A Systematic Review and Meta Analysis of Non-Randomized Interventional Studies on the Pamidronate Treatment Efficacy for Patients with Bone Fibrous Dysplasia

Nicolas Daniel Widjanarko, M.D., Anthony Ekaputra, M.D., Jessica Felicia Ang, M.D.

Faculty of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia.

ABSTRACT

Objective: Pamidronate is one of the main therapies for Fibrous Dysplasia (FD), with documented enhancements in patients' clinical characteristics. Nevertheless, its usage has yielded inconclusive results. Therefore, this review aimed to investigate pamidronate's impact on several clinical and biochemical outcomes in FD patients.

Materials and Methods: This review was conducted under the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. MEDLINE, ProQuest, Wiley, and EBSCO search databases were used to search the literature. Risk of Bias In Non-Randomized Studies of Interventions (ROBINS-I) was applied for quality assessment of the included studies and Review Manager (RevMan) 5.4 was employed in performing the meta-analysis.

Results: There are eight and seven studies used in the meta-analysis and systematic review, respectively. The results showed there are two studies with a low risk of bias and six with a moderate category. All papers included in this meta-analysis showed significant differences in the reduction of bone pain ($p<0.00001$) and serum alkaline phosphatase (SAP) ($p=0.04$) after pamidronate treatment compared to the before-treatment groups.

Conclusion: The findings of this study indicated that pamidronate therapy had been proven to significantly reduce bone pain and increase SAP in FD patients. However, trials with more age-specific samples and a lower risk of bias should be carried out to determine the statistical significance of overall results.

Keywords: Fibrous dysplasia; pamidronate; bone pain; serum alkaline phosphatase; bone mineral density (Siriraj Med J 2023; 75: 851-863)

INTRODUCTION

Fibrous Dysplasia (FD) is a rare skeletal disorder characterized by an abnormal fibrous tissue development within bone which leads to deformities and functional impairments. This condition exhibits an estimated prevalence of approximately 1 in 20,000 individuals worldwide.[1] Furthermore, FD typically manifests during childhood or adolescence, with the majority of cases being diagnosed before the age of 30.[2] The common manifestations are bone pain, skeletal deformities, and an increased propensity for fractures. Craniofacial FD can lead to facial asymmetry and vision/hearing impairments, while long bone involvement often causes limb-length discrepancies and pathologic fractures.[3] This indicates that early intervention is essential in managing FD-related complications and preventing functional disabilities. Several studies have also identified various timely treatment strategies, such as surgical interventions

Corresponding author: Nicolas Daniel Widjanarko
E-mail: nicolaswidjanarko310@gmail.com
Received 21 September 2023 Revised 21 October 2023 Accepted 26 October 2023
ORCID ID:http://orcid.org/0000-0003-4093-0782
https://doi.org/10.33192/smj.v75i12.265453

All material is licensed under terms of the Creative Commons Attribution 4.0 International (CC-BY-NC-ND 4.0) license unless otherwise stated.

and pharmacological therapies, which aim to alleviate pain, mitigate bone deformities, and enhance the overall quality of life for affected individuals.[4]

Bisphosphonates are therapeutically valuable analogs of naturally occurring pyrophosphate. These compounds find utility in conditions related to accelerated bone resorption, like Paget's disease, bone metastases, osteoporosis, and FD. Furthermore, previous reports have shown that chemical alterations on their side chain can substantially increase their efficacy.[5] Bisphosphonates have a complex molecular structure for their action, with a cumulative inhibitory impact on pathologic bone loss. These compounds prevent bone resorption by being absorbed and transported to the mineral surfaces which interferes with osteoclast function. Bisphosphonates also exert an anti-osteoclast effect by inducing osteoblasts to create an osteoclast inhibitory factor, thereby inhibiting bone resorption and stimulating formation.[6]

Pamidronate, a biphosphonate, was derived from inorganic pyrophosphate (PPi) and exhibits a strong affinity for hydroxyapatite crystals found in bone remodeling zones. Furthermore, pamidronate as a second-generation bisphosphonate includes R-2 side chains that contain nitrogen, compared to early variants. The key distinction lies in the farnesyl pyrophosphate synthase inhibition, an enzyme that is expressed in mammalian cells and is essential for the formation of lipids. This indicates that cellular apoptosis only appears in osteoclasts, due to the capacity of the compound to be maintained in bone before endocytosis during osteoclast-mediated matrix digestion and bone mineral breakdown.[7] Pamidronate also has intravenous (IV) preparations, thereby reducing the number of doses as well as gastrointestinal side effects experienced by certain patients treated with oral bisphosphonates.[8]

Pamidronate as one of the primary therapy for FD, has been shown to develop the patients' clinical features by reducing pain, bone turnover markers, and raising bone mineral density (BMD). Furthermore, its intravenous administration for polyostotic and monostotic FD has also been proven to be effective in reducing fracture rates in the afflicted regions.[9] BMD increase was observed after pamidronate treatment, but the response varied among patients.[10] This treatment also has an initial pain-relieving effect from its direct analgesic properties, but the exact pain-relieving mechanism is still being searched for.[11] The use of pamidronate contributes to the reduction of serum alkaline phosphatase (SAP). SAP level is a vital laboratory finding correlated with osteoblastic activity which is often applied as an important prognostic marker for FD and bone-related malignant tumors, such as osteosarcoma.[12] A study by Park et al., showed high SAP is related to the recurrence and progression into a more severe condition of FD, indicating that the marker can be used as a reliable predictor for the disease evolvement.[13]

Individualized pamidronate administration for FD management has shown inconclusive results.[14] Hence, this review aims to analyze the pamidronate treatment effect on several clinical and biochemical parameters in patients with FD.

MATERIALS AND METHODS

This review was completed under the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 statement.[15]

Variable of interest

This study aimed to evaluate the pamidronate treatment effect on bone pain, serum alkaline phosphatase (SAP), and bone mineral density (BMD) in patients suffering from FD.

Eligibility Criteria

Types

This review consisted of both published and unpublished studies examining the impact of pamidronate treatment on patients diagnosed with bone FD. Meanwhile, studies falling under the categories of reviews, cross-sectional analyses, cohort investigations, case reports, case series, conference abstracts, book sections, commentaries/editorials, and papers entailing non-human subjects were omitted. Articles lacking complete text and those unrelated to the relevant subject matter were disregarded.

Participants

Inclusion criteria were polyostatic or monostatic FD patients with normal renal and hepatic function, who were not taking drugs that affect bone metabolism. The FD diagnosis was according to clinical history, biochemical examination, and radiographic findings. Furthermore, there were no limitations for age, gender, and race.

Outcome of interest

The interest outcome of this study was the bone pain assessment for patients receiving pamidronate treatment, which was measured and reported as proportion (%) data, while SAP and BMD z-scores were measured and reported in numerical (continuous) data.

Search strategy and study selection

MEDLINE, EBSCO-Host, Wiley, and ProQuest electronic databases were used to search for eligible

studies by the year 2023. Furthermore, EBSCO-Host and ProQuest databases were screened for grey literature to identify potential unpublished studies with suitable PICO criteria. Papers were identified by three independent authors by using the following keywords: *(("polyostotic fibrous dysplasia"[All Fields] OR "bone fibrous dysplasia" [All Fields] OR "bone dysplasia"[All Fields]) AND ("pamidronate"[All Fields]) AND ("bone mineral density"[All Fields] OR "bone pain"[All Fields] OR "serum alkaline phosphatase"[All Fields]))*.

All acquired studies were imported into the Mendeley reference manager program. They were then checked for duplication, followed by titles and abstracts screening. The papers were assessed separately by the authors and eliminated if the title and/or abstract were not appropriate for this review. The selected papers were reviewed in full-text assessment using the aforementioned eligibility criteria, and suitable articles were included in the review. The differences observed were settled among the review team members.

Data collection process

The included studies were analyzed and the data extracted were first author, country, design, sample size, baseline characteristics (age and sex), FD diagnosis criteria, FD severity assessment, Pamidronate treatment protocol, Pamidronate regimen follow-up duration, and pamidronate treatment side effects.

Summary measures

The numerical data were in the form of mean ± standard deviation (SD) for normally distributed, or median (interquartile range) for non-normally distributed. The p-value and 95% Confidence Interval (CI) were also included for each item to show the results' significance. A p-value less than or equal to 0.05 was statistically significant.

Assessment of risk bias/ Quality assessment

Each study was evaluated using the Cochrane Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) for non-randomized controlled trials. The tool consisted of seven main domains, which were divided into 3 main categories: (1) Pre-intervention, consisting of (a) Bias because of confounding, (b) Bias in the participants' selection, (2) intervention, consisting of (c) Bias in interventions classification, (3) Post-intervention, comprising (d) Bias because intended interventions deviations, (e) Bias because of missing data, (f) Bias in outcomes measurement, and (g) Bias in reported result selection. From each domain, the bias risk was considered as low, moderate, serious, critical risk, and no information. Each trial's overall quality was divided into five groups based on the degree of bias present: (1) low risk of bias (low for all domains), (2) moderate risk of bias (low or moderate for all domains), (3) serious risk (serious at least one domain, but not at critical risk in any domain), (4) critical risk (critical in at least one domain), (5) no information (lack of information in one or more key domains where judgment was needed). All authors separately evaluated each article, and any disagreements were addressed among the whole review team until agreement was obtained.

Synthesis of results and Statistical analysis

For all outcomes, the odds ratios (ORs) for bone pain and the standardized mean differences (SMDs) for SAP and BMD were calculated as the effect size. The ORs were computed based on the proportion differences between the two groups, and the SMDs were computed based on the mean changes from baseline to the end of each group. Statistical analyses were carried out for between-group comparison, before and after pamidronate treatment. For some studies, the SAP values from individual patients were added to obtain the mean value, and the SD was calculated using the SD Calculator.[16] Considering that some showed primary results applying different methods, the meta-analyses were performed using a random effect model. This model presupposed that the treatment impact was distributed over certain populations and gave each study a more equal weighting. The combined effect measures of the direct comparisons from an individual intervention were compared using the inverse variance method for continuous data and the Cochran Mantel Haenszel test (CMH) for proportional data.

Heterogeneity across trials was assessed using the I^2 statistic. An I^2 value of < 25%, 25-50%, and >50 was placed in the low, moderate substantial, and high categories, respectively. When heterogeneity was present, possible causes were investigated through sensitivity analyses. A proportional result was obtained as weighted ORs and a continuous result as weighted SMDs. Differences across studies were calculated based on population sample sizes. Furthermore, publication bias was analyzed visually through a funnel plot, where each trial impact was plotted with its inversed SE. All studies were conducted using RevMan software version 5.4.

RESULTS

PRISMA

Fig 1 provides a selection process overview of the study and its outcomes. The initial search strategy yielded 269

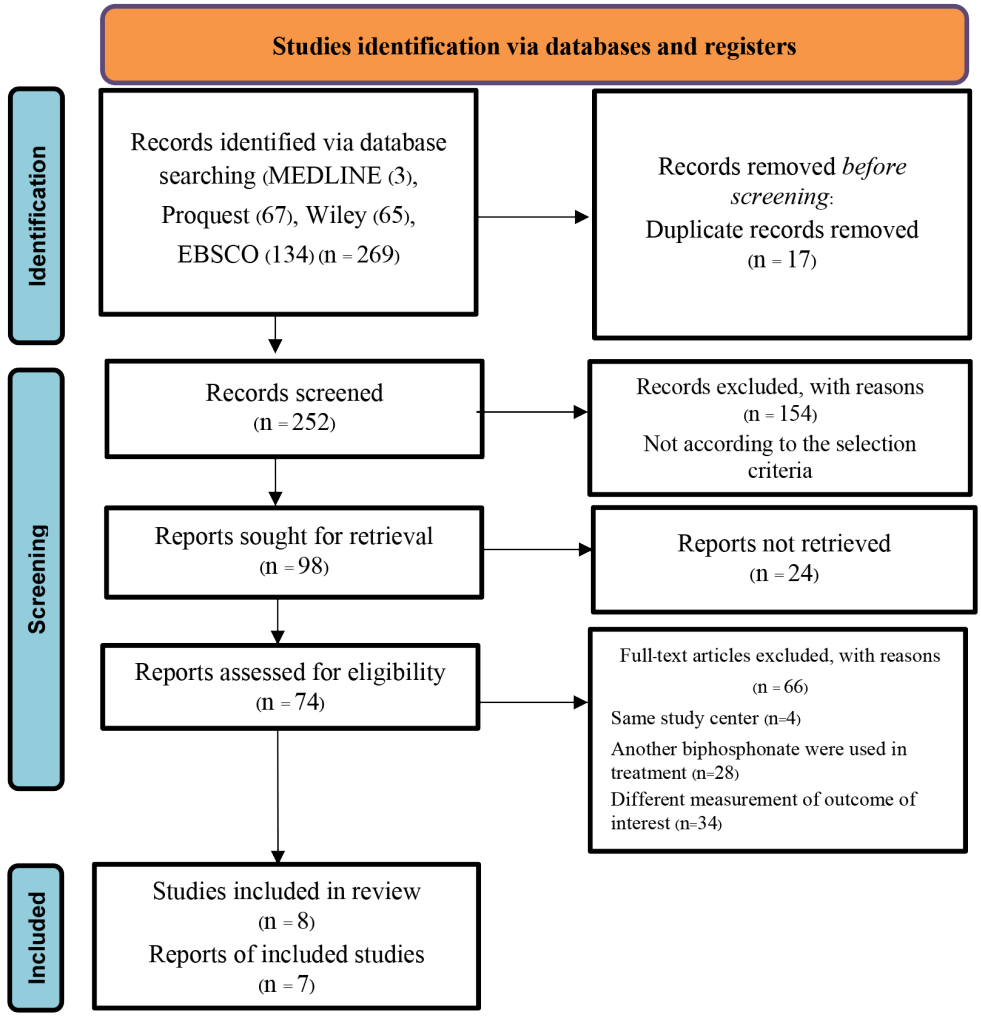


Fig 1. PRISMA 2020 flow diagram of included studies.

potentially relevant studies from the keywords searching using the Medical Subject Heading (MeSH). Among these papers, 252 were selected for comprehensive full-text evaluation, and only 74 full-access articles were retrieved. Furthermore, 62 studies were excluded according to the predefined criteria, namely the same study center (n=4), the combination of other bisphosphonate treatments (n=28), and different measurements for the outcome of interest (n=34). Eight studies were included in the systematic review and seven were included in the meta-analysis which was eligible for data extraction. Among the included papers, there was no specific publication date. Unpublished studies with appropriate inclusion criteria were not found, indicating that it was likely not to affect the conclusions of the review.

Quality assessment

Among the eight studies that were evaluated using ROBINS-I, six of them[6,14,17–20] had a low risk of bias, while two[21,22] had a high risk. A study by Chapurlat et al., 2004[14] was the continuation of Chapurlat et al., 1997[17] with a larger population number. According to Cochrane's recommendations, the Robvis tool was used to summarize the bias risk (Figs 2A and 2B), which was rated as "low", "moderate", "serious" and "critical" across various domains.[23]

A total of eight studies consisting of 143 children and adults with FD fulfill the criteria. The included studies' characteristics comprised of number of participants (N), mean age (years), sex (%), FD diagnosis criteria, FD severity assessment, treatment protocol, follow-up duration, and pamidronate treatment side effects, as shown in Table 1. All the papers were open trials with non-randomized study designs. At the time of diagnosis, the youngest age of the participant was one year and the oldest aged 63 years. Meanwhile, at the treatment onset, the youngest aged three years and the oldest was 69 years. Seven studies[6,14,17,19–22] utilized clinical evaluation as the basis of FD diagnosis, and one study[18] relied on radiologic findings to uphold the FD diagnosis. All papers administered pamidronate via an intravenous route with

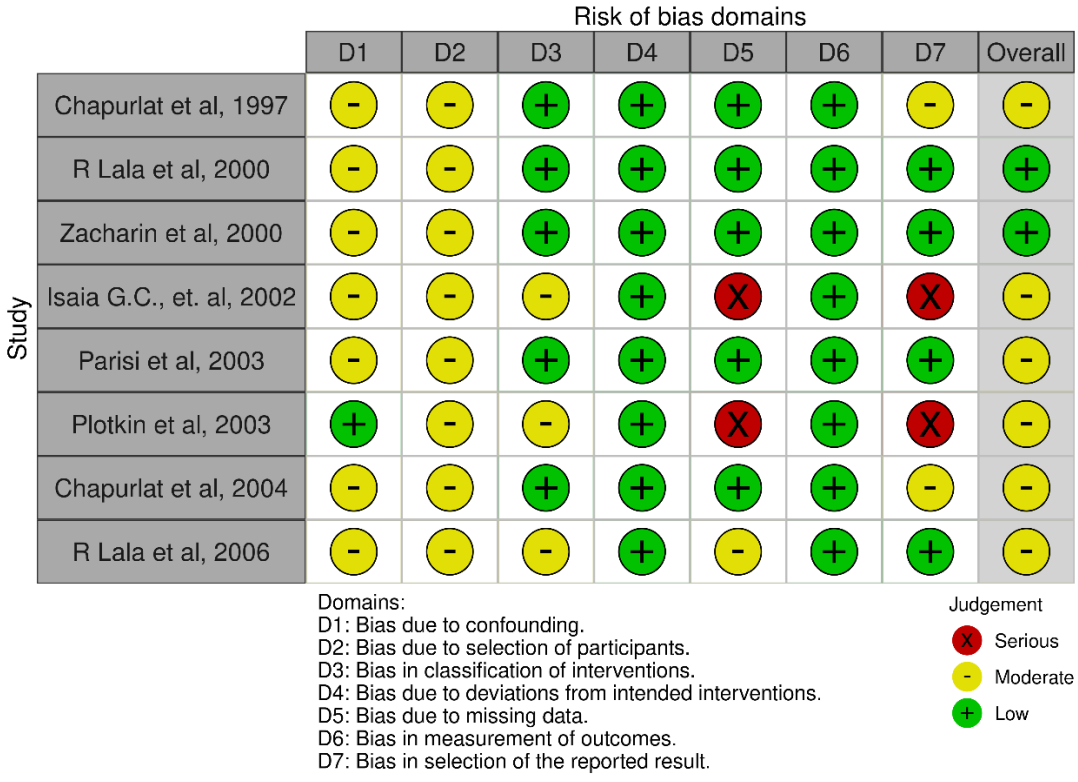


Fig 2A. Results of risk of bias assessment within studies illustrated with the Robvis tool.

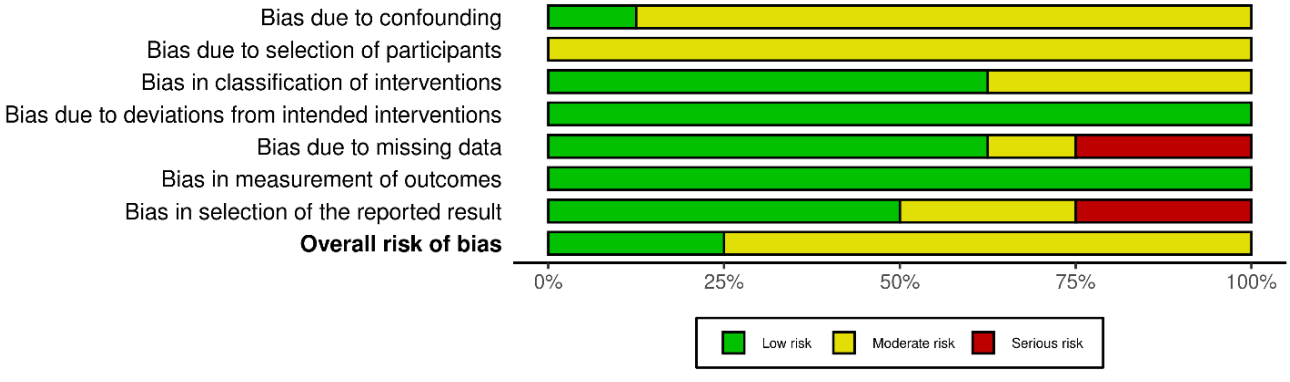


Fig 2B. Risk of bias domains summary in included studies.

a standard dose of 60mg/day or 0.5–1 mg/kgBW/day for three consecutive days. The regimen intervals ranged from four months to one year, with most of them having 6-month intervals for two years of treatment duration. The most common reported side effects included fever (hyperthermia/hyperpyrexia),[6,14,17–22] bone pain,[6,17–21] hypocalcemia,[6,17,19–21] and osteomalacia.[14,17]

Final Results

The seven studies included in the quantitative synthesis showed that bone pain and SAP were lower in the after-treatment group than in the before-treatment group, with a p-value ranging from 0.001 to 0.05. The meta-analysis results were described as a forest plot (Figs 3A and 3B) and the subsequent publication bias as a funnel plot (Figs 4A and 4B). The accumulation diagrams of forest plots showed the pooled OR for bone pain and SMD for SAP, as the final effect size obtained from the combination of all papers. Furthermore, the final weight of the combined value was shown in a rhombus shape, and a square shape indicated a weight for each study. The size of each square was determined by its weight in the meta-analysis, which was calculated based on the study population samples.

TABLE 1. Study Characteristics.

No.	Author, Publication Year, Country	Types of Study	Total population (n)	Mean/ Median Age (range) (years)	Sex (n) (%)	Fibrous Dysplasia Diagnosis Criteria	Bone Fibrous Dysplasia Severity Assessment	Pamidronate Treatment Protocol	Pamidronate Regimen Follow up Duration	Pamidronate Treatment Side Effects (%)
1	Chapurlat et al, 1997, France[17]	Open Trial, Non-Randomized Trial	20	At the time of diagnosis: 18 (1.5– 46) At the onset of treatment: 31 (13-69)	9 Females (81.81%) 11 Males (55%)	Diagnosed clinically, with support of biochemical and X-Rays examination	N/A	IV pamidronate over 3 days with 180 mg/course (60 mg/day). The drug was given in normal saline or glucose solution (1 l/day), as a 4-h infusion on 3 consecutive days. Two patients aged 13 years old were given pamidronate 1 mg/kg/day.	39 months	- Transient fever (40%). - Hypocalcemia. - Stiffness. - Bone pain (20%). - Osteomalacia (5%).
2	R Lala et al, 2000, Italy[21]	Non-Randomized Interventional Studies	9	At the onset of treatment: 9.63 (5.7 – 14.6)	7 Females (77.7%) 2 Males (22.2%)	Diagnosed clinically	Feuillan's Score (mild/moderate/ severe)	Pamidronnate was given at 0.5 mg iv/kg/day for 2 consecutive days with 1-year interval (from 1993 to 1994) and increased to 1 mg/kg/day for 3 consecutive days because clinical improvement with 6 months interval Dose was limited to 180 mg (over 3 days).	30 months	- Short term hypocalcemia - Pain and fever during at the end of pamidronate infusion
3	Zacharin et al, 2000, Italy[22]	Open Trial, Non-Randomized Trial	5	At the onset of treatment: 14.4 ± 9.79 (3.0-11.0)	3 Females (33.33%) 6 Males (66.67%)	Diagnosed clinically	N/A	Pamidronate was given by intravenous infusion 1 mg/ kg/d for 3 days every 6 months for 2 years.	24 months	- Mild acute reaction on first exposure to bisphosphonate with 38.5C fever for 24 hours in older children and young adults. - No child younger than 5 years was febrile.
4	Isaia G.C., et. al, 2002, Italy[19]	Non-Randomized Interventional Studies	11	At the time of diagnosis: 13.4 (6.9-19.9)	8 Females (72.7%) 3 Males (27.3%)	Diagnosed clinically	Feuillan's Score (mild/ moderate/ severe)	Pamidronate was given by intravenous infusion at 0.5 mg/kg/daily for 3 consecutive days at 12-month interval from 1994 - 1995. Pamidronate at 1 mg/kg/daily for 3 consecutive days at 6-month intervals from 1995 - 1997, and thereafter with the same dose every 4 months.	72 months	- Transient pain of the affected bones in 8 patients (72,7%). - Hyperpyrexia. - Transient hypocalcemia.

TABLE 1. Study Characteristics. (Continue)

No.	Author, Publication Year, Country	Types of Study	Total population (n)	Mean/ Median Age (range) (years)	Sex (n) (%)	Fibrous Dysplasia Diagnosis Criteria	Bone Fibrous Dysplasia Severity Assessment	Pamidronate Treatment Protocol	Pamidronate Regimen Follow up Duration	Pamidronate Treatment Side Effects (%)
5	Parisi et al, 2003, Argentina[6]	Open Trial, Non-Randomized Trial	8	At the time of diagnosis: 16 (4–30) At the onset of treatment: 26 (15–43)	7 Females (87.5%) 1 Males (12.5%)	Clinical history, radiographic fingdings, and bone biopsy	N/A	IV pamidronate infusion of 180 mg (60 mg/day over 3 consecutive days) every 6 months. Two patients did not receive the second pamidronate due to personal decision.	12 months	- Transient fever (28.57%). - Transient bone pain (28.57%). - Hypocalcemia (14.28%). - Ocular inflammation (28.57%).
6	Plotkin et al, 2003, Canada[18]	Non-Randomized Interventional Studies	18	At the onset of treatment: 9.83 (6.2 – 17.5)	8 Females (44%) 10 Males (56%)	The presence of radiologically detectable bone lesions at two or more sites plus genetic studies confirmed a FD-specific heterozygous mutations in codon 201 of the Gs gene.	N/A	Pamidronate was given on 3 consecutive days (the first 3-d cycle include 0.5 mg/kg on day 1 and 1 mg/kg on d 2 and 3). In subsequent cycles, 1–1.5 mg/kg daily for 3 days and repeated every 4 months. Each dose was diluted in 0.9% saline solution and given slowly over 4 hours.	24 months.	- An acute phase reaction in the form of a flu-like syndrome during the first treatment cycle, lasted for 24–48 h and resolved without complications.
7	Chapurlat et al, 2004, France[14]	Open Trial, Non-Randomized Trial	58	At the time of diagnosis: 18 (1 – 63) At the onset of treatment: 28 (5 – 63).	30 Females (51.72%) 28 Males (48.27%)	Diagnosed clinically, with the support of biochemical analysis, X-Rays examination, and bone biopsy	N/A	IV pamidronate 60 mg during 3 consecutive days, every 6 months. Cycles were repeated for 2 years, after 2 years, pamidronate was given only once a year in patients with excellent response. In children, the dose was 1 mg/kg/day during 3 days, every 6 months	50 months.	- Fever in 23% patients. -Venous irritation in 3 patients. - Venous thrombosis in 1 patient. - osteomalacia in 1 patient.
8	R Lala et al, 2006, Italy[20]	Non-Randomized Interventional Studies	14	At the onset of treatment: 11.4 (5.3 – 18.7)	10 Females (71.42%) 4 Males (28.58%)	Diagnosed clinically	Feuillan's Score (mild/ moderate/ severe)	Pamidronate was given by intravenous infusion at 0.5 mg/ kg/day for 3 consecutive days at 12-month intervals from 1994-1995 Pamidronate at 1 mg/ kg/day for 3 consecutive days at a 6-month interval from 1995-1998, after that every 4 months with the same dosage.	64 months	- Transient pain of the affected bones in 3 patients. - Transient hyperpyrexia during the first Pamidronate infusion in 11 patients. - Transient hypocalcemia (180-220 mMol/1).

TABLE 2A. Bone Pain.

Author Year, Country	Bone Pain (Number of patients with bone pain/number of total patients)		
	Before treatment	After treatment	P-value
R Lala et al, 2000, Italy[21]	5/9	1/9	<0.06**
Isaia G.C., et. al, 2002, Italy[19]	8/11	3/11	N/A*
Parisi et al, 2003, Argentina[6]	7/7	4/7	N/A*
Chapurlat et al, 2004, France[14]	44/58	23/58	0.001
R Lala et al, 2006, Italy[20]	8/14	0/14	N/A*

*N/A: Not available.
**considered as significant

TABLE 2B. Serum Alkaline Phosphatase (SAP).

Author Year, Country	SAP values (mean ± SD)		
	Before treatment	After treatment	P-value
Zacharin et al, 2000, Italy[22]	818.5 ± 181.7	654.0 ± 171	NS**
Parisi et al, 2003, Argentina[6]	315 ± 184	194 ± 150	0.05
Chapurlat et al, 2004, France[14]	185 ± 176	151.7 ± 460.6	0.015
R Lala et al, 2006, Italy[20]	1745.6 ± 1454.1	1018.5 ± 872.6	N/A*

*N/A: Not available.
**NS: Not significant.

TABLE 2C. Bone Mineral Density (BMD).

Author Year, Country	BMD Z-score (mean ± SD)		
	Before treatment	After treatment	P-value
Zacharin et al, 2000, Italy[22]	0.82 ± 0.06	0.94 ± 0.07	<0.05
Isaia G.C., et. al, 2002, Italy[19]	-2.77 ± 1.38	N/A	0.003
Parisi et al, 2003, Argentina[6]	-0.5 ± 0.7	N/A	0.02 (FDa)*
	(-1.4 ± 0.3)	N/A	0.05 (CL)**
Chapurlat et al, 2004, France[14]	0.831	0.973	0.003

*FDa = Fibrous Dysplasia Areas
**CL = Contralateral Side

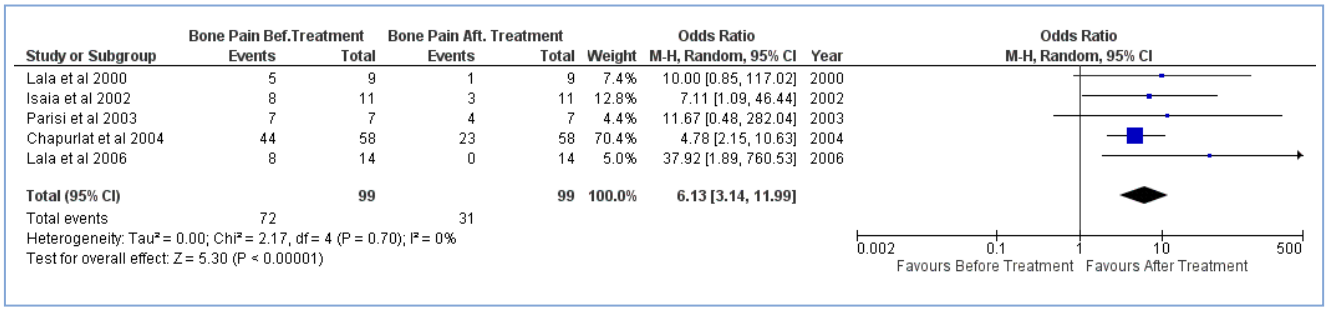


Fig 3A. Data Results in the Meta Analysis (Forest Plot) for Bone Pain Before and After Treatment of Pamidronate.

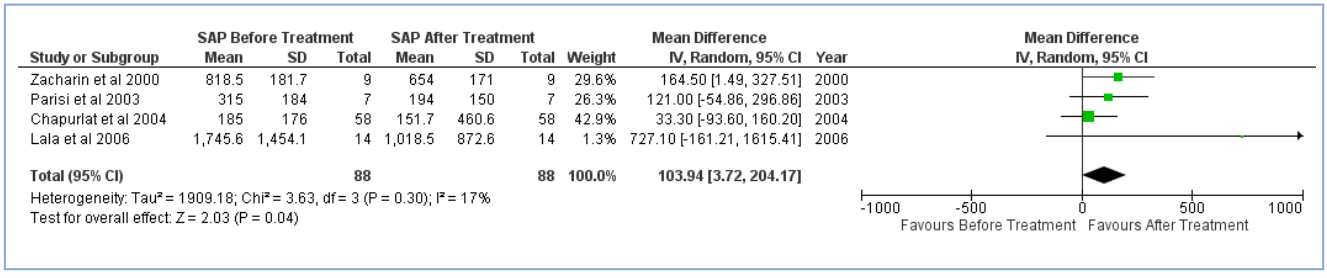


Fig 3B. Data Results in the Meta Analysis (Forest Plot) for Serum Alkaline Phosphatase (SAP) Before and After Treatment of Pamidronate.

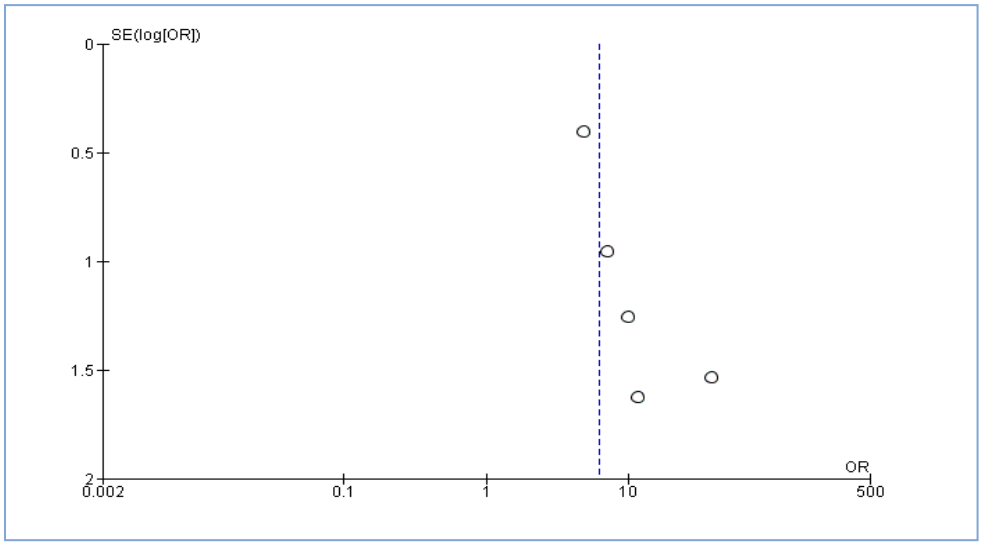


Fig 4A. Publication Bias as Funnel Plot Diagram for Bone Pain Assessment Before and After Treatment of Pamidronate in Patients with FD.

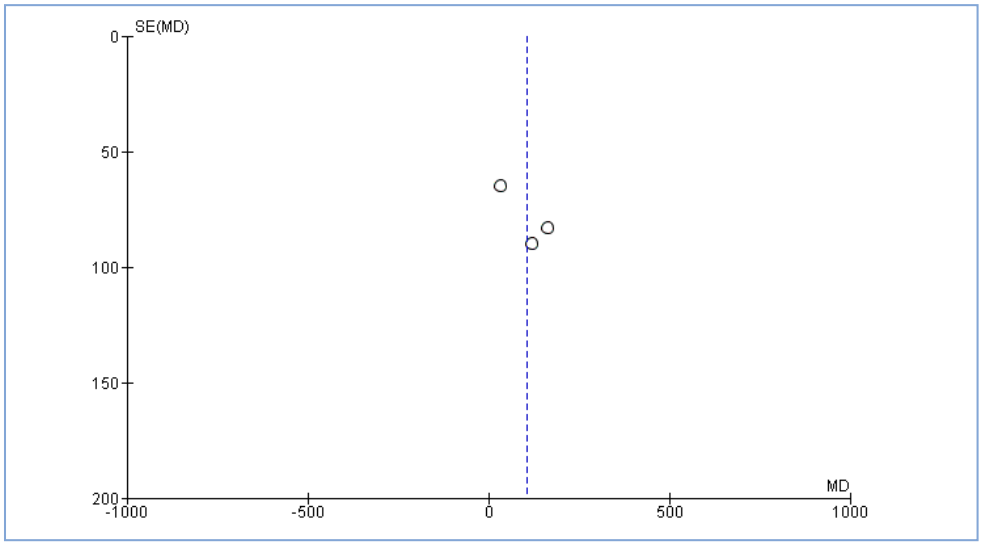


Fig 4B. Publication Bias as Funnel Plot Diagram for Serum Alkaline Phosphatase (SAP) Before and After Treatment of Pamidronate in Patients with FD.

All data in this meta-analysis showed significant differences in bone pain and SAP reduction after pamidronate treatment compared to the before-treatment groups, as shown in Figs 3A and 3B, with a p-value of <0.00001 and 0.04 respectively. The two outcomes were considered to have a low heterogeneity, with I^2 results of 0% and 17%, respectively. The publication bias represented as a Funnel Plot Diagram was shown in Figs 4A and 4B for bone pain reduction and SAP, respectively.

DISCUSSION

FD was a benign bone lesion characterized by altered osteogenesis, leading to intramedullary fibro osseous proliferation. The excessive fibro osseous tissue subsequently replaced the normal bone tissue. This phenomenon could lead to an increased risk of fracture, leading to pathologic fracture, specifically in weight-bearing bones on the lower extremities. Along with the poor FD bone quality, this could cause deformities and increased severity of pain.[24] Notwithstanding, McCune Albright syndrome (MAS) was a condition, where FD simultaneously occurred with endocrine dysfunction and skin pigmentation.[25]

Pamidronate was a second-generation bisphosphonate that inhibited osteoclast-mediated bone resorption and was widely used as a treatment among patients with FD, osteogenesis imperfecta, cerebral palsy, and chronic neuropathy.[26] The outcomes typically included clinical, radiological, and biochemical measurements for FD diagnosis. Bone pain, SAP, and BMD were the most reported outcomes to be analyzed.

An FD lesion could precipitate normal bone resorption and create a phosphaturic factor, leading to a deficiency of phosphate and consequent osteomalacia. This condition then led to lower BMD values, particularly in the trabecular-predominant bone locations.[27] Treatment with bisphosphonates could prevent the process, thereby enabling rapid restoration of BMD in the affected regions. The efficacy of pamidronate to increase BMD was proven by Lee et al. when the BMD Z-scores and lumbar spine (mg/cm^2) from the pamidronate group increased after the therapy during their follow-up (both p<0.001). All patients also experienced improvements in bone pain after the use of pamidronate.[28] These findings were consistent with the results of this current study. Zacharin et al.,[22] reported a significant increase in BMD z-score (0.82 ± 0.06 to 0.94 ± 0.07, p=<0.05), and Chapurlat et al.,[14] showed a significant elevation of BMD z-score (0.831 to 0.973, p=0.003) after several cycles of Pamidronate treatments.

Pain was one of the major complaints in patients with FD. Furthermore, thinly myelinated sensory nerve fibers (A-delta) and CGRP+ nerve fibers, which were rich in peptides, were the main nerve fibers found in innervate bone. The periosteum, mineralized bone, and marrow all exhibited this pattern of innervation. Patients with FD experienced excessive bone growth, pathological bone remodeling, and ectopic sensory plus sympathetic nerve fiber sprouting in the marrow and mineralized bone. These conditions led to alterations in the sensory nerve fibers, thereby causing bone pain formation.[29] Majoor et al. stated that pain was the most frequent complaint in FD patients regardless of age, bone involvement, and types of FD (monostotic or polyostotic).[30]

Compared to other forms of pain, FD pain could be well managed to retain functional status and life quality. The cumulative OR of 6.13 and the I^2 value of 0% from the meta-analysis indicated a substantial impact of pamidronate in reducing bone pain, with no significant heterogeneity among the included studies. This suggested that the results of this study were consistent and similar, thereby increasing the reliability of the meta-analysis findings.[6,14,19–21] After the first round of pamidronate therapy, pain intensity was decreased, and an additive effect was shown after numerous cycles of therapy. Lala et al., (2000) reported a gradual decrease alongside pamidronate treatment cycles. Furthermore, low pain (1–3) gone after the first therapeutic cycle, and moderate or severe pain (4–9) gone after the third cycle.[21] Isaia et al. observed that only 1/11 individuals had the sensation at the end of treatment (2000), down from 3/11 patients two years before (1998), and 8/11 patients at the start of treatment cycles in 1994.[19] These findings suggested that cumulative doses of pamidronate could reduce bone resorption and increase bone formation, leading to pain depletion.

Serum alkaline phosphatase (SAP) was a plasma membrane enzyme as a marker for bone formation and as a predictor for disease activity in metabolic bone diseases.[31] Adenyl cyclase in FD patients was constantly active due to the GNAS 1 mutation, and this led to elevated cAMP activity, which promoted aberrant osteoblasts and hyperfunction of skeletal progenitor cells.[32] Ma et al., revealed that the increase in ALP level was due to elevated levels of calcitonin through the action of cAMP.[33] Bone SAP was directly inhibited by three BPs that contained nitrogen atoms in their structure (Pamidronate, Alendronate, and Zolendronate), in a time- and dose-dependent manner. SAP activity was enhanced by low dosages of BPs (10^{-10}-10^{-5} M), but it was inhibited by high doses (10^{-4} M). Since SAP was a metalloenzyme that was dependent on zinc and magnesium, the BP-induced SAP

inhibition could be the consequence of metal chelation by the drug's phosphonate groups. This hypothesis was supported by the findings that an increase of Zn^{2+} or Mg^{2+} could reverse SAP inhibition.[34]

Decreased levels of SAP indicated a decline in bone turnover during the use of Pamidronate, indicating that the enzyme could be used to monitor the treatment response.[35] Based on the forest plot results, pamidronate treatment significantly and positively affects SAP levels among the included studies (95%CI: 3.72 – 204.17, p=0.04). The pooled mean difference of 103.94, along with a low to moderate heterogeneity suggested a consistent treatment effect. Studies from Parisi et al., and Chapurlat et al., showed a significant reduction of SAP levels after pamidronate treatment, from 315±184 to 194±150 (p=0.05)[27] and 185±176 to 151.7±460.6 (p=0.015), respectively.[14] Although a marked reduction of the enzyme levels was observed in Zacharin et al., (818.5 ± 181.7 to 654.0 ± 171), the result was not significant. This occurred in some patients six months after the second pamidronate therapy round, which indicated time between pamidronate infusions needed to be shorter in more severe cases, leading to a more notable SAP reduction.[22]

Pamidronate treatment was associated with a variety of side effects, including acute phase response, musculoskeletal discomfort, jaw osteonecrosis, hypocalcemia, and various ophthalmic events,[36] as reported in most of the included studies. However, all side effects were relieved by supportive therapies, only limited to the initial treatment, and did not persist after the second cycle of pamidronate infusion. The safety of Pamidronate treatment was also supported by Jjuszczak et al., who found that 39 out of 42 (93%) patients agreed Pamidronate is effective for NSAIDs-refractory chronic recurrent multifocal osteomyelitis in children, without reported prominent side effects.[37]

Demographic characteristics from each study significantly differed from others. The age in some studies varied greatly, while those in others varied considerably. The majority of cases were identified in children, while some studies focused on pediatric populations,[14,17,27] and others included a wider range of ages.[18–22] However, it was challenging to determine the extent of the correlation between age and FD. Hart et al, reported that clinically significant bone lesions often became visible by the age of five, and nearly no substantial lesions were developed after the age of fifteen. Adult FD lesions could become less active, due to the apoptosis of bone marrow mesenchymal stromal cells (BMSCs) carrying mutations.[38] In terms of ethnicity, the correlation between FD and the patient's race from different countries (France,[14,17] Italy,[19–22] Argentina,[27] Canada[18]) was not readily evident, taking into account that FD was generally considered to be unrelated to a specific race or ethnicity. This diversity could represent various racial groups, thereby allowing the conclusions to be generalized to broader populations.

Although GNAS mutation testing was the "gold standard" for FD diagnosis, it could be complicated by the sensitivity of the procedure and the degree of mosaicism in the afflicted tissue.[39] Other diagnostic methods were standard PCR and NGS, but both had limited value for evaluating mutations.[40] Therefore, several knowledgeable medical professionals could frequently rely on clinical findings and specific FD characteristics on a radiographic exam (ground-glass appearance),[41] making a diagnosis without the necessity for biopsy or molecular approach, as mentioned in most of the included studies.

Some studies had adjusted confounding factors, such as disease severity by classifying using Feuillan's score.[19–21] Patients with varying degrees of disease severity could respond differently to treatment. This indicated that including disease severity as a covariate in analyses could help account for this. The variation in gender distribution across studies showed that there might be differences in the proportion of females and males among participants, but FD had an equal sex distribution throughout all populations.[42]

Strengths and limitations of the study

Based on previous findings, this was the first systematic review and meta-analysis on pamidronate treatment in FD of the bone, both in children and adult populations. Our research comprised several primary studies that follow the development of Pamidronate usage from time to time, from the first published study in 1997 until the latest in 2006. Thus, we have exhibited a broad view regarding this matter. An additional novelty of our studies found that SAP, aside from BMD, was proven to be significantly reduced following Pamidronate treatment, furthermore demonstrating that this enzyme might be used to surveil the effectiveness of the treatment in the future. The grey literature was also included to minimize the potential publication bias.

All studies were open and non-randomized trials. While these could provide initial insights into the potential effectiveness of pamidronate for FD, their findings were considered to be less robust compared to randomized controlled trials (RCTs). Therefore, further RCTs were required to enhance the evidence and better understand the outcomes. The small sample size and the absence of a control group can potentially undermine the robustness of our findings, as it may not have provided adequate statistical power to detect more subtle effects.

CONCLUSION

In conclusion, the reduction in bone pain and the decrease in SAP levels appeared to be favorable treatment outcomes associated with Pamidronate treatment in individuals with FD. The meta-analysis results supported the conclusion that Pamidronate was effective in improving these conditions.

ACKNOWLEDGEMENTS

The authors are grateful to all colleagues from Atma Jaya Catholic University of Indonesia for the support and contributions provided.

Conflict of interest

No conflict of interest.

Funding

No specific grant nor funding from any agencies or sponsors.

REFERENCES

1. Chapurlat RD, Meunier PJ. Fibrous dysplasia of bone. Baillieres Best Pract Res Clin Rheumatol. 2000;14(2):385-98.
2. Lietman SA, Levine MA. Fibrous dysplasia. Pediatr Endocrinol Rev PER. 2013;10 Suppl 2:389-96.
3. Berglund JA, Tella SH, Tuthill KF, Kim L, Guthrie LC, Paul SM, et al. Scoliosis in Fibrous Dysplasia/McCune-Albright Syndrome: Factors Associated With Curve Progression and Effects of Bisphosphonates. J Bone Miner Res Off J Am Soc Bone Miner Res. 2018;33(9):1641-8.
4. Collins MT, Kushner H, Reynolds JC, Chebli C, Kelly MH, Gupta A, et al. An instrument to measure skeletal burden and predict functional outcome in fibrous dysplasia of bone. J Bone Miner Res Off J Am Soc Bone Miner Res. 2005;20(2):219-26.
5. Rudge ES, Chan AHY, Leeper FJ. Prodrugs of pyrophosphates and bisphosphonates: disguising phosphorus oxyanions. RSC Med Chem. 2022;13(4):375-91.
6. Parisi MS, Oliveri B, Mautalen CA. Effect of intravenous pamidronate on bone markers and local bone mineral density in fibrous dysplasia. Bone. 2003;33(4):582-8.
7. Drake MT, Clarke BL, Khosla S. Bisphosphonates: Mechanism of Action and Role in Clinical Practice. Mayo Clin Proc Mayo Clin. 2008;83(9):1032-45.
8. Yoon JH, Choi Y, Lee Y, Yoo HW, Choi JH. Efficacy and safety of intravenous pamidronate infusion for treating osteoporosis in children and adolescents. Ann Pediatr Endocrinol Metab. 2021;26(2):105-11.
9. Brendan Chan, Margaret Zacharin. Pamidronate Treatment of Polyostotic Fibrous Dysplasia: Failure to Prevent Expansion of Dysplastic Lesions During Childhood. J Pediatr Endocrinol Metab. 2006;19(1):75-80.
10. Parisi MS, Oliveri B. Long-term pamidronate treatment of polyostotic fibrous dysplasia of bone: A case series in young adults. Curr Ther Res Clin Exp. 2009;70(2):161-72.
11. Liu J, Zhao C, Liu B, Liu H, Wang L. Analgesia and curative effect of pamidronate disodium combined with chemotherapy on elderly patients with advanced metastatic bone cancer. Oncol Lett. 2019;18(1):771-5.
12. Ren HY, Sun LL, Li HY, Ye ZM. Prognostic Significance of Serum Alkaline Phosphatase Level in Osteosarcoma: A Meta-Analysis of Published Data. BioMed Res Int. 2015;2015:160835.
13. Park BY, Cheon YW, Kim YO, Pae NS, Lee WJ. Prognosis for craniofacial fibrous dysplasia after incomplete resection: age and serum alkaline phosphatase. Int J Oral Maxillofac Surg. 2010;39(3):221-6.
14. Chapurlat RD, Hugueny P, Delmas PD, Meunier PJ. Treatment of fibrous dysplasia of bone with intravenous pamidronate: long-term effectiveness and evaluation of predictors of response to treatment. Bone. 2004;35(1):235-42.
15. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst Rev. 2021;10:89.
16. Standard Deviation Calculator [Internet]. [cited 2023 Sep 2]. Available from: https://www.calculator.net/standard-deviation-calculator.html
17. Chapurlat RD, Delmas PD, Liens D, Meunier PJ. Long-term effects of intravenous pamidronate in fibrous dysplasia of bone. J Bone Miner Res Off J Am Soc Bone Miner Res. 1997;12(10):1746-52.
18. Plotkin H, Rauch F, Zeitlin L, Munns C, Travers R, Glorieux FH. Effect of pamidronate treatment in children with polyostotic fibrous dysplasia of bone. J Clin Endocrinol Metab. 2003;88(10):4569-75.
19. Isaia GC, Lala R, Defilippi C, Matarazzo P, Andreo M, Roggia C, et al. Bone turnover in children and adolescents with McCune-Albright syndrome treated with pamidronate for bone fibrous dysplasia. Calcif Tissue Int. 2002;71(2):121-8.
20. Lala R, Matarazzo P, Andreo M, Marzari D, Bellone J, Corrias A, et al. Bisphosphonate treatment of bone fibrous dysplasia in McCune-Albright syndrome. J Pediatr Endocrinol Metab JPEM. 2006;19 Suppl 2:583-93.
21. Lala R, Matarazzo P, Bertelloni S, Buzi F, Rigon F, de Sanctis C. Pamidronate treatment of bone fibrous dysplasia in nine children with McCune-Albright syndrome. Acta Paediatr 2000;89(2):188-93.
22. Zacharin M, O'Sullivan M. Intravenous pamidronate treatment of polyostotic fibrous dysplasia associated with the McCune Albright syndrome. J Pediatr. 2000;137(3):403-9.
23. Igelström E, Campbell M, Craig P, Katikireddi SV. Cochrane's risk of bias tool for non-randomized studies (ROBINS-I) is frequently misapplied: A methodological systematic review. J Clin Epidemiol. 2021;140:22-32.
24. Hartley I, Zhadina M, Collins MT, Boyce AM. Fibrous Dysplasia of Bone and McCune-Albright Syndrome: a Bench to Bedside Review. Calcif Tissue Int. 2019;104(5):517-29.
25. Spencer T, Pan KS, Collins MT, Boyce AM. The clinical spectrum of McCune-Albright syndrome and its management. Horm Res Paediatr. 2019;92(6):347-56.
26. Laine J, Kadado A, James C, Novotny S. The Role of Bisphophonates in Pediatric Orthopaedics: What Do We Know After 50 Years? Current Concept Review. J Pediatr Orthop Soc N Am [Internet]. 2019 Nov 1 [cited 2023 Sep 1];1(1). Available from: https://www.jposna.org/index.php/jposna/article/view/33
27. Parisi MS, Oliveri MB, Mautalen CA. Bone mineral density response to long-term bisphosphonate therapy in fibrous dysplasia. J Clin Densitom Off J Int Soc Clin Densitom.

2001;4(2):167-72.
28. Lee JM, Kim JE, Bae SH, Hah JO. Efficacy of pamidronate in children with low bone mineral density during and after chemotherapy for acute lymphoblastic leukemia and non-Hodgkin lymphoma. Blood Res. 2013;48(2):99-106.
29. Chapurlat RD, Gensburger D, Jimenez-Andrade JM, Ghilardi JR, Kelly M, Mantyh P. Pathophysiology and medical treatment of pain in fibrous dysplasia of bone. Orphanet J Rare Dis. 2012; 7(1):S3.
30. Majoor BCJ, Traunmueller E, Maurer-Ertl W, Appelman-Dijkstra NM, Fink A, Liegl B, et al. Pain in fibrous dysplasia: relationship with anatomical and clinical features. Acta Orthop. 2019;90(4): 401-5.
31. Shu J, Tan A, Li Y, Huang H, Yang J. The correlation between serum total alkaline phosphatase and bone mineral density in young adults. BMC Musculoskelet Disord. 2022;23:467.
32. Wang J, Du Z, Li D, Yang R, XiaodongTang, Yan T, et al. Increasing serum alkaline phosphatase is associated with bone deformity progression for patients with polyostotic fibrous dysplasia. J Orthop Surg. 2020;15(1):583.
33. Ma J, Liang L, Gu B, Zhang H, Wen W, Liu H. A retrospective study on craniofacial fibrous dysplasia: preoperative serum alkaline phosphatase as a prognostic marker? J Cranio-Maxillo-fac Surg Off Publ Eur Assoc Cranio-Maxillo-fac Surg. 2013;41(7): 644-7.
34. Vaisman DN, McCarthy AD, Cortizo AM. Bone-specific alkaline phosphatase activity is inhibited by bisphosphonates: role of divalent cations. Biol Trace Elem Res. 2005;104(2):131-40.
35. Greenblatt MB, Tsai JN, Wein MN. Bone Turnover Markers in the Diagnosis and Monitoring of Metabolic Bone Disease. Clin Chem. 2017;63(2):464-74.
36. Chilbule SK, Madhuri V. Complications of pamidronate therapy in paediatric osteoporosis. J Child Orthop. 2012;6(1): 37-43.
37. Juszczak B, Sułko J. Patient-reported effectiveness and safety of Pamidronate in NSAIDs-refractory chronic recurrent multifocal osteomyelitis in children. Rheumatol Int. 2022;42(4):699-706.
38. Hart ES, Kelly MH, Brillante B, Chen CC, Ziran N, Lee JS, et al. Onset, progression, and plateau of skeletal lesions in fibrous dysplasia and the relationship to functional outcome. J Bone Miner Res Off J Am Soc Bone Miner Res. 2007;22(9): 1468-74.
39. Lee SE, Lee EH, Park H, Sung JY, Lee HW, Kang SY, et al. The diagnostic utility of the GNAS mutation in patients with fibrous dysplasia: meta-analysis of 168 sporadic cases. Hum Pathol. 2012;43(8):1234-42.
40. Elli FM, de Sanctis L, Bergallo M, Maffini MA, Pirelli A, Galliano I, et al. Improved Molecular Diagnosis of McCune–Albright Syndrome and Bone Fibrous Dysplasia by Digital PCR. Front Genet. 2019;10:862.
41. Kushchayeva YS, Kushchayev SV, Glushko TY, Tella SH, Teytelboym OM, Collins MT, et al. Fibrous dysplasia for radiologists: beyond ground glass bone matrix. Insights Imaging. 2018;9(6):1035-56.
42. Bhadada SK, Bhansali A, Das S, Singh R, Sen R, Agarwal A, et al. Fibrous dysplasia & McCune-Albright syndrome: An experience from a tertiary care centre in north India. Indian J Med Res. 2011;133(5):504-9.