nonsignificant in the multivariate analysis, while age and number of comorbid conditions predicted self-rated health. Satisfactory family help and improvement in health in comparison to the prior 5 years were the only independent predictors of improved QoL.

The strength of this study is that it is the first study from India to assess the HR-QoL in individuals with PDB. Besides control of symptoms, treatment of PDB is also indicated to prevent long-term complications, and a very long follow-up period should be employed to detect long-term effects on QoL.[5,28] Our study has limitations of small sample size and short duration of follow-up. However, as there was a significant improvement in QoL with a small sample size, these values may be extrapolated.

Conclusion

There was significant improvement in HR-QoL in individuals with PDB following bisphosphonate therapy.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by [Kripa Elizabeth Cherian], [Nitin Kapoor] and [Thomas V Paul]. The first draft of the manuscript was written by [Fibi Ninan] and all authors [Fibi Ninan, Kripa Elizabeth Cherian, Nitin Kapoor, Thomas V Paul, Felix Jebasingh, Remya Rajan, HS Asha, Nihal Thomas] commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval statement

This work was approved by the institutional review board and ethics committee

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Nil.

Conflicts of interest

There are no conflicts of interest.

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