Effect of Bisphosphonate Therapy in Pediatric Skeletal Dysplasia: A Cross-Sectional Study

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ABSTRACT

Skeletal dysplasia is a group of rare, often progressive genetic disorders that impact bone development and joint function. These conditions commonly present with joint pain, stiffness, and limited mobility, resulting in reduced quality of life in affected children. Bisphosphonates have been explored as a potential symptomatic therapy in some patients with skeletal dysplasia, though evidence remains limited. To assess the clinical characteristics of pediatric patients with skeletal dysplasia in a tertiary center and evaluate the symptomatic and functional outcomes associated with bisphosphonate therapy. This cross-sectional study included 11 pediatric patients diagnosed with various forms of skeletal dysplasia at King Abdulaziz University Hospital. Diagnoses were confirmed clinically and genetically. Musculoskeletal symptoms (joint pain, stiffness, swelling, and range of motion) and functional status were evaluated using structured interviews and validated tools, including the Visual Analog Scale (VAS) for pain and the Short Form-12 (SF-12) for physical (PCS) and mental (MCS) component scores. Seven patients received bisphosphonate treatment (zoledronic acid), allowing for between-group and within-patient comparisons. Data was analyzed using non-parametric statistical tests. The mean age at disease onset was 5.6 ± 3.6 years, with diagnosis delayed until 9.7 ± 5.0 years. The most common diagnosis was Progressive Pseudorheumatoid Dysplasia (PPD). High parental consanguinity (91%) and family history (55%) were observed. At baseline, 82% reported joint pain, 73% had a limited range of motion, and 64% experienced stiffness and swelling. Bisphosphonate-treated patients had lower symptom prevalence than non-users, with significantly higher PCS scores (48.8 ± 14.6 vs. 43.1 ± 9.3; p = 0.03). Within-patient analysis revealed a significant improvement in PCS following treatment (from 30.2 ± 13.4 to 48.8 ± 14.6; p = 0.01) and a trend toward reduction in joint pain (from 100% to 29%; p = 0.06). Bisphosphonate therapy, particularly with zoledronic acid, may offer symptomatic relief and improve physical function in pediatric patients with skeletal dysplasia. Although limited by a small sample size and a short follow-up period, these findings suggest a potential role for bisphosphonates as part of a multimodal management strategy in selected patients. Further longitudinal studies with larger cohorts are warranted to confirm efficacy and long-term safety.

INTRODUCTION

The term familial arthropathy is a broad, descriptive term rather than a specific diagnosis and includes various conditions. The global prevalence of these disorders remains unclear; however, they are considered relatively common[1]. Familial arthropathies are a group of diseases defined by progressively increasing articular involvement. Many of these illnesses present with noninflammatory arthropathy and normal acute-phase reactants[1]. It is not unusual to mislabel diseases like these as juvenile idiopathic arthritis (JIA), the most prevalent inflammatory rheumatic disease in children. Although JIA hardly appears as a familial illness, extensive family investigations of patients and first-degree relatives have been reported[1].

Progressive Pseudorheumatoid Dysplasia (PPD, also known as spondyloepiphyseal dysplasia tarda with progressive arthropathy) is a rare, autosomal recessive bone disorder characterized by gradual destruction of articular cartilage, causing pain, stiffness, and joint swelling, which frequently results in a major decline in quality of life and functional disability[1]. Laboratory tests for rheumatoid factor and inflammation are always negative in PPD. A lack of response to anti-rheumatic medications is common[2]. It is commonly misdiagnosed as JIA; however, the joint issues in JIA are related to inflammation, unlike those in PPD[3]. PPD is an uncommon condition associated with mutations in the gene encoding the Wnt1-inducible signaling pathway protein 3 (WISP3). The WISP3 gene is located on chromosome 6q22 and comprises five coding exons, encoding a 354-amino acid protein[4].

Multicentric osteolysis, nodulosis, and arthropathy (MONA) is a rare autosomal recessive skeletal disorder characterized by progressive osteolysis of the carpal and tarsal bones, subcutaneous nodule formation on the palms and soles, and progressive osteoarthropathy, including joint contractures, pain, swelling, and stiffness[5]. This condition results from inactivating mutations in the matrix metalloproteinase 2 (MMP2) gene[6].

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Currently, treatment options for MONA remain limited. However, research suggests that bisphosphonates may help alleviate symptoms in certain skeletal disorders. A retrospective study conducted in Austria and Switzerland examined three siblings affected by the MONA spectrum disorder and assessed the impact of bisphosphonate therapy. The findings indicated a positive outcome, with reduced skeletal pain and improved bone mineral density[7].

There are few studies evaluating the effectiveness of bisphosphonate therapy in patients with familial arthropathy. Therefore, this study aims to assess the impact of bisphosphonate treatment on patients' clinical symptoms at King Abdulaziz University Hospital.

METHODS

This was a cross-sectional study conducted on pediatric patients with skeletal dysplasia. A total of 11 patients were included, with diagnosis confirmed through clinical and genetic evaluations. Ethical approval was obtained from the King Abdulaziz University Ethics Committee. Informed consent was obtained verbally from all participants' guardians before inclusion in the study. The families were contacted via telephone, during which consent was confirmed, and a structured interview was conducted.

Data collection involved a comprehensive interview that gathered demographic information, clinical history, and a symptom profile over the preceding three months. Participants were asked about musculoskeletal symptoms, including joint pain, swelling, stiffness, and limitations in range of motion. Functional assessment was performed using the Short Form-12 (SF-12), which includes the Physical Component Score (PCS) and Mental Component Score (MCS), as well as the Visual Analog Scale (VAS) for pain. Seven patients had received bisphosphonate therapy, enabling intra-individual comparisons of symptoms and functional scores before and after treatment. Zoledronic acid was used for these patients at a dose of 0.05 mg/kg (maximum 4 mg). The agent's decision was based on the medication's availability and accessibility.

Data were analyzed using SPSS version 29. Descriptive statistics were reported as frequencies and percentages for categorical variables and mean with standard deviation (SD) for continuous variables. Given the small sample size and skewed distribution, nonparametric tests were used for the analysis. Fisher's Exact Test was used to compare categorical variables, specifically the presence of musculoskeletal symptoms, between bisphosphonate users and non-users. To compare functional scores (PCS and MCS) between the two groups, the Mann–Whitney U Test was used. Within the bisphosphonate-treated group, changes in PCS and MCS before and after treatment were analyzed using the Wilcoxon Signed-Rank Test. Additionally, McNemar's Test was used to assess within-group changes in categorical symptoms following bisphosphonate therapy.

RESULTS

A total of 11 pediatric patients with skeletal dysplasia were included. The mean age at disease onset was 5.6 ± 3.6 years, and the mean age at diagnosis was 9.7 ± 5.0 years. The majority were male (64%), and a high proportion had parental consanguinity (91%). The most common diagnosis was PPD (Table 1).

At baseline, common symptoms included joint pain (82%), limited range of motion (73%), joint swelling (64%), and joint stiffness (64%). The mean VAS pain score was 8.5 ± 1.4, PCS was 34.8 ± 13.2, and MCS was 58.0 ± 7.2 (Table 2).

Table 1. Baseline Characteristics of the participant (11 patients)

Item	Summary
Skeletal dysplasia	PPD (n=5)
	MONA (n=2)
	Multiple Hereditary Exostosis (MHE) (n=1)
	matrix metalloproteinases 6 (MMP6) (n=1)
	Noonan syndrome (n=1)
	Alkaptonuria (n=1)
Gender (M/F) % (n)	64%/36% (7/4)
Age at the onset of disease (Mean ±SD)	5.6 ± 3.6 years
Age at the diagnosis (Mean ±SD)	9.7 ± 5.0 years
Presence of Consanguinity % (n)	91% (10)
Other family member affected % (n)	55% (8)
Bisphosphonate use % (n)	64% (7)
Other symptoms	knee deformity; contractures; Foot deformity; LLD; Scoliosis

LLD, Leg Length Discrepancy; PPD, Progressive Pseudorheumatoid Dysplasia; MMP6, Matrix Metalloproteinases 6; MHE, Multiple Hereditary Exostosis; MONA, Multicentric osteolysis, Nodulosis, and arthropathy syndrome.

Table 2. Baseline symptoms and functional score (11 patients)

Item	Summary
Joint pain % (n)	82% (9)
Joint swelling % (n)	64% (7)
Joint stiffness % (n)	64% (7)
Limited range of motion % (n)	73 % (8)
VAS score (Mean ±SD)	8.5 ± 1.4
MSC (Mean ±SD)	58.0 ± 7.2
PCS (Mean ±SD)	34.8 ± 13.2

VAS, Visual Analog Scale; MCS, Mental Component Score; PCS, Physical Component Score.

Table 3. Group Comparison: Bisphosphonate vs No Bisphosphonate

Item	Bisphosphonate Group (7 patients)	No Bisphosphonate Group (4 patients)	p-value
Joint pain % (n)	29% (2)	50% (2)	0.57
Joint swelling % (n)	43% (3)	75% (3)	0.54
Joint stiffness % (n)	29% (2)	75% (3)	0.24
Limited range of motion % (n)	43% (3)	100% (4)	0.19
PCS (Mean ±SD)	48.8 ± 14.6	43.1 ± 9.3	**0.03***
MCS (Mean ±SD)	61.0 ± 1.4	53.6 ± 11.4	0.15

MCS, Mental Component Score; PCS, Physical Component Score. *P-vale <0.05

Table 4. Within-Patient Comparison: Before vs After Bisphosphonate Treatment (7 patients)

Item	Before Treatment	After Treatment	p-value
Joint pain % (n)	100% (7)	29% (2)	0.06
Joint swelling % (n)	57% (4)	43% (3)	1.0
Joint stiffness % (n)	57% (4)	29% (2)	0.5
Limited range of motion % (n)	57% (4)	43% (3)	1.0
PCS (Mean ±SD)	30.2 ± 13.4	48.8 ± 14.6	**0.01***
MCS (Mean ±SD)	60.6 ± 1.9	61.0 ± 1.4	0.3173

MCS, Mental Component Score; PCS, Physical Component Score. *P-vale <0.05

Group Comparison: Bisphosphonate vs. No Bisphosphonate

Bisphosphonate users (n=7) had lower rates of joint pain (29% vs. 50%), joint swelling (43% vs. 75%), joint stiffness (29% vs. 75%), and limited range of motion (43% vs. 100%) compared to non-users. However, differences were not statistically significant (all $p > 0.05$). PCS scores were significantly higher in the bisphosphonate group (48.8 ± 14.6) than in non-users (43.1 ± 9.3; $p = 0.03$). MCS scores did not differ significantly (61.0 ± 1.4 vs. 53.6 ± 11.4; $p = 0.15$) (Table 3).

Within-Patient Comparison: Before vs. After Bisphosphonate Treatment

Among the bisphosphonate-treated patients (n=7), joint pain decreased from 100% to 29% ($p = 0.06$), indicating a trend toward improvement. Other symptoms showed reductions but were not statistically significant (Table 4).

PCS significantly improved from 30.2 ± 13.4 before treatment to 48.8 ± 14.6 after treatment ($p = 0.01$). MCS showed no significant change (60.6 ± 1.9 to 61.0 ± 1.4; $p = 0.31$).

McNemar's test for symptom change within the bisphosphonate group showed a trend toward improvement for joint pain ($p = 0.06$) and joint stiffness ($p = 0.50$), but these did not reach statistical significance.

DISCUSSION

The current study provides important insights into the clinical characteristics, symptom burden, and potential therapeutic benefit of bisphosphonate treatment in pediatric patients with skeletal dysplasia. Most patients presented with significant musculoskeletal symptoms, including joint pain (82%), limited range of motion (73%), joint swelling (64%), and stiffness (64%), highlighting the functional impact of these rare disorders on affected children. The mean age at disease onset (5.6 years) and the delayed diagnosis (mean age 9.7 years) also underscore the diagnostic challenge and the potential period of misdiagnosis or an untreated disease burden in this population.

When comparing patients who received bisphosphonates with those who did not, a notable trend toward symptom improvement was observed in the treated group, even though most differences did not reach statistical significance. Specifically, lower rates of joint-related symptoms and higher physical component summary (PCS) scores were recorded in the bisphosphonate group. These findings suggest that bisphosphonate therapy may contribute to improved physical functioning and symptom control, particularly with respect to joint pain and mobility, thereby improving the quality of life for these patients.

Importantly, within-patient comparisons before and after bisphosphonate treatment revealed a significant improvement in PCS scores (from 30.2 to 48.8; $p = 0.01$), indicating improved physical quality of life. Additionally, there was a marked reduction in joint pain prevalence—from 100% to 29%—after treatment, although this trend narrowly missed statistical significance ($p = 0.06$), likely due to the small sample size. Other symptoms, such as joint stiffness and swelling, also showed reductions, albeit non-significant, suggesting a general trend toward clinical benefit. However, this reduction in stiffness and swelling is believed to be a placebo effect and not related to bisphosphonate.

Their known pharmacological mechanism supports the potential therapeutic effect of bisphosphonates in skeletal dysplasia: they inhibit osteoclast activity, thereby reducing bone resorption and remodeling abnormal bone architecture. While the primary indication for bisphosphonates in pediatrics is osteoporosis, emerging evidence from conditions such as chronic recurrent multifocal osteomyelitis (CRMO) indicates that agents such as pamidronate can alleviate bone pain, suggesting broader anti-inflammatory and analgesic properties[8].

Multiple prior studies have documented the benefits of bisphosphonate treatment in skeletal dysplasia subtypes, including progressive pseudorheumatoid dysplasia (PPD) and multicentric osteolysis nodulosis arthropathy (MONA). However, most reports are limited to case studies or small case series[7,9,10]. Our study contributes to this growing body of evidence by offering a comparative analysis between treated and untreated patients, as well as pre- and post-treatment comparisons within the same individuals. This dual approach strengthens the internal validity of our observations despite the small cohort size.

It is important to note, however, that the post-treatment follow-up period was only two years, which may be insufficient to capture the full long-term effects or potential adverse outcomes of bisphosphonate use in children. Moreover, the decision to initiate or withhold bisphosphonate therapy was based on family preference rather than randomization, which may introduce selection bias.

Despite these limitations, the findings are promising and align with prior observations that suggest bisphosphonates may improve the physical component of quality of life, reduce skeletal pain, and enhance mobility in patients with skeletal dysplasia. These results highlight the need for larger, multicenter, prospective studies with longer follow-up to validate the observed benefits, assess long-term safety, and better understand the role of bisphosphonates across different subtypes of skeletal dysplasia.

CONCLUSION

In conclusion, our study suggests that bisphosphonate therapy, particularly zoledronic acid, may provide symptomatic relief and functional improvement in patients with pediatric skeletal dysplasia. While further research is warranted, clinicians may consider bisphosphonates as part of a multimodal management strategy in selected patients suffering from pain and functional limitations due to skeletal dysplasia.

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