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REVIEW

Bone Disease among Children with Sickle Cell Disease: A Scoping Review of Incidence and Interventions

Aep Maulid Mulyana[1,*], Windy Rakhmawati[2,*], Iqbal Pramukti[3,*], Mamat Lukman[3,*], Riki Wartakusumah[4,*], Henny Suzana Mediani[2,*]

[1]Faculty of Nursing, Universitas Padjadjaran, Bandung, West Java, 40132, Indonesia; [2]Department of Pediatric Nursing, Faculty of Nursing, Universitas Padjadjaran, Bandung, West Java, 40132, Indonesia; [3]Department of Community Health Nursing, Faculty of Nursing, Universitas Padjadjaran, Bandung, West Java, 40132, Indonesia; [4]Department of Nursing Science, Faculty of Medicine Public Health, and Nursing, Universitas Gadjah Mada, Sleman, Yogyakarta, 55284, Indonesia

*These authors contributed equally to this work

Correspondence: Henny Suzana Mediani, Department of Pediatric Nursing, Faculty of Nursing, Universitas Padjadjaran, Bandung, West Java, 40132, Indonesia, Tel +62 822-1739-1965, Email henny.mediani@unpad.ac.id

Background: Children with sickle cell disease (SCD) are more likely to have deficient serum levels of vitamin D for bone metabolism. However, appropriate interventions are essential to prevent its progression and alleviate symptoms.

Purpose: The aim of this study is to determine interventions for managing bone disease in children with SCD.

Methods: This study uses a scoping review. A literature review was conducted using PubMed, CINAHL, ScienceDirect, Scopus, and Google Scholar search engines. The study was eligible for inclusion if it included articles published from 2013 to 2023, full-text, and original study design. Study quality was assessed using the Joanna Briggs Institute (JBI) appraisal tool.

Results: This review identified six studies and 114 children with SCD, including 57 boys (50%) and 57 girls (50%). The majority of SCD types experienced were HbSS (86.84%), HbS-B^0 Thal (7.01%), HbSC (5.27%), and the HbSS Arab-Indian haplotype (0.88%). Bone disease problems that often arise in children with SCD include Avascular Necrosis (AVN) (78.08%), Osteonecrosis of the Femoral Head (ONFH) (18.42%), and other bone problems (3.50%). Meanwhile, four types of intervention findings were used in managing bone disease among children with SCD: 1). Surgical procedures 53 (41.09%) included total hip arthroplasty (THA), Osteotomy, and Multiple epiphyseal drilling with Autologous Bone Marrow Implantation (AMBI); 2). Invasive procedures 67 (51.93%) included intravenous bisphosphonates, hydroxyurea (HU), and core decompression (CD) with bone marrow aspirate concentrate injection: 3). Oral pharmacological or Vitamin D3 (cholecalciferol) 4 (3.10%); 4). Non-pharmacology or physical therapy 5 (3.88%).

Conclusion: Our findings highlight that surgical, invasive, pharmacological, and physical therapy interventions positively impact increasing bone mineral density (BMD) and functional improvement of bone disease among children with SCD. The interventions provided excellent functional outcomes with minimal complications and no life-threatening side effects.

Keywords: bone disease, children, intervention, incidence, sickle cell disease

Introduction

Sickle cell disease (SCD) arises due to a genetic mutation in the gene that encodes the β-globin protein. This mutation leads to an anomalous haemoglobin structure, haemoglobin S (HbS), and dysfunctional red blood cells.[1] SCD is an inherited haemoglobinopathy leading to chronic anaemia and microvascular occlusion.[2] Sickle cell disease is the most prevalent inherited blood disorder in the human population, impacting millions of people worldwide.[3] Although statistical data may differ globally, approximately 4.4 million individuals are affected by sickle cell disease.[4] Every year, an estimated 300,000 babies are born with this condition worldwide.[5]

People who have sickle cell disease and carry two copies of the βS gene mutation are at the highest risk of experiencing the typical common symptoms and complications of the condition.[6] Children with SCD are more likely to have deficient serum

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levels of vitamin D for bone metabolism.[7] Previous studies showed that of 306 children and adolescents, 31% had low areal BMD.[8]

In recent years, the problem of bone disease has continued to be of concern. Recent studies shows that children with SCD often experience severe vitamin D deficiency, as a result of which children can experience bone complications that manifest as bone deformities, Avascular Necrosis (AVN), vaso-occlusive bone pain crisis, infarction, osteoporosis, osteopenia, osteonecrosis, dactylitis, or osteomyelitis.[7,9] Bone disease is a common orthopedic complication associated with sickle cell disease.[10] The incidence has been documented in children as young as 5 years old and increases with age, and the prevalence rate varies from 3.2% to 39.4%, which mostly includes children and adults with SCD.[11]

Bone disease in pediatric with SCD, requires careful and prompt treatment to prevent its progression and alleviate symptoms. Some interventions that can be used in the management of bone-related issues. Nonoperative treatment is the first line of treatment: pain control, physiotherapy, and modification of activities to restrict overhead activities and manual labour, including administering vitamin D,[12] and operative management such as intravenous bisphosphonates, stem cell implantation, and bone marrow transplantation.[13–15] In implementing these interventions, several barriers have been encountered, such as the lack of recent or specific references, resulting in different guidelines for each location. As a result, comprehensive and up-to-date guidance can be challenging to obtain, potentially leading to variations in practice across various regions.[12,14]

Studies regarding bone disease interventions in children with SCD need to be carried out comprehensively and systematically including available interventions, outcomes, and long-term implications. However, this research is essential for improving and optimizing healthcare strategies for children with SCD. Therefore, this study's aim is to determine interventions for managing bone disease in children with SCD.

Materials and Methods

Study Design

This study uses a systematic scoping review and follows the framework by Arksey and O'Malley.[16,17] This method is suitable for this study to explore comprehensive and relevant studies on one topic. The framework consists of five stages: 1) Identifying research questions; 2) Identifying relevant research results; 3) Screening articles according to criteria; 4) Analyzing, organizing and summarising the included articles; and 5) Reporting results.[18]

Search Strategy

Search study using PRISMA-ScR guidelines for a systematic scoping review.[19] A literature review was conducted using four databases, including PubMed, CINAHL, ScienceDirect, Scopus, and Google Scholar search engine. The keyword adjusts the medical subject heading (MeSH) using boolean OR dan AND, including

> SCD, sickle cell disease, sickle cell, sickle cell anemias, sickle cell disorders, intervention, management, treatment, prevention, avascular necrosis, AVN, death of bone tissue, bone necrosis, osteonecrosis, bone aseptic necrosis, osteoporosis, bone diseases, bone mineral disease, children, child, pediatric, kids.

Eligibility Criteria

The criteria in this study are based on the PICO question framework: Participants/population: Children with SCD; Intervention (s): Intervention or treatment; Comparator(s): Not applicable; Outcome: Incidence and intervention in bone disease among children with sickle cell disease. A study was eligible for inclusion if it included articles published from 2013 to 2023, full-text, and original study design. Studies were excluded if they were not in English and the adult population. All researchers independently screen articles, including duplicate topics, titles, abstracts, full text, and appraised study quality.

Quality Appraisal

Study quality was assessed using critical appraisal checklist tools for cohort study from the Joanna Briggs Institute (JBI).[20] The evaluation for the cohort study was consistent with eleven questions and four categories: yes, no, unclear, and not applicable. Score 0 for "No" and 1 for "Yes", with a total quality score ranging from 0 to 11.

Data Extraction and Analysis

Data extraction was displayed using the tabulation method in Microsoft Excel (Microsoft Corp., New York, USA). The extracted items included study characteristics (author, year, study design, country, population, and sample); participant characteristics and SCD (age, gender, SCD type, incidence, type of bone disease); intervention and outcomes (intervention, type of intervention, instruments, intervention procedures, follow-up, intervention effects, and results).

Results

Description of Study Selection

The article search results obtained were 2084 articles from four databases and grey literature. After checking for duplicating the collected articles, filtering the collected titles, and limiting the years, 44 articles remained. Then, after selection based on inclusion criteria, 14 articles remained. Therefore, after screening based on inclusion, six articles were included in this study (Figure 1). Then, the articles were analyzed using the JBI Critical Appraisal Tool assessment for the Retrospective and Prospective cohorts (Table 1).

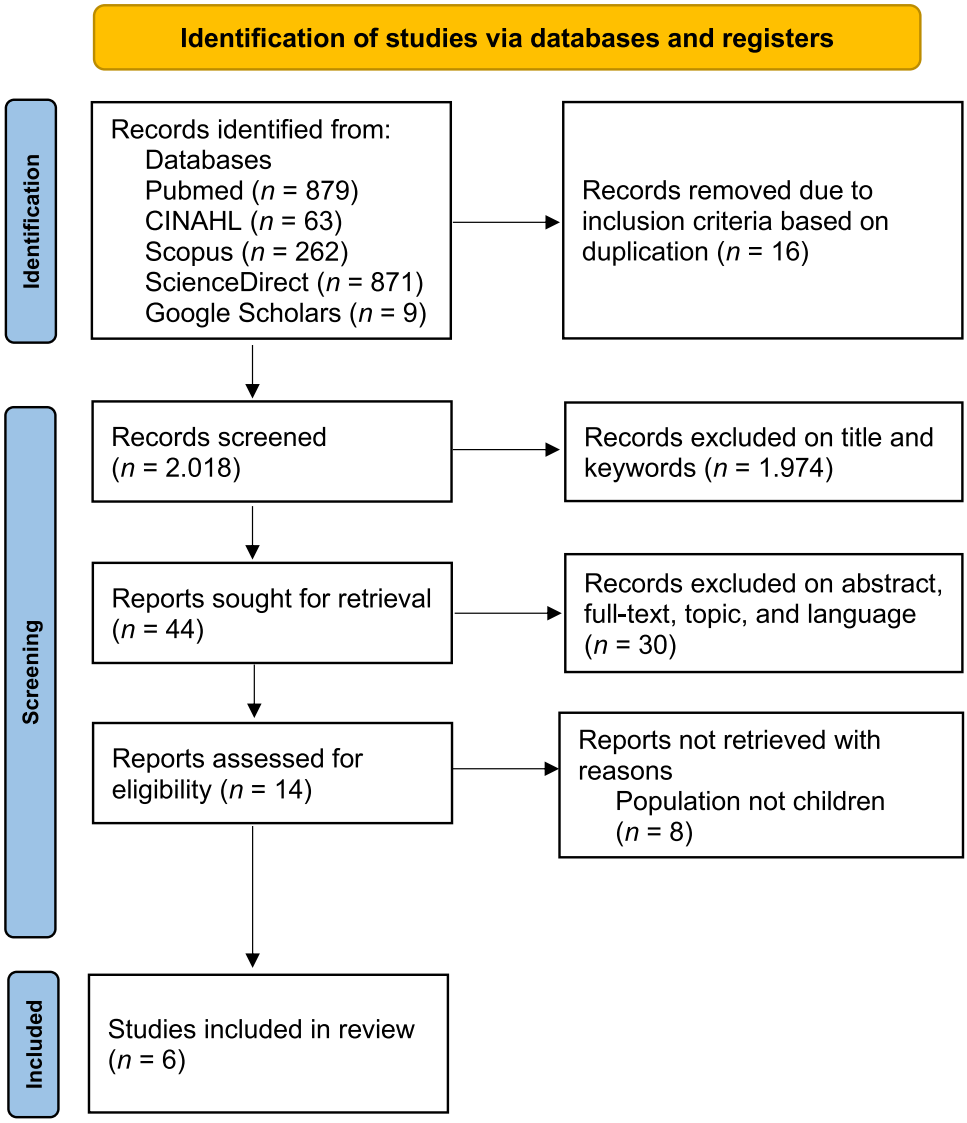

Figure 1 PRISMA Flow diagram. Adapted from Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated :guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. Creative Commons.

Table 1 Critical Appraisal Tool

Study	Study Design	JBI Critical Appraisal Tool
Williams et al (2018)[12]	Prospective cohort	7/11 (63.63%)
Grimbly et al (2022)[13]	Retrospective cohort	6/11 (54.54%)
Novais et al (2015)[15]	Retrospective cohort	7/11 (63.63%)
Alabi et al (2021)[21]	Prospective cohort	7/11 (63.63%)
Gatin et al (2016)[22]	Prospective cohort	7/11 (63.63%)
Itzep et al (2019)[23]	Retrospective cohort	6/11 (54.54%)

Characteristics of Study

This study included six reviewed articles. This study's total sample of participants was 114 children with SCD, boys and girls aged 4–19 years. The study designs included a retrospective cohort (n = 3) and a prospective cohort (n = 3). The research conducted included the USA (n = 3), Nigeria (n = 1), Canada (n = 1), and France (n = 1). The SCD types in this review are HbSS, HbS-B^0, HbSC, and HbSS Arab-Indian haplotype. Bone disease problems in children with SCD analyzed included AVN (n = 3), ONFH (n = 2), and Chronic arthritis, non-displaced fracture, Central end plate depression of thoracic, and Joint bony infarct (n = 1) (Table 2).

Incidence of Bone Disease in Children with SCD

This study found 114 children with SCD, including 57 boys (50%) and 57 girls (50%). The majority of SCD types experienced were HbSS (86.84%), HbS-B^0 (7.01%), and HbSC (5.27%), and the HbSS Arab-Indian haplotype only occurred in one person from the total sample included. Bone disease problems that often occur in children with SCD are AVN (78.08%), ONFH (18.42%), and other bone problems (3.50%). The incidence of children with SCD was found on three continents, including America (67.54%), Africa (23.69%), and Europe (8.77%). Meanwhile, four types of intervention findings used in the management of children with SCD who experience bone disease include surgical procedures 53 (41.09%), invasive 67 (51.93%), oral pharmacology 4 (3.10%), and non-pharmacology 5 (3.88%) (Table 3).

Interventions and Outcomes in the Management of Bone Disease in Children with SCD

Surgical Interventions

We found four studies that included surgical intervention in the management of bone disease in SCD children, namely total hip arthroplasty (THA), Osteotomy, Multiple epiphyseal drilling with Autologous Bone Marrow Implantation (AMBI), and Surgical.[15,21–23] THA can be given to children with SCD aged 12–19 with HbSS type who experience AVN; osteotomy and multiple epiphyseal drilling with AMBI can be performed on children with SCD type HbSS, HbS-B^0, HbSC aged 4–18 years who experience ONFH.[15,21,22]

THA, osteotomy, and multiple epiphyseal drilling with AMBI intervention in SCD children with AVN and ONFH, there were no life-threatening side effects, considered safe and beneficial, although challenging. The intervention provided excellent functional results with minimal complications.[21] The study by Itzep et al revealed that the results of surgical management alone did not show radiographic improvement in SCD children with AVN.[23]

Invasive Interventions

We found two studies that included three invasive interventions in managing bone disease in SCD children, namely IV bisphosphonates, HU, and CD with bone marrow aspirate concentrate injection.[13,23] Positive results from these interventions were increased 25(OH)D levels, areal bone mineral density (aBMD), and radiographic improvement in AVN. Overall, there were no reports of complications with the invasive treatments used. However, after the IV bisphosphonates procedure, there

Table 2 Characteristics of Studies Reporting Bone Disease Management of Children with SCD (n = 6)

Ref	Country	Study Design	Population	Sample (N)	Gender		Age (range)	Type of SCD	Event	Bone Disease
					Male (N)	Female (N)				
Williams et al (2018)[12]	USA	Prospective cohort	Children with SCD	4	1	3	11–16	HbSS	4	Chronic arthritis, non-displaced fracture, Central end plate depression of thoracic, and Joint bony infarct
Alabi et al (2021)[21]	Nigeria	Prospective cohort	Children with SCD	27	8	19	12–19	HbSS	27	AVN
Grimbly et al (2022)[13]	Canada	Retrospective cohort	Children with SCD	46	26	20	<18 years	HbSS HbS-B^0 HbSC HbSS Arab-Indian haplotype	40 3 2 1	AVN
Novais et al (2015)[15]	USA	Retrospective cohort	Children with SCD	11	9	2	9–18	HbSS HbS-B^0 HbSC	5 3 3	ONFH
Gatin et al (2016)[22]	France	Prospective cohort	Children with SCD	10	5	5	4–15	HbSS	10	ONFH
Itzep et al (2019)[23]	USA	Retrospective cohort	Children with SCD	16	8	8	7–19	HbSS HbSC HbS-B^0	13 1 2	AVN

Abbreviations: SCD, Sickle cell disease; ONFH, Osteonecrosis of the Femoral Head; HbSS, sickle cell anemia hemoglobin SS disease; HbS-B^0 Thal, sickle beta thalassemia with no HbA; HbSC, sickle cell disease; AVN, Avascular Necrosis.

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Table 3 Percentage Analysis by Demographic Variable in Selected Studies

Subgroup	Number of Studies (N)	Sample Size (N)	Percentage (%)
Overall studies	6	114	100
Age			
0–19	6	114	100
Gender			
Male	6	57	50.0
Female	6	57	50.0
Country Region			
Eropa	1	10	8.77
Amerika	4	77	67.54
Afrika	1	27	23.69
Study Design			
Retrospective cohort	3	73	64.03
Prospective cohort	3	41	35.97
Type of SCD			
HbSS	6	99	86.84
HbS-B^0	3	8	7.01
HbSC	3	6	5.27
HbSS Arab-Indian haplotype	1	1	0.88
Bone Disease			
AVN	3	89	78.08
ONFH	2	21	18.420
Other	1	4	3.50
Type of Interventions			
Physical therapy	1	5	3.88
Oral pharmacological	1	4	3.10
Invasive	2	67	51.93
Surgical	4	53	41.09

Abbreviations: ONFH, Osteonecrosis of the Femoral Head; HbSS, sickle cell anemia hemoglobin SS disease; HbS-B^0 Thal, sickle beta thalassemia with no HbA; HbSC, sickle cell disease; AVN, Avascular Necrosis.

was one episode of symptomatic hypocalcemia that was treatable with oral calcium and calcitriol for 5 days,[13] and none showed results in radiographic improvement after the CD procedure with bone marrow aspirate concentrate injection.[23]

Invasive IV bisphosphonates intervention can be given to SCD children with AVN problems aged <18 years, and HU and CD interventions with bone marrow aspirate concentrate injection can be used for SCD children with AVN problems aged 7–19 years. The types of SCD include sickle cell anemia hemoglobin SS disease (HbSS), sickle beta thalassemia with no HbA (HbS-B^0), sickle cell disease (HbSC), and HbSS Arab-Indian haplotype.

Oral Pharmacological Interventions

We found that one study using Vitamin D3 (cholecalciferol) gave positive results on bone strength in children with SCD, including increased serum 25(OH)D levels, BMD, and normalization of PTH. The use of Vitamin D3 (cholecalciferol) can be given to children with sickle cell anemia hemoglobin SS disease (HbSS) aged 11–16 years who have bone disease problems such as chronic arthritis, non-displaced fracture, central end plate depression of the thoracic, and joint bony infarct.[12]

Non-Pharmacological Interventions

Physical therapy can be done as an effort to treat children with SCD with types HbSS, HbSC and HbS-B^0, aged 7–19, and experiencing AVN. However, physical therapy did not provide significant results in improving radiographic AVN.[23] (Table 4).

Table 4 Interventions in the Management of Bone Disease in Children with SCD (n = 6)

Ref	Sample (N)	Intervention	Type of Intervention	Procedure	Instrument	Follow-up	Intervention effect	Outcome
Williams et al (2018)[12]	4	Vitamin D3 (cholecalciferol)	Oral pharmacological	Children received oral vitamin D3 100,000 IU weekly for two months, followed by once-monthly doses of 100,000 IU for 22 months. In addition, monitoring for hypercalcemia and hypercalciuria is carried out. Finally, after the study, the patient was prescribed oral vitamin D 600 IU daily	DXA	12 month	All children showed positive results from vitamin D3 therapy without hypervitaminosis D or hypercalcemia.	After the intervention, serum 25(OH)D levels increased, BMD increased, and PTH normalized.
Alabi et al (2021)[21]	27	THA	Surgical	Harris Hip Scoring (HHS) and Oxford Hip Scoring (OHS) assessments; Assessment of genotype, bilaterality, and previous treatments; determine the child's stable Hb before surgery; Regional anesthesia (spinal or epidural); Surgical time ranges from 80–185 minutes. The implants used are made of metal on an acetabular polyethylene layer, namely Depuy, Surgival, and Zimmers; The size of the acetabular shell used ranges from 44 mm to 54 mm; Uncemented THA was performed using a direct lateral approach. Subperiosteal detachment of the iliopsoas muscle and adductor tenotomy are performed when indicated. Finally, weight-bearing ambulation was initiated on the second postoperative day.	HHS dan OHS	24 month	Two children experienced superficial surgical wound infections that were resolved using antibiotics and wound care. Additionally, there are no life-threatening side effects. Arthroplasty in SCD children with AVN is considered safe and beneficial, although challenging. The intervention provided excellent functional outcomes with minimal complications.	The mean preoperative HHS and OHS each increased significantly with a p-value <0.0001 at two years, namely HHS from 27.7 ± 6.6 to 93.0 ± 2.2 and OHS from 10.0 ± 4.9 52.8 ± 2.7.
Gatin et al (2016)[22]	10	Osteotomy	Surgical	Postel Merle d'Aubigne´ and Harris scoring before and surgery; anesthesia; exchange transfusion, heterologous transfusion and perioperative analgesia support; traction on the legs; Surgery begins with a triple acetabular osteotomy, if the acetabular coverage of the femoral head is insufficient, a varus femoral osteotomy is performed.	MRI and HPMA	12 month	No complications. All children had functional benefits after surgery. There was one child who experienced lung disease (pneumonia) 2 days after surgery without acute respiratory distress syndrome because the child had ACS. Pneumonia can be treated with antibiotics without complications.	All children had significant objective functional improvement by Wilcoxon Signed-Rank test (0.00338) in pain and range of motion with a mean increase in Harris score of 29 points.

(*Continued*)

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Table 4 (Continued).

Ref	Sample (N)	Intervention	Type of Intervention	Procedure	Instrument	Follow-up	Intervention effect	Outcome
Novais et al (2015)[15]	11	Multiple epiphyseal drilling with AMBI	Surgical	The patient is positioned supine and receives general anesthesia; Sterilization and closure of the entire lower extremity including the hemipelvis; 1–2 cm incision in the anterior superior iliac spine towards the iliac crest; A fenestrated 11-G needle for bone marrow aspiration is inserted into the iliac spine and bone marrow is aspirated with a total volume of approximately 60–120 mL. The aspiration was concentrated into approximately 15 mL of bone marrow cells using a bone marrow aspiration cell system (Harvest Technologies Corporation, Plymouth, MA); An approximately 3 cm incision is made on the lateral thigh and dissection down to the fascia layer. The fascia lata divides longitudinally, and the vastus lateralis divides in the midline just distal to the broad tubercle of the femur; Under C-arm guided fluoroscopic imaging, three 2.8 mm Steinman pins were inserted into the necrotic zone of the femoral head to perform drilling of the femoral epiphysis; Select the Steinman pin most central to the necrotic area to use as a guide for the perforation trocar (8-G trocar). The selected Steinman pin was removed and exchanged for the trocar; A 2 mL 50% solution (ioversol and sterile saline) was injected to ensure the marrow could migrate to the femoral head. The concentrated marrow is injected slowly into the femoral head to reduce leakage, and fluoroscopy is used to confirm the dissipation of the previously injected contrast, indicating that the marrow has displaced the contrast into the necrotic bone. The trocar and Steinman pins were then removed; Postoperative hospital stay of approximately 24 hours for hydration, pain management, and observation; There is no use of a brace or cast, and the patient is instructed to bear weight on the affected extremity and use crutches for two months.	CHOHES and Steinberg	12 month	There were no reports of complications. However, when evaluated, two children required further surgical procedures, and one child underwent hip dislocation surgery	There was no significant difference in the degree of femoral head involvement assessed using necrotic arc angle (P = 0.2251), femoral head collapse on AP (P = 0.4258) and lateral (P = 0.4609) radiographs. The majority of hips in the Steinberg stage of disease had either improvement (4/14 hips) or no further development of the necrotic process (7/14 hips)

Itzep et al (2019)[23]	5	Surgical	Surgical	NA	MRI	NA	NA	The results of surgical management showed no radiographic improvement
Grimbly et al (2022)[13]	46	IV bisphosphonates	Invasive	Administer vitamin D supplementation of at least 50 nmol/L before IV bisphosphonate therapy to optimize serum 25(OH)D levels. IV bisphosphonate therapy is administered according to the bone pain/osteoporosis protocol via one of three regimens: 1. IV pamidronate: annual dose (4.5–9 mg/kg body weight/year) given every 4 months, namely 1 mg/kg/day for 3 days each (9 mg/kg/year) or 1.5 mg/kg in 1 day (4.5 mg/kg/year) 2. IV zoledronic acid: annual dose of 0.05–0.1 mg/kg body weight, divided into two doses every 6 months or 3. Give an initial dose of pamidronate followed by zoledronic acid to reduce side effects	DXA	Five month	There were no reports of osteonecrosis, pain events, hemolytic crisis, stroke, or other complications. There was only one episode of symptomatic hypocalcemia that was treatable with five days of oral calcium and calcitriol.	Children who received IV bisphosphonate therapy had a mean 25(OH)D level of 58 nmol/L (n=23, SD 34.9), above the normal limit. The rate of bone formation increased by 265% of the healthy pre-IV bisphosphonate average. However, DXA did not show a significant increase in height-adjusted LS or TBLH aBMD Z scores, namely LS HAZ aBMD Z-score (0.4) TBLH HAZ BMD Z-score (0.4)
Itzep et al (2019)[23]	16	HU	Invasive	Children are given HU with an MTD of 48%-45%.	MRI	NA	There were no reports of complications and none of the children who received HU underwent observation arthroplasty	Study results show that radiographic improvement in AVN occurs at a younger age
Itzep et al (2019)[23]	5	CD with bone marrow aspirate concentrate injection	Invasive	NA	MRI	NA	NA	None showed results in radiographic improvement
Itzep et al (2019)[23]	5	Physical therapy	Physical therapy	NA	MRI	NA	NA	Only one in five children showed radiographic improvement

Abbreviations: AMBI, Autologous Bone Marrow Implantation; CHOHES, the Children's Hospital Oakland Hip Evaluation Scale; HU, The University of Pennsylvania (Steinberg); HU, hydroxyurea; DXA, dual-energy x-ray absorptiometry; HHS, Harris Hip Scoring; OHS, Oxford Hip Scoring; MRI, Radiographs, magnetic resonance imaging; HPMA, Harris and Postel Merle d'Aubigne´ scores; PTH, parathyroid hormone; BMD, bone mineral density; 25 (OH)D, serum 25- hydroxyvitamin D; THA, total hip arthroplasty; LS, Lumbar spine; TBLH, total body less head; aBMD, areal BMD; HAZ, height-for-age Z-score; MTD, maximum tolerated dose; CD, core decompression; IV, Intravenous.

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Discussion

Principal Finding

This study aims to conduct a scoping review to determine interventions for managing bone disease in children with Sickle cell disease (SCD). This scoping review obtained several findings, including incidence, interventions, and outcomes in children with SCD who have bone disease.

Sickle cell disease is an inherited blood disorder characterized by phenotypic diversity.[24] Previous studies have shown that SCD causes bone loss and changes in bone anatomy.[25] Low serum vitamin D3 levels are a risk for abnormal BMD in SCD.[26,27] SCD patients have very low bone mass density (BMD).[27,28]

This study found 114 children with SCD boys (50%) and girls (50%) aged 4–19 years who had bone disease. Another study revealed that 39 SCD children (23 boys and 16 girls) with an average age of 10.3 years had bone disease.[29] This study highlights that age and type of malignancy contribute to the incidence of bone disease in SCD children.

Bone disease in patients with SCD varies from manifestations to more chronic and debilitating complications, including osteonecrosis, osteoporosis, osteopenia, growth disorders, chronic infections,[27] and other bone-related complications such as vaso-occlusive pain, ischemic damage, osteomyelitis, and bone marrow hyperplasia or sickle bone disease (SBD).[25] Findings from this study showed several bone disease problems in children with SCD analyzed, including AVN (n = 3), ONFH (n = 2), and chronic arthritis, non-displaced fracture, central end plate depression of thoracic, and joint bony infarct. The most frequent occurrence of bone disease in SCD children was AVN 89 (78.08%). In line with the previous study, out of 33 patients with SCD and low BMD, including osteoporosis (36%) and (24%).[27]

Previous studies have revealed that the majority of children with SCD and bone disease have the HbSS genotype.[13] Meanwhile, the previous study shows that SCD types SS and SC have more bone disease.[25,28] Findings from the six studies we analyzed revealed that several types of SCD in children with bone disease include HbSS, HbS-B^0, HbSC, and HbSS Arab-Indian haplotype. However, children with HbSS-type SCD had the highest rate of bone disease 99 (86.84%).

Sickle cell disease has a very high morbidity and mortality rate.[30] In developed countries, cutting-edge technology has driven the development of treatments for SCD. However, in developing countries, medical management of SCD is still limited, relying on the use of hydroxyurea, blood transfusions and analgesics.[24] Although bone complications may not directly contribute to increased mortality, SCD can be a significant source of comorbidities and adverse impact on quality of life. Findings in the six studies analyzed showed four types of intervention findings used in the management of children with SCD who experience bone disease, including surgical procedures 53 (41.09%), invasive 67 (51.93%), oral pharmacology 4 (3.10%), and non-pharmacology 5 (3.88%). This study highlighted that the interventions analyzed positively improved and increased BMD and functional improvement in the bones of children with SCD.

Our findings in the current study are supported by previous studies. Several interventions effectively support SCD patients with bone disease: nutritional interventions,[24] ω-3 fatty acid supplementation,[31] high-dose oral cholecalciferol,[1,12] and adding hip core decompression to physical therapy.[32] Another study revealed a reduction in morbidity and mortality in children with SCD due in part to the availability of a comprehensive care program that includes immunizations and vaccinations, prophylactic therapy, vitamin supplements, and empowerment of patients and families through education.[30]

Strength and Limitations

This study has several limitations that could potentially bias the findings. The article search was limited to four databases and one search engine, making it possible that there was still literature in other databases and causing the literature to be incomplete. Some studies did not describe intervention procedures, and follow-up and the sample sizes involved in the studies were small. In addition, the quality assessment of articles using JBI only involved two people, which potentially biased the quality assessment results, not being able to access some full-text articles, and limiting references to only English may have limited the research results.

However, despite its limitations, several benefits of this research must also be acknowledged. First, this study implemented a comprehensive search strategy, strict inclusion and exclusion criteria, systematic data extraction, and quality assessment of articles. Second, focus on interventions in managing bone disease in children with SCD. This study is the first scoping review to identify bone disease in children with SCD, including incidence and interventions. Third,

this study involves countries worldwide, including America, Europe and Africa. Although the available evidence is still limited, the findings of this study provide strong indications regarding the applicability of interventions used in the management of children with CSD who experience bone dissection. However, the findings of this study represent three continents and can be valuable information for healthcare providers as a basis for policy-making and strategic interventions.

Implications for Clinical Practice

The implications of our study findings suggest that several types of interventions used in managing bone disease problems may have benefits in reducing bone disease problems in children with SCD. This review offers a broader range of intervention methods, allowing nurses, child health specialists, medical personnel, or other healthcare providers to determine appropriate intervention methods in managing bone disease in children with SCD. The findings of this study support that intervention methods that have multiple benefits with minimal adverse effects should be adopted to meet the healthcare needs of children with SCD. In addition, this study provides an overview of how government and health service facilities can collaborate to adopt safe control and management system policies in managing bone disease for children with SCD.

Conclusion

Based on the results of this scoping review, six articles describe the interventions used in managing bone disease problems in children with SCD. Our study found 114 children with SCD from America, Africa and Europe, and most of the types of SCD experienced were HbSS, bone disease problems that often occur in children with SCD were AVN and ONFH. Our study has identified four types of intervention: pharmacological, namely Vitamin D3 (cholecalciferol); Surgical, including THA, Osteotomy, Multiple epiphyseal drilling with AMBI, and Surgical only; Invasive, including IV bisphosphonates, HU, CD with bone marrow aspirate concentrate injection; non-pharmacological, namely physical therapy. Overall, the interventions provided excellent functional outcomes with minimal complications and no life-threatening side effects, safe and beneficial, although challenging.

This study highlights that surgical, invasive, pharmacological, and physical therapy interventions positively impact bone mineral density and functional improvement in children with SCD who experience bone disease. This research can provide additional information for further research on a similar topic. As a direction for future research, a meta-analysis of the efficacy of each intervention in helping improve the quality of life of pediatric patients with SCD who experience bone disease is needed. A meta-analysis study with a larger sample could strengthen the current findings.

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Disclosure

The authors declare no conflicts of interest in this work.

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