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| RESEARCH ARTICLE

The Vertebral Manifestations of Sickle Cell Disease: A Literature Review

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| ABSTRACT

Sickle cell disease (SCD) is the most common monogenic inherited blood disorder, causing extremely high morbidity and mortality rates worldwide. SCD has established manifestations in the musculoskeletal system, particularly the vertebrae. Despite its prevalence, there is a profound scarcity of literature about this important topic. This literature review aims to shed light on the commonest vertebral manifestations in patients with SCD from a pathophysiological and clinical perspective, identify the best diagnostic investigations for every manifestation, discuss the diagnostic difficulties of differentiating between each manifestation, and highlight the current medical and surgical treatments. The results of the literature review demonstrated that patients with SCD are at a much higher risk of developing vertebral manifestations such as vaso-occlusive crises (VOCs) and osteomyelitis acutely, and osteopenia, osteoporosis, and osteonecrosis chronically, with the younger population being the most affected age group. The vertebral column and its manifestations in SCD are primarily affected by the pathophysiologic mechanisms of hemolysis and VOCs. Our findings indicate that the lumbar vertebrae are most affected by manifestations of SCD and should, therefore, be considered the primary site for investigations. There remains a major obstacle in diagnosing and distinguishing between VOCs and osteomyelitis, which complicates and prolongs the treatments and leads to longer hospital stays and poorer outcomes. Finally, we concluded that vertebral manifestations of SCD, while not significantly affecting mortality, cause substantial morbidity and severely impact quality of life. A consistent management strategy is required, focusing on conservative care and a multidisciplinary approach that integrates medical, surgical, and rehabilitative interventions. Continued research to tackle the issue at its genetic source might improve outcomes and quality of life for SCD patients, particularly as we await advances in genetic editing like the CRISPR-Cas9 gene therapy.

| KEYWORDS

Sickle cell disease (SCD), Vertebrae, Spine, Vaso-occlusive crises (VOCs), Osteomyelitis, Osteopenia, Osteoporosis, Osteonecrosis

| ARTICLE INFORMATION

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1. Introduction:

1.1 Background Information:

As of 2024, sickle cell disease (SCD) remains the most prevalent monogenic blood disorder worldwide. It is an inherited form of anemia that affects millions all over the globe and breeds fatal and painful consequences. SCD refers to a group of blood disorders that have a shared underlying pathophysiology but exhibit different phenotypic characteristics.

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SCD is an autosomal recessive disease that can be inherited via its homozygous presence or with a mutation in the β-globin gene on chromosome 11. The primary culprit, however, in SCD remains the sickle hemoglobin (HbS) that gives the red blood cell (RBC) its hallmark sickle-shaped appearance, resulting in low oxygen tension. HbS is formed due to a hydrophilic glutamic acid being switched out for a hydrophobic valine at an amino acid in the sixth codon of the β-globin gene (Figure 1). Abnormal HbS is polymerized into long fibers under hypoxic or acidic conditions, possibly resulting in acute and chronic pain, severe hemolytic anemia, chronic inflammation, persistent hemolysis, recurrent vaso-occlusive crises (VOCs), irreversible end-organ (lungs, spleen, kidneys, central nervous system, liver, and skeleton) damage from infarcts, aplastic crises, and early deaths (Hoffbrand & Moss, 2016; Paulukonis *et al*, 2016).

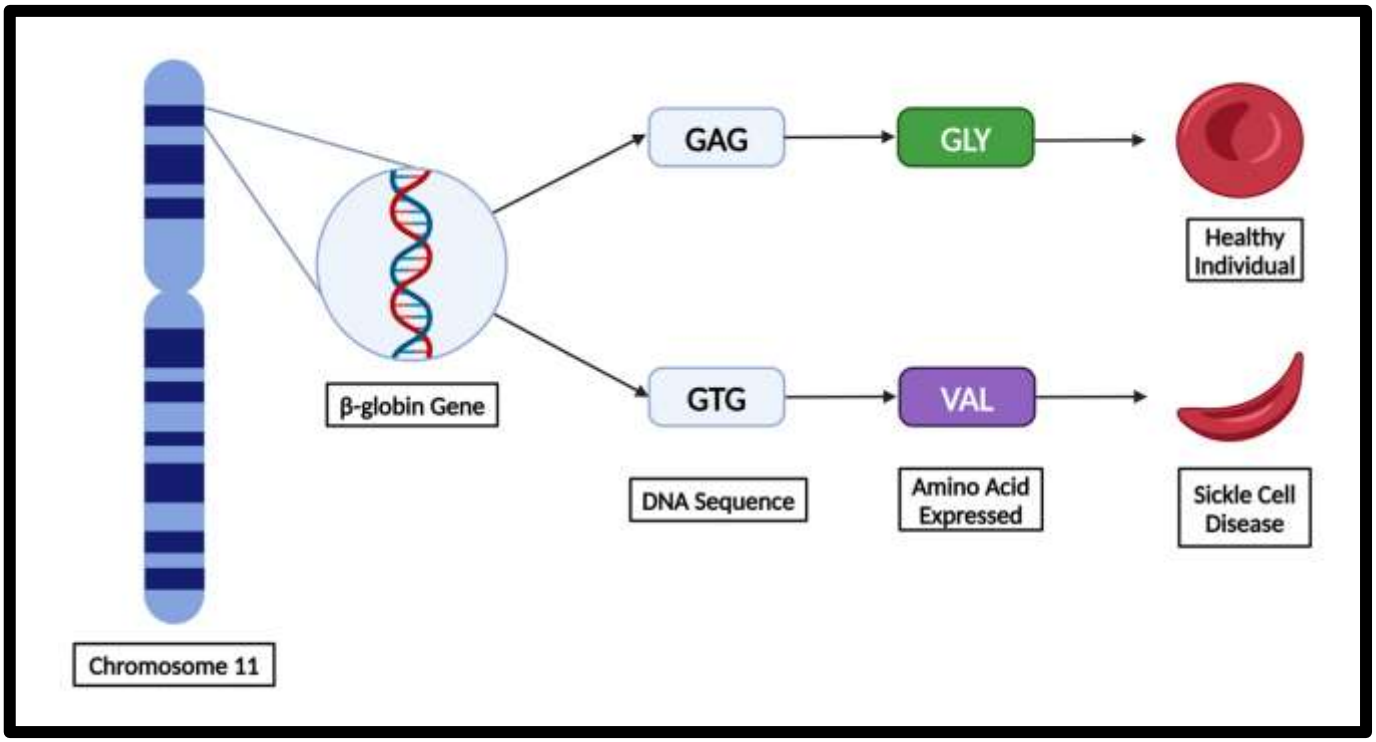

Fig. 1 A simplified version of the pathophysiology of SCD from a basic genetic level (Al Farii *et al*, 2020). Created with BioRender.com.

Unfortunately, once an RBC shifts into its sickled form, it cannot revert to its normal biconcave disc shape, even if normal oxygen tension is restored. This poses a significant problem, as the loss of RBC flexibility and normal shape prevents them from effectively navigating through the capillary bed (Hoffbrand & Moss, 2016). Common triggers for RBC sickling include high altitudes (hypoxia), infection, low temperatures, dehydration, and pregnancy (Rees *et al*, 2010).

1.2 Epidemiological Relevance:

The Centers for Disease Control and Prevention (CDC) reported that between 2016 and 2020, there were 3,305 cases of SCD in newborns recorded across 11 states involved in the Sickle Cell Data Collection program (Kayle *et al*, 2024).

In 1995, Bahrain's local population was 558,879. According to Al Arrayed & Haites, in 1995, 1% of the Bahraini population was affected by SCD, equivalent to 5,589 affected individuals (Al Arrayed & Haites, 1995; Bahrain Open Data Portal, 2024). The population of Bahrain has risen to approximately 1.5 million since then. As of March 2024, Bahrain's Supreme Council of Health published that sickle cell patients amounted to approximately 7,000, about 0.47% of the total population (Al Shakhouri *et al*, 2024). Although a decrease in the percentage is noted, it does not mean that SCD is on its way to being eliminated in the country as the number of affected individuals is ever rising. Additionally, various other aspects should be considered, including the growing number of foreign residents, changes in environmental conditions, the rise in premarital medical screening, and improvements in counseling and awareness efforts.

1.3 The Osteoarticular Effects of SCD:

The musculoskeletal system is especially affected by the sickling of RBCs. Some of the more common manifestations of SCD are seen in the shoulder, hip, and vertebral column. Regarding the vertebral column, the extent of vertebral manifestations in SCD is linked to the duration and severity of the condition. These manifestations are not usually life-threatening; however, they often cause a decreased quality of life and increase morbidity in affected patients. The manifestations themselves can be divided into two phases: an acute phase and a chronic phase. Acutely, SCD patients usually present with severe and painful VOC in the bone, osteomyelitis, collapse of the vertebrae (osteoporosis-related), stress, and compression fractures. Chronically, repeated sickling can lead to osteonecrosis, osteopenia and osteoporosis (Table 1). Although these manifestations are mostly seen in the hips and shoulders, they are not restricted to these areas, as the vertebral column is also frequently involved (Huo *et al*, 1990; Vanderhave *et al*, 2018).

Table 1: Commonest Vertebral Manifestation of SCD by Order.

Acute Manifestations	**1**	Vaso-Occlusive Crises
	2	Osteomyelitis
Chronic Manifestations	**3**	Osteopenia and Osteoporosis
	4	Osteonecrosis

The impacts of SCD on the shoulder and hip have been extensively studied and reported on; however, a notable lack of data remains in the area of vertebral manifestations in SCD. In this literature review, we will explore the implications of SCD on the vertebral column from an osteoarticular perspective. Our comprehensive review, current as of August 30, 2024, provides an in-depth summary of available research and highlights existing gaps in the literature. This review also suggests potential areas for further investigation and aims to inform and improve future management options.

1.4 Methods:

Multiple databases were used and referred to throughout the paper to ensure a diverse and unbiased literature search. Papers relating to the topic were acquired from the PubMed database, Google Scholar, Science Direct, and Embase. The referenced papers were published between 1 February 1960 and 20 June 2024. This review only includes studies that were published in English. The search combination of keywords used to identify relevant articles was: Sickle Cell Disease, Sickle Cell Anemia, Osteoarticular, Orthopedics, Musculoskeletal, Spinal Manifestations, Vertebra Manifestations, Hemolysis, Vaso-occlusion, Osteomyelitis, Osteonecrosis, Osteopenia, and Osteoporosis. The processes of title and abstract screening, data extraction, and full-text review were independently completed by two researchers, with a third researcher resolving any arising conflicts or disagreements. The World Health Organization webpage was frequently used and referred to for guidelines on diagnosis and statistical data for analysis. Moreover, external webpages such as UpToDate.com were often referenced. Due to the lack of relevant literature in some aspects of the paper, non-peer-reviewed work was cited. An external search of articles and papers from numerous other journals was also done to increase the literature pool analyzed. A diverse list of studies, ranging from case reports to clinical trials, was evaluated and discussed. 75 articles were acquired, 6 webpage resources, and 1 book.

Inclusion criteria: English publication, open access texts, and detailed methodology and results.

Exclusion criteria: Editorials, commentary, letters to the editor, opinion pieces, unavailability of full text, and research in progress/incomplete research.

2. Literature Review:

2.1 Results:

2.11 Pathophysiology of SCD with Relation to Vertebral Pathologies:

Generally, it was established that the manifestations of SCD on the musculoskeletal system (hip, shoulder, etc.) were brought about by hemolysis and VOC. Therefore, these processes were also investigated to determine whether they play a role in developing vertebral pathologies. Interestingly, the literature indicates that the vertebral column undergoes similar pathogenic and disease processes as other parts of the musculoskeletal system. As a result, those two processes were further investigated and identified as the primary triggers of the pathogenesis of SCD-related vertebral pathologies.

It has been reported that sickle hemoglobin damages the RBC membrane through deformation caused by polymer formation. Damaged sickled RBCs, along with activated endothelial cells, can generate a proinflammatory environment that becomes more severe during VOC episodes (Browne *et al*, 1998; Manwani & Frenette, 2013). Moreover, because VOC and hemolysis cause occlusion of the microvasculature with sickled RBCs, chronic tissue ischemia and infarction occur, resulting in pain and swelling in the affected tissues (Almeida & Roberts, 2005; Rudy *et al*, 2019). However, other literature reviews have also identified that infections, bone marrow hyperplasia, and the activation of neutrophils, phospholipase A2, adhesion molecules, and other tissue factors are significant factors in the development of vertebral pathologies as well (Kaklamanis *et al*, 1984).

2.12 Acute Manifestations:

Vaso-occlusive Crises:

VOCs are the most common vertebral and osteoarticular manifestation of SCD (Almeida & Roberts, 2005; Huo *et al*, 1990; Rudy *et al*, 2019). As reported by multiple case studies and review articles, vaso-occlusion causes spinal cord infarctions and anatomical changes to the shape of the vertebrae, which is one of the most severe manifestations of SCD in the vertebral column (Emodi & Okoye, 2001; Kaklamanis *et al*, 1984; Kosaraju *et al*, 2017; Rudy *et al*, 2019).

According to the literature, acute painful VOCs are the most common presentation affecting the pediatric population, with the adult population also reporting incidence of VOCs, albeit less frequently (Almeida & Roberts, 2005; Rudy *et al*, 2019). A cross-sectional study reported that more than 66% of patients had VOCs in the lumbosacral levels, while 20% had it in the level of the thoracic vertebrae (Buison *et al*, 2004; Rudy *et al*, 2019). Another retrospective cohort study reported that amongst 172 patients with osteoarticular manifestation of SCD, 8 patients experienced VOCs and vertebral collapse (Sadat-Ali *et al*, 1994).

Clinically, patients would usually present with severe localized pain and tenderness, fever, swelling, and erythema, and their lab results would show increased inflammatory markers and leukocytosis (Almeida & Roberts, 2005; Buison *et al*, 2004; Rudy *et al*, 2019; Smith, 1996). Although there is no universally accepted imaging gold standard, numerous articles and case studies have reported that radiographic imaging may show vertebral collapse and the typical "fish mouth" appearance, which can also be observed in and mistaken for osteomyelitis (Almeida & Roberts, 2005; Gowri *et al*, 2022; Ntagiopoulos *et al*, 2009). Most patients would typically recover without complications; however, some would develop other acute and chronic complications as a direct effect of VOCs (Almeida & Roberts, 2005; Smith, 1996; Kim & Miller, 2002).

Osteomyelitis:

Infectious diseases are some of the most well-known and recognized pathologies that affect the sickle cell population in general. Osteomyelitis has been identified as the leading osteoarticular infectious cause in SCD. Some of the literature even identified osteomyelitis as more common than VOCs in SCD patients, with some experiencing nausea, vomiting, fever, chills, swelling, lower limb pain, with or without neurological deficits, and limited range of motion (Rudy *et al*, 2019). Other papers concluded that acute osteomyelitis is significantly more prevalent among SCD patients than in the general population (Almeida & Roberts, 2005). According to a retrospective cohort study that followed up with 273 patients with SCD, 15 patients were diagnosed with osteomyelitis, with frequent localizations found at the vertebrae (De Gheldere *et al*, 2006). Some patients may also present with spondylodiscitis, which is a rarer form of osteomyelitis caused by the *Salmonella spp.* (Rudy *et al*, 2019). The literature identified elevated levels of bilirubin, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and persistent leukocytosis in some patients as primary laboratory findings (Al Farii *et al*, 2020; Rudy *et al*, 2019). Positive cultures are the gold standard that the literature sets for diagnosing osteomyelitis in SCD. However, other articles suggested that integrating imaging modalities (e.g., CT/MRI) is just as important in the overall diagnosis (Al Farii *et al*, 2020).

2.13 Chronic Manifestations:

Osteopenia and Osteoporosis:

Numerous articles suggest that bone marrow hyperplasia is the primary cause of reduced bone mineral density (BMD) in SCD. This eventually results in osteopenia, which later progresses to osteoporosis (Brinker *et al*, 1998; Nelson *et al*, 2003). Vitamin D deficiency is frequently observed in individuals with SCD, with reported prevalence rates ranging from 25% to as high as 98%, depending on the study (UpToDate, 2024b, "Management of Bone and Joint Complications"). One clinical investigation found that SCD patients showed lower BMD and Vitamin D levels, making them at a greater risk of developing osteopenia and osteoporosis than the general population, particularly in the vertebral column (Eskiocak *et al*, 2022). Another clinical trial supported this finding by

demonstrating that patients with SCD had lower BMD values across all scan regions, ranging from about 6% to 21% lower than expected when compared to the general population (Brinker *et al*, 1998).

One cross-sectional study identified that the incidence of osteopenia and osteoporosis is significantly higher among young adults and children than in other age and sex-matched control groups. The same study concluded that 64-72% of young adults and children have lower BMD and total bone area, thereby increasing their risk of stress fracture and vertebral collapse (Buison *et al*, 2005; Miller *et al*, 2006; Mohammed *et al*, 1993). The most common presentations of an SCD patient with osteopenia and osteoporosis are fragility fractures, pathological fractures, and vertebral collapse. Although asymptomatic, some patients complain of acute or chronic back pain, thus requiring mechanical support (supportive back brace) and analgesia (Almeida & Roberts, 2005).

Osteonecrosis:

Although not as commonly seen as in the femoral head, osteonecrosis of the vertebral column has been reported in a retrospective cohort study amongst SCD patients, where 610 patients were followed up for 7 years, and 16% (98) developed osteonecrosis of the vertebral column (Grimbly *et al*, 2022). Of the 98 patients who developed osteonecrosis, about 49% (48) of them had developed it in the lumbar vertebrae, 41% (40) in the thoracic vertebrae, and 10% (10) in both segments of the vertebral column (Daltro *et al*, 2021). A different case-series report revealed that 91.7% of the participants developed osteonecrosis, with 72.7% of cases occurring in the lumbar vertebrae and the remaining 27.3% affecting both the thoracic and lumbar regions. Interestingly, both aforementioned studies reported that some patients had associated osteoporosis and osteomyelitis; however, none experienced any SCD manifestations in their cervical region (Nagy & Nabil, 2020). One retrospective cohort study reported that the incidence of vertebral osteonecrosis was 5.2% among a sample of 172 SCD patients who had already developed a vertebral pathology beforehand (Sadat-Ali *et al*, 1994).

2.2 Discussion:

The literature review highlighted several mechanisms through which SCD can lead to vertebral manifestations. These mechanisms, driven by hypoxia, hemolysis, anemia, vaso-occlusion, and infections, subsequently cause various complications. Due to hypoxia, dehydration, and other factors, the abnormal Hb tetramer can polymerize, leading to vaso-occlusion. Typically, RBCs have little interaction with the endothelium; however, due to SCD, they interact more frequently, leading to endothelial damage and dysfunction (De Franceschi *et al*, 2011; Hebbel *et al*, 2009; Vaishya *et al*, 2015; Wautier & Wautier, 2020). The hallmark features of SCD are attributed to the effects of HbS, which increase RBC adherence to the endothelium, activate local vaso-activity and pro-inflammatory pathways, and promote inflammation and adhesion, leading to hemolysis and sickle vaso-occlusion; the main mechanisms that cause the commonest and most severe manifestations (Almeida & Roberts, 2005; De Franceschi *et al*, 2011; Hebbel *et al*, 2009; Manwani & Frenette, 2013).

The abnormal sickling of RBCs in SCD causes various vertebral manifestations that are associated with vaso-occlusion, hemolysis, infection, and ischemia. The damage to the membrane of the RBC decreases its life span significantly and eventually leads to intravascular and extravascular hemolysis. The anemia caused by SCD promotes conditions that stimulate RBC production, such as bone expansion and pathological fractures associated with hematopoietic marrow hyperplasia and osteoporosis (Kosaraju *et al*, 2017). While it is well-established that the primary defect in SCD lies in the hemoglobin molecule, secondary changes can also occur in the RBC's metabolism and cell membrane structure and function. These changes, including ionic imbalances and alterations in surface charges at the cell membrane, may contribute to VOCs that result in ischemia, which subsequently leads to various manifestations, including bone infarcts, osteonecrosis, and the formation of H-shaped vertebrae (Almeida & Roberts, 2005; Huo *et al*, 1990; Kosaraju *et al*, 2017; Massart & Allemeersch, 2023). Moreover, it also decreases blood flow through small vessels that supply the bones, creating ischemic zones susceptible to vertebral osteomyelitis and pathogen colonization and invasion (Figure 2). Ischemia from vaso-occlusion can also cause soft tissue hematomas, superinfection with abscess formation, and muscle necrosis (Almeida & Roberts, 2005; Kosaraju *et al*, 2017; Manwani & Frenette, 2013).

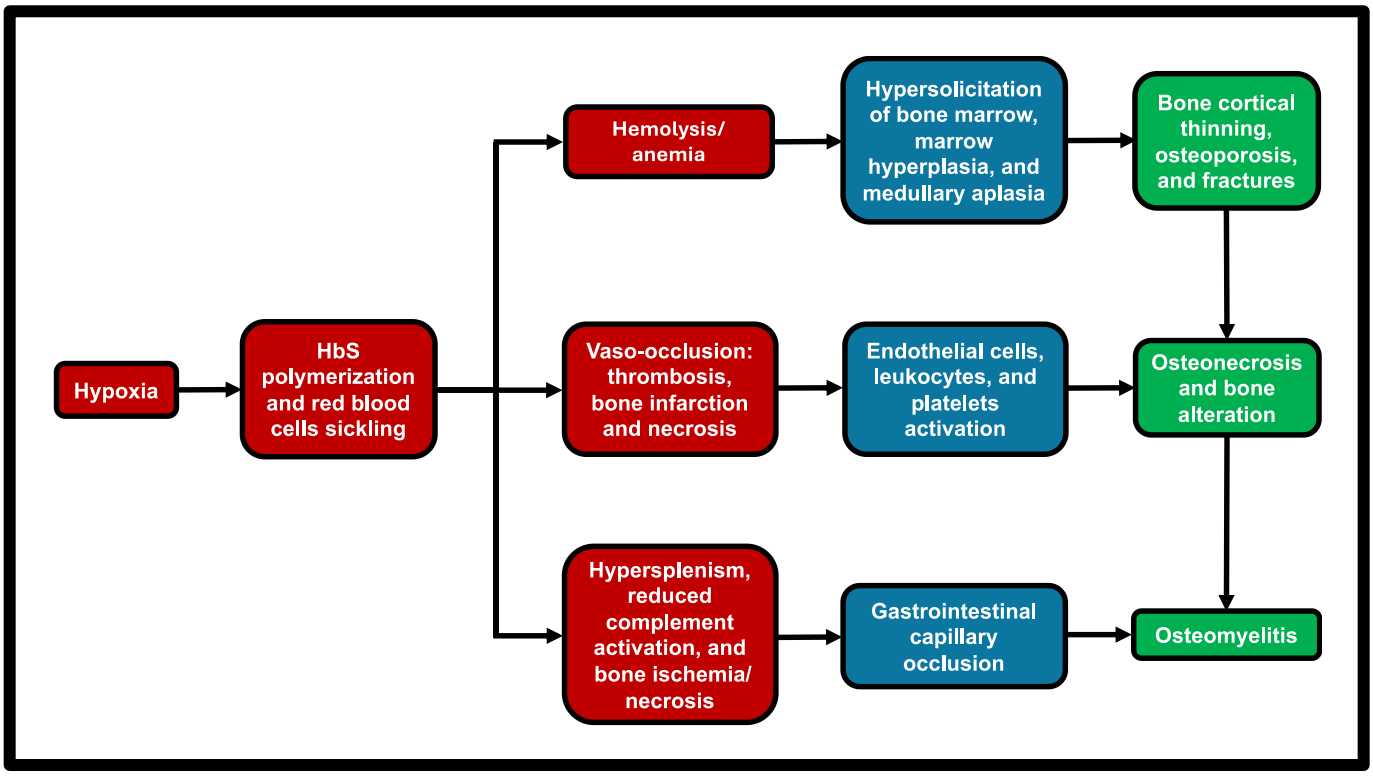

Fig. 2 Summary of the pathophysiology of vertebral manifestations of SCD (da Silva Junior *et al*, 2012; Kosaraju *et al*, 2017).

VOCs were the most cited pathological manifestation that led to hospitalization in the literature (Almeida & Roberts, 2005; Huo *et al*, 1990). According to the literature, VOCs are often the first sign of vertebral involvement as an SCD manifestation. A patient with VOCs would usually present with severe localized back pain (Almeida & Roberts, 2005; Rudy *et al*, 2019). Although it is a very common presentation in children, it remains a recurring manifestation in all age groups with SCD. Painful VOC can manifest itself in any bone with marrow (e.g., knee, hip, sternum, etc.); however, the vertebral column remains one of the most affected parts of the musculoskeletal system. Repeated infarcts can cause the development of areas of necrosis and resulting weakness, leading to a vertebral column that is highly susceptible to pathological fractures. Marrow hypercellularity, which results in reduced blood flow and regional hypoxia, may partially account for the bone marrow's susceptibility to microvascular occlusion; however, the complete reasons remain unclear (Almeida & Roberts, 2005; Smith, 1996). Our review suggests that this presentation might be a result of vertebral bone cortical or marrow infarction that leads to cortical pressure and collapse as a result of inflammation and edema.

Most papers have agreed that clinical judgment and biochemical and lab investigations are necessary for investigating and later treating acute VOCs (Almeida & Roberts, 2005). However, a significant gap persists regarding the role of radiology, as no definitive radiological gold standard has been established. An article noted that a series of X-rays over several months would typically reveal areas of poorly defined translucency, which may progress to arc-like subchondral and intramedullary lucent zones along with patchy sclerosis. It also highlighted rare and notable radiographic signs of bone infarction, such as the "vanishing" vertebrae, as documented in multiple case studies (Almeida & Roberts, 2005; Francine *et al*, 2024; Gowri *et al*, 2022; Ntagiopoulos *et al*, 2009). However, early bone marrow infarctions are typically not visible as acute VOC usually shows up as normal bone on radiographs (Gauthier & Winikoff, 2010; Rudy *et al*, 2019).

Both the “fish mouth” vertebrae sign, and the H-shaped vertebrae are radiologically pathognomonic for vertebral manifestations of SCD, with both forming as a result of the compression forces of adjacent intervertebral disc (Almeida & Roberts, 2005; Daltro *et al*, 2021; Massart & Allemeersch, 2023; Ntagiopoulos *et al*, 2009; Rudy *et al*, 2019; Williams *et al*, 2004). H-shaped vertebrae are distinguished from the "fish mouth" vertebrae seen in osteopenia and other SCD manifestations by the nature of the endplate depressions in the radiographs. In the “fish mouth” vertebrae, there is a noticeable prominence of vertebral trabeculae, with an increased radiolucency of the vertebral bodies, and the depressions are smooth, biconcave, and extend from corner to corner, whereas in H-shaped vertebrae, they are abrupt and step-like (Almeida & Roberts, 2005; Daltro *et al*, 2021; Massart & Allemeersch, 2023; Patil, 2024; Schwartz *et al*, 1979; Williams *et al*, 2004). Moreover, they can be identified by posteroanterior and lateral spinal radiographs (Almeida & Roberts, 2005; Kosaraju *et al*, 2017; Ntagiopoulos *et al*, 2009; Rudy *et al*, 2019). The change in the vertebral shape in the “fish mouth” vertebrae is due to the ischemia of the middle part of the growth plate (Ntagiopoulos *et al*, 2009; Rudy *et al*, 2019). The outer areas of vertebral endplates remain intact; however, the central area suffers extensive damage. This is due

to the different vascularization of the endplates; the central area is supplied by the long branches of the vertebral nutrient artery, whereas the outer areas receive blood from short perforating branches of the periosteal vessels (Aguilar *et al*, 2005; Kosaraju *et al*, 2017; Rudy *et al*, 2019). Vaso-occlusion and other damaging mechanisms are more likely to affect the longer end vessels than the shorter ones (Aguilar *et al*, 2005; Daltro *et al*, 2021; Rudy *et al*, 2019; Vaishya *et al*, 2015).

The appearance of "vanishing vertebrae" on radiographs is extremely rare and can be explained by a combination of compressive forces along the spine, vaso-occlusive infarction, reactive changes in the bone, and secondary infections (Coello *et al*, 2024; Ozoh *et al*, 1990; Rudy *et al*, 2019). Other radiological findings may include biconcave vertebral bodies, coarse trabecular pattern, a stepladder effect, significant central collapse, persistent anterior vertebral notching, and compression deformities (Hendrickse *et al*, 1960; Rudy *et al*, 2019). Additionally, multiple osteolytic lesions may be observed in the lumbar vertebrae, accompanied by a height reduction of the affected vertebral bodies (Rudy *et al*, 2019).

To identify areas of bone infarction, radioisotope bone scans using combined Tc-99m-diphosphonate (for bone uptake measurement) and Tc-99m-labeled sulfur colloid (for bone marrow uptake measurement) were suggested (Almeida & Roberts, 2005; Cerci *et al*, 2007; Kim & Miller, 2002; Rudy *et al*, 2019). Despite it being a sensitive scan, it has been proven to be unreliable in terms of distinguishing bone infarctions from other SCD manifestations, such as osteomyelitis; thus, it is not routinely used as a diagnostic imaging tool (Almeida & Roberts, 2005; Kim & Miller, 2002). Magnetic resonance imaging (MRI) may be a more sensitive imaging modality in detecting infarctions by showing abnormal soft tissue changes and periosteal signal intensity; however, it is also poor in distinguishing between bone and marrow infarcts with osteomyelitis in the acute phase due to the overlap between the two conditions, in which an MRI scan would show reactive marrow edema with surrounding hyperemia (Almeida & Roberts, 2005; Bonnerot *et al*, 1994; Deely & Schweitzer, 1997; Frush *et al*, 1999; Gauthier & Winikoff, 2010; Mankad *et al*, 1990; Rudy *et al*, 2019; Umans *et al*, 2000). Therefore, our review found that MRI and other imaging modalities should be reserved as last resorts for patients with symptoms persisting after conventional treatment or when there is high clinical suspicion of osteomyelitis and other SCD manifestations (Almeida & Roberts, 2005; Deely & Schweitzer, 1997; Keeley & Buchanan, 1982).

The literature seems to universally agree that rest and physical therapy have minimal impact on the overall treatment of VOCs. Long-term benefits can be achieved with proper orthotic support for the affected thoracic or lumbar regions, as it can decrease the need for medication. However, in cases of severe collapse, surgical intervention may be necessary (Vaishya *et al*, 2015).

Osteomyelitis has been cited as the second most reported SCD manifestation in the vertebral column. Our review found that VOCs more frequently trigger osteomyelitis due to elevated marrow pressure from marrow hyperplasia and the tissue-related reaction to the bone infarcts (Huo *et al*, 1990). As stated earlier, differentiating between bone infarcts and osteomyelitis in its acute phase is challenging, both clinically and radiologically, as both manifestations present similarly with tenderness over the affected spinal region, fever, and elevated inflammatory markers. The overlap between bone infarction and osteomyelitis can lead to delayed diagnosis of osteomyelitis, which may only be suspected when specific symptoms (erythema, swelling, and high-grade fever) persist despite standard VOCs treatment for one to two weeks (Almeida & Roberts, 2005; Jean-Baptiste & De Ceulaer, 2000; Nagy & Nabil, 2020). Several cited research attributed the increased incidence of osteomyelitis amongst SCD patients in the vertebral column to increased hemolysis and excess iron (the main bacterial nutrient for increasing red cell turnover), dysfunctional complement activity, tissue infarction, and splenic dysfunction (immunodeficiency) (Figure 2) (Almeida & Roberts, 2005; Nagy & Nabil, 2020).

Several studies have identified *Salmonella spp.* (especially the non-typical gram-negative bacillus serotypes: *Salmonella enteritidis, Salmonella typhimurium, Salmonella paratyphi B,* and *Salmonella enterica*) as the most common pathogens, followed by *Staphylococcus aureus* and rarely tuberculosis (possibly multifocal), in cases of osteomyelitis among SCD patients (Almeida & Roberts, 2005; Al-Tawfiq *et al*, 2008; Ebong *et al*, 1986; Kooy *et al*, 1996; Nagy & Nabil, 2020; Rudy *et al*, 2019). The most common infective pathway in SCD involves capillary blockages and microinfarcts, leading to the entry of gastrointestinal bacteria, particularly *Salmonella*, into the bloodstream (Anand & Glatt, 1994; Barrett-Connor, 1971; Huo *et al*, 1990). However, there are reports of cases of vertebral osteomyelitis secondary to SCD being caused by anaerobic organisms (*Bacteroides fragilis*), with most cases showing recovery following courses of intravenous antibiotics. Osteomyelitis caused by *B. fragilis* seems to be more common than before (Almeida & Roberts, 2005; Al-Tawfiq *et al*, 2008; Ebong *et al*, 1986; Nagy & Nabil, 2020; Rudy *et al*, 2019). SCD patients with osteomyelitis would usually present with chills, fever, vomiting, nausea, and non-radiating localized lower back pain without neurological symptoms. They may also appear jaundiced, with lab results showing elevated ESR and bilirubin. Most of the cases appear to respond well to the antibiotic's treatment, which gives the impression that acute hematogenous anaerobic osteomyelitis might be treatable with antibiotics alone, without the need for surgical debridement (Al-Tawfiq *et al*, 2008; Rudy *et al*, 2019).

In the early acute stage of osteomyelitis, blood cultures are often sterile because patients with VOCs are typically treated with broad-spectrum antibiotics upon admission. The diagnosis can be confirmed with a technetium-99m bone scan and MRI, especially when clinical signs are unclear (Almeida & Roberts, 2005; Barrett-Connor, 1971). Early radiographic changes such as periostitis, soft-tissue edema, and regional osteopenia are non-specific and may not appear until one to two weeks, and can also occur in

VOCs, reducing their diagnostic utility. More definitive signs, like lucent areas indicating bone destruction, usually only appear in the advanced stages of the disease (Almeida & Roberts, 2005). Ultrasonography can detect extraosseous issues like periosteal elevation and is advantageous due to its rapid, painful, area-specific, and non-invasive nature, but it has limited sensitivity (74%) as similar findings may be seen in VOCs (Almeida & Roberts, 2005; Riebel *et al*, 2003; Sidhu & Rich, 1999; William *et al*, 2000). Computed tomography (CT) scans can be used; however, they are also limited as their findings are not specific (Almeida & Roberts, 2005; William *et al*, 2000). Bone scans and MRI can be utilized to diagnose osteomyelitis; however, they both have limited specificity and sensitivity in their ability to effectively distinguish osteomyelitis from bone infarction. Combining 99mTc-sulphur colloid with 99MTc with gallium or 99MTc-diphosphonate enhances diagnostic accuracy, as marrow uptake typically remains normal in osteomyelitis but is usually elevated in cases of infarction. However, it is worth mentioning that contrast-enhanced MRI has a slightly better accuracy in diagnosing osteomyelitis. (Almeida & Roberts, 2005; Bonnerot *et al*, 1994; Deely & Schweitzer, 1997; Frush *et al*, 1999; Kim & Miller, 2002; Umans *et al*, 2000). MRI is most effective for localizing the lesion and assessing the patient's response to antibiotic treatment after osteomyelitis has been confirmed through cultures (Almeida & Roberts, 2005; Bonnerot *et al*, 1994).

Despite advances in imaging, diagnosing osteomyelitis in SCD still largely depends on clinical evaluation and identifying causative organisms through cultures from blood or bone samples. While imaging is helpful, it often cannot conclusively distinguish between infection and infarction, leading to potential false positives or negatives. Therefore, clinical presentation, imaging findings, and laboratory results must be integrated to diagnose accurately (Almeida & Roberts, 2005; Keeley & Buchanan, 1982).

The mainstay of treatment for osteomyelitis is the administration of antibiotics. The hospital guidelines and the causative microorganism determine the choice of antibiotics. A third-generation cephalosporin (e.g., ceftriaxone) can be administered as a first-line treatment for confirmed or suspected osteomyelitis due to its coverage of *Salmonella* infections. For older children, ciprofloxacin could be alternatively used due to its excellent oral bioavailability. In adults, empirical antibiotic therapy should also include coverage for other bacterial species, such as *Staphylococcus* (Almeida & Roberts, 2005).

For confirmed cases, treatment should be administered for a minimum of 6 weeks. If radiological imaging shows fluid accumulation at the infection site, drainage is recommended. Unfortunately, there is no universal agreement on the timing for drilling or draining, and these invasive procedures are generally reserved for patients who do not respond to antibiotic therapy or who have localized encapsulated septic collections (Almeida & Roberts, 2005). Lesions of osteomyelitis are usually managed by external fixation, conventional debridement, soft tissue, and delayed bone reconstruction (Bahebeck *et al*, 2004). Delayed or inadequate treatment can lead to various short- and long-term complications, such as recurrent infections (e.g., sinus tract infections, abscesses, etc.), fractures, vertebral body collapse, paralysis, permanent neurological deficits, chronic back pain, disability, and even death (UpToDate, 2024b, "Complications of vertebral osteomyelitis").

In the chronic setting, repetitive infarctions, bone alterations, and resulting marrow hyperplasia may lead to bone changes that contribute to osteoporosis and osteonecrosis. While uncommon, osteoporosis and osteonecrosis can co-occur (Almeida & Roberts, 2005; Mohammed *et al*, 1993; Rudy *et al*, 2019). Chronic anemia-induced erythropoietic marrow hyperplasia impacts the bone trabeculae, leading to absorption, softening, thinning of the cortex, deformities, and osteoporosis (Almeida & Roberts, 2005; Brinker *et al*, 1998; Nelson *et al*, 2003; Rudy *et al*, 2019; Soliman *et al*, 1998; VanderJagt *et al*, 2002). The main concern with vertebral osteoporosis is the increased risk of pathological fractures (thereby preventing the vertebral column from withstanding physiological stress), which are primarily caused by reduced BMD and vitamin D levels secondary to bone marrow hyperplasia (Buison *et al*, 2004; Gauthier & Winikoff, 2010; Lal *et al*, 2006; Mohammed *et al*, 1993; Nagy & Nabil, 2020; Rudy *et al*, 2019). A literature review found that levels of the C-terminal component of pro-collagen type 1 (a marker of bone resorption) were elevated in patients with SCD both before and after treatment. Although the precise mechanism behind low BMD and decreased vitamin D levels in SCD patients is not fully understood, some studies propose that increased bone resorption, driven by inflammatory cytokines such as interleukin-6 and tumor necrosis factor-α, which are released in the bone during ischemic events, may partly explain the pathophysiology of low BMD in these patients (Rudy *et al*, 2019; Teitelbaum, 2007).

Some patients may develop vertebral collapse from either osteoporosis or bone infarctions; however, the majority remain asymptomatic (Almeida & Roberts, 2005). Like in VOCs, some may develop the "fish mouth" vertebrae (Almeida & Roberts, 2005; Williams *et al*, 2004). Radiography is used in clinical settings to identify low BMD levels, but its effectiveness is restricted by a relatively low sensitivity of 75% and a specificity of 36% (Meeuwes *et al*, 2013). Dual-Energy X-ray Absorptiometry (DEXA) scan to identify the T-score has been considered as the gold standard for screening other manifestations of SCD or diagnosing osteopenia and osteoporosis (Table 2). Several studies involving children and young adults with SCD determined that the lumbar vertebrae are the best area for assessing BMD (Meeuwes *et al*, 2013; Kanis, 2008, p. 61; Nagy & Nabil, 2020). Pathologic osteoporotic fractures may require treatment through either internal or external fixation, depending on the specific case, and weakened bone may require protection by the external cast (Vaishya *et al*, 2015).

Table 2: World Health Organization diagnostic thresholds and descriptive categories for males and females using DEXA scan measurements (T-Score) (Kanis, 2008, p. 61).

Category	**T-Score**
Normal bone mass	Greater than or equal to -1 SD
Low bone mass (osteopenia)	Less than -1 and greater than -2.5 SD
Osteoporosis	Less than or equal to -2.5 SD
Severe osteoporosis (established osteoporosis)	-2.5 SD or below in the presence of one or more fragility fractures.

The role of bisphosphonates in treating osteopenia in SCD patients has not been thoroughly studied. However, low BMD levels of the lumbar vertebrae and reduced vitamin D are (in clinical practice) considered as indications for treating SCD patients (Buison *et al*, 2004; Lal *et al*, 2006; Mohammed *et al*, 1993; Rudy *et al*, 2019). There is limited evidence supporting the routine use of vitamin D supplementation to decrease the incidence of osteoporosis (UpToDate, 2024b, "Other aspects of bone health"). Nevertheless, given the lack of high-quality data specifically for this population, it is recommended that individuals with osteopenia or osteoporosis be treated similarly to those in the general population with bed rest, analgesia (e.g., paracetamol, tramadol, pethidine hydrochloride, and meloxicam), bisphosphonates (e.g., Alendronic acid), and lumbar support be employed for the overall management (Nagy & Nabil, 2020; (UpToDate, 2024b, "Other aspects of bone health").

Several studies have reported that many patients presented with vertebral osteonecrosis after experiencing VOCs (Almeida & Roberts, 2005; Nagy & Nabil, 2020). The shared pathophysiology across all forms of osteonecrosis is bone ischemia caused by the occlusion of blood vessel lumens, leading to microfractures, collapse of cancellous bone, and eventually, collapse of the articular surface (UpToDate, 2024a, "Causes of Bone or Joint Pain"). Chronically, bone deformities resulting from repetitive sickling and recurrent infarctions following bone marrow hyperplasia contribute significantly to the pathophysiology of osteonecrosis (Almeida & Roberts, 2005; Rudy *et al*, 2019). The complex process of bone resorption and formation, along with the pattern of cell death, can lead to mechanical insufficiency in the vertebral body, ultimately resulting in vertebral collapse (Formica *et al*, 2018b; Lafforgue, 2006; Shah *et al*, 2015). The pathophysiology of osteonecrosis can be idiopathic or related to genetic factors, cytotoxicity, fat embolism, immunological factors, or VOCs (reduced intraosseous blood flow) (Rees *et al*, 2010; Vaishya *et al*, 2015). One of the commonest secondary mechanisms is post-traumatic origin, which is referred to in the literature as "Kümmell's disease." This condition may arise from disrupted or diminished blood supply due to insufficient revascularization of the bone marrow (Formica *et al*, 2018b; Hajnovic *et al*, 2018; Ma *et al*, 2010; Young *et al*, 2002). Other risk factors that may precipitate the development of vertebral osteonecrosis include diabetes, hypothyroidism, osteopenia and osteoporosis, rheumatic diseases, dermatomyositis, pancreatitis, renal diseases, sarcoidosis, temporal arteritis, steroid intake, chemotherapy, azathioprine, human immunodeficiency virus and its treatment, and Gaucher disease type 1 (Formica *et al*, 2018a; Ma *et al*, 2010).

Some patients may present with multifocal osteonecrosis in the vertebrae, femoral head, humeral head, tibial plateau, and femoral condyles (De Gheldere *et al*, 2006). Patients with vertebral osteonecrosis experience a reduced range of motion in the affected area, with a sudden onset of severe back pain during the acute phase, often described as throbbing, burning, or shocking, most commonly occurring in the lumbar vertebrae (can also occur in other spinal segments) and radiating to the shoulders, ribs, or lower limbs. The pain worsens with lumbar vertebrae movements and is alleviated by analgesics and postural correction (Daltro *et al*, 2021; Nagy & Nabil, 2020).

In the clinical setting, a vertebral biopsy is the gold standard for diagnosing vertebral osteonecrosis in SCD (Formica *et al*, 2018a). If a biopsy is unavailable, multiple views, plain-film radiographs, and MRI have been suggested as alternatives to support the diagnosis of vertebral osteonecrosis (Daltro *et al*, 2021; Formica *et al*, 2018a). Imaging makes it possible to visualize and view the intervertebral disc and canal, pedicles, morphologies and relationships of the intervertebral structures (Daltro *et al*, 2021). Like osteomyelitis, plain-film radiographs are neither sensitive nor specific in confirming or excluding osteonecrosis from acute painful VOCs as the bone appears normal on the radiograph. However, later signs may include vertebral anatomical changes (e.g., H-shaped vertebrae) due to osteonecrosis (Gauthier & Winikoff, 2010; Nagy & Nabil, 2020). The MRI findings of vertebral osteonecrosis show multifocal vertebral end-plate depression, followed by collapse and fragmentation of the area (Nagy & Nabil, 2020). During the acute phases, there may be a "fluid sign" present on a background of an associated diffuse bone marrow edema pattern near the vertebral endplates, characterized by low signal intensity. In the chronic phases, heterogeneous (sclerotic and fibrotic pattern) high-signal intensity may be noted by the presence of a "double-line" sign (Formica *et al*, 2018a; Kosaraju *et al*, 2017). Moreover, a vacuum phenomenon may also be observed on X-rays and CTs in multiple intervertebral discs adjacent to the collapsed endplates, however, it is an extremely rare occurrence (Formica *et al*, 2018b; Ma *et al*, 2010; Young *et al*, 2002). The intravertebral vacuum cleft was identified as a pathognomonic marker of vertebral body osteonecrosis, and MRI features were recognized as indicative of vertebral body osteonecrosis (Formica *et al*, 2018a). As previously mentioned, osteonecrosis and

osteoporosis can occur together, making it necessary to perform a DEXA scan in an osteonecrotic patient to rule out osteoporosis (Meeuwes *et al*, 2013; Nagy & Nabil, 2020).

In the clinical setting, vertebral osteonecrosis in SCD is mainly treated conservatively with rest, weight loss, orthosis, intermittent oral analgesics (e.g., NSAIDs), physical therapy (e.g., hydrotherapy), and lifestyle modifications (e.g., postural training) (Bahebeck *et al*, 2004; Daltro *et al*, 2021; da Silva Junior *et al*, 2012; Nagy & Nabil, 2020). Osteoporosis medical therapy may be used to treat vertebral osteonecrosis in adult patients with SCD (Nagy & Nabil, 2020). It is also recommended that major surgical intervention can be appropriate for certain patients (Formica *et al*, 2018a).

3. Conclusion and Future Perspectives:

In conclusion, while the vertebral manifestations of SCD do not significantly contribute to overall mortality, they nevertheless present substantial and complex forms of morbidity with profoundly undesirable implications for patient care and quality of life.

It is well-established that the vertebrae undergo the same pathogeneses as the rest of the bones in the body in SCD, subsequently leading to the development of VOCs and osteomyelitis acutely, osteopenia and osteoporosis and osteonecrosis chronically as vertebral manifestations of SCD.

The lumbar region is the most affected site for acute and chronic vertebral manifestations in SCD patients. While the thoracic vertebrae can also be involved, it is less frequently affected, and the cervical region is rarely involved. Consequently, the lumbar vertebrae are recommended as the initial and primary focus for investigation in patients with SCD.

Our review has emphasized that vertebral manifestations of SCD are common, severely debilitating, contribute to increased morbidity and chronic pain, ultimately leading to a decline in the patient's overall well-being. Despite the clinical, biochemical, and radiological (bone scans/CT/MRI) advancements, there remains a major hurdle in differentiating between VOCs and osteomyelitis. This diagnostic ambiguity and limitations of current imaging modalities often complicate the treatment process, leading to prolonged hospital admissions, unsatisfactory outcomes, and persistent health issues that require even more invasive procedures.

Moreover, there also seems to be an inconsistency in the protocols and management strategies for severe vertebral manifestations of SCD, leading to poor outcomes in the long run, even with aggressive treatments, which necessitates more comprehensive and novel therapeutic approaches, and while our review suggests that the mainstay of treatment should be conservative (rest, analgesics, antibiotics, orthosis, etc.), with the exception of a select few cases requiring surgical intervention, a multi-disciplinary approach that combines advancements in medical and surgical interventions and rehabilitative initiatives are emerging as the most promising front for future research. In the meantime, as we await new genetic therapies (e.g., CRISPR-Cas9), clinicians should focus on monitoring and managing these manifestations as they emerge.

Finally, efforts should focus on preventing and addressing these manifestations through meticulous evaluation and monitoring during routine clinic visits. With this approach, we could potentially address the sophisticated nature of SCD-related vertebral manifestations, thus providing an efficient management strategy that aims to alleviate chronic pain, improve mobility, and ultimately reduce morbidity by improving the quality of life amongst these patients. Continued investments in research and innovations are of utmost importance to overcome the scarcity of research in this area and achieve better clinical outcomes.

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References:

[1] Aguilar, C., Vichinsky, E. & Neumayr, L. (2005). "Bone and joint disease in sickle cell disease". *Hematology Oncology Clinics of North America.* [Online]. Vol. 19, no. 5, pp. 929-941. Available from: doi: 10.1016/j.hoc.2005.07.001 [Accessed 8th August 2024].

[2] Al Arrayed, S. & Haites, N. (1995). "Features of sickle-cell disease in Bahrain". *Easterns Mediterranean Health Journal.* [Online]. Vol. 1, no. 1. Available from: https://iris.who.int/bitstream/handle/10665/117239/emhj_1995_1_1_112_119.pdf?sequence=1&isAllowed=y [Accessed 24th July 2024].

[3] Al Farii, H., Zhou, S. & Albers, A. (2020). "Management of Osteomyelitis in Sickle Cell Disease: Review Article". *Journal of the American Academy of Orthopedic Surgeons: Global Research and Reviews.* [Online]. Vol. 4, no. 9, pp. e20.00002-10. Available from: doi: 10.5435/JAAOSGlobal-D-20-00002 [Accessed 30th July 2024].

[4] Almeida, A. & Roberts, I. (2005). "Bone involvement in sickle cell disease". *British Journal of Haematology.* [Online]. Vol. 129, no. 4, pp. 482-490. Available from: doi: 10.1111/j.1365-2141.2005.05476.x [Accessed 30th July 2024].

[5] Al Shakhouri, M. (Saturday 2 March 2024). 7 thousand sickle cell patients in Bahrain. *Al Ayam.* [Online]. Available from: https://www.alayam.com/alayam/first/1047045/News.html [Accessed 24th July 2024].

[6] Al-Tawfiq, J. A. (2008). "Bacteroides fragilis bacteremia associated with vertebral osteomyelitis in a sickle cell patient". *Internal Medicine.* [Online]. Vol. 47, no. 24, pp. 2183-2185. Available from: doi: 10.2169/internalmedicine.47.1271 [Accessed 11th August 2024].

[7] Anand A. J. & Glatt A. E. (1994). "Salmonella osteomyelitis and arthritis in sickle cell disease". *Seminars in Arthritis and Rheumatism.* [Online]. Vol. 24, no. 3, pp. 211-221. Available from: doi: 10.1016/0049-0172(94)90076-0 [Accessed 12th August 2024].

[8] Bahebeck, J., Atangana, R., Techa, A., Monny-Lobe, M., Sosso, M. & Hoffmeyer P. (2004). "Relative rates and features of musculoskeletal complications in adult sicklers". *Acta Orthopaedica Belgica.* [Online]. Vol. 70, no. 2, pp. 107-111. Available from: http://actaorthopaedica.be/assets/190/03-Bahebeck_et_al.pdf [Accessed 12th August 2024].

[9] Bahrain Open Data Portal. (2024). *1995 Mid-year Population by Nationality and Sex* Information & eGovernment Authority. Available from: https://www.data.gov.bh/explore/dataset/03-mid-year-population-by-nationality-and-sex/table/?disjunctive.nationality&disjunctive.sex&sort=-year&refine.year=1995&dataChart=eyJxdWVyaWVzIjpbeyJjaGFydHMiOlt7ImFsaWduTW9udGgiOnRydWUsInR5cGUiOiJsaW5lIiwiZnVuYyI6IlNVTSIsInlBeGlzIjoicG9wdWxhdGlvbiIsInNjaWVudGlmaWNEaXNwbGF5Ijp0cnVlLCJjb2xvciI6InJhbmdlLVNldDEifV0sInhBeGlzIjoieWVhciIsIm1heHBvaW50cyI6bnVsbCwidGltZXNjYWxlIjoibW9udGgiLCJzb3J0IjoiIiwic2VyaWVzQnJlYWtkb3duIjoibmF0aW9uYWxpdHkiLCJzZXJpZXNCcmVha2Rvd25UaW1lc2NhbGUiOiIiLCJjb25maWciOnsiZGF0YXNldCI6IjAzLW1pZC15ZWFyLXBvcHVsYXRpb24tYnktbmF0aW9uYWxpdHktYW5kLXNleCIsIm9wdGlvbnMiOnsiZGlzanVuY3RpdmUubmF0aW9uYWxpdHkiOnRydWUsImRpc2p1bmN0aXZlLnNleCI6dHJ1ZSwic29ydCI6Ii15ZWFyIiwicmVmaW5lLnllYXIiOiIxOTk1In19fV0sImRpc3BsYXlMZWdlbmQiOnRydWUsImFsaWduTW9udGgiOnRydWUsInRpbWVzY2FsZSI6IiJ9 [Accessed 24th July 2024].

[10] Barrett-Connor, E. (1971). "Bacterial infection and sickle cell anemia. An analysis of 250 infections in 166 patients and a review of the literature". *Medicine (Baltimore).* [Online]. Vol. 50, no. 2, pp. 97-112. Available from: https://doi.org/10.1097/00005792-197103000-00002 [Accessed 13th August 2024].

[11] Bonnerot, V., Sebag, G., de Montalembert, M., Wioland, M., Glorion, C., Girot, R. & Lallemand, D. (1994). "Gadolinium-DOTA enhanced MRI of painful osseous crises in children with sickle cell anemia". *Pediatric Radiology.* [Online]. Vol. 24, no. 2, pp. 92-95. Available from: doi: 10.1007/BF02020160 [Accessed 8th August 2024].

[12] Brinker, M. R., Thomas, K. A., Meyers, S. J., Texada, T., Humbert, J. R., Cook, S. D. & Gitter, R. (1998). "Bone mineral density of the lumbar spine and proximal femur is decreased in children with sickle cell anemia" *American Journal of Orthopedics*. [Online]. Vol. 27, no. 1, pp. 43-49. Available from: https://europepmc.org/article/med/9452835 [Accessed 30th July 2024].

[13] Browne, P., Shalev, O. & Hebbel, R. P. (1998). "The molecular pathobiology of cell membrane iron: the sickle red cell as a model". *Free Radical Biology and Medicine.* [Online]. Vol. 24, no. 6, pp. 1040-1049. Available from: doi: 10.1016/s0891-5849(97)00391-2 [Accessed 4th August 2024].

[14] Buison, A. M., Kawchak, D. A., Schall, J. I., Ohene-Frempong, K., Stallings, V. A. & Zemel, B. S. (2004). "Low vitamin D status in children with sickle cell disease". *The Journal of Pediatrics.* [Online]. Vol. 145, no. 5, pp. 622-627. Available from: doi: 10.1016/j.jpeds.2004.06.055 [Accessed 4th August 2024].

[15] Buison, A. M., Kawchak, D. A., Schall, J. I., Ohene-Frempong, K., Stallings, V. A., Leonard, M. B. & Zemel, B. S. (2005). "Bone area and bone mineral content deficits in children with sickle cell disease". *Pediatrics.* [Online]. Vol. 116, no. 4, pp. 943-949. Available from: doi: 10.1542/peds.2004-2582 [Accessed 12th August 2024].

[16] Cerci, S. S., Suslu, H., Cerci, C., Yildiz, M., Ozbek, F. M., Balci, T. A., Yesildag, A. & Canatan, D. (2007). "Different findings in Tc-99m MDP bone scintigraphy of patients with sickle cell disease: report of three cases". *Annals of Nuclear Medicine.* [Online]. Vol. 21, no. 5, pp. 311-314. Available from: doi: 10.1007/s12149-007-0025-z [Accessed 8th August 2024].

[17] Coello, S. L., Blanco, D. F. & Klass, I. (2024). "Vanishing vertebra: A rare finding in sickle cell disease". *European Society of Radiology.* [Online]. Available from: https://eurorad.org/case/18577#:~:text=The%20vanishing%20vertebra%20phenomenon%2C%20characterised,included%20radiographic%20evidence%20%5B4%5D [Accessed 8th August 2024].

[18] Daltro, G., Lima, V., Ferreira, S. I. C., Vitório, F., Rhangel, T. & Daltro, P. B. (2021). "Spine Osteonecrosis Related to Sickle Cell Disease". *Journal of Hematology and Blood Disorders.* [Online]. Vol. 7, no. 1. Available from: https://www.annexpublishers.com/articles/JHBD/7105-Spine-Osteonecrosis-Related-to-Sickle.pdf [Accessed 1st August 2024].

[19] da Silva Junior, G. B., Daher Ede, F. & da Rocha, F. A. (2012). "Osteoarticular involvement in sickle cell disease". *Revista Brasileira de Hematologia e Hemoterapia.* [Online]. Vol. 34, no. 2, pp. 156-164. Available from: doi: 10.5581/1516-8484.20120036 [Accessed 16th August 2024].

[20] Deely, D. M. & Schweitzer, M. E. (1997). "MR imaging of bone marrow disorders". *Radiologic Clinics of North America.* [Online]. Vol. 35, no. 1, pp. 193-212. Available from: https://europepmc.org/article/med/8998215 [Accessed 8th August 2024].

[21] De Franceschi, L., Cappellini, M. D. & Olivieri, O. (2011). "Thrombosis and sickle cell disease". *Seminars in Thrombosis and Hemostasis.* [Online]. Vol. 7, no. 1. Available from: doi: 10.1055/s-0031-1273087 [Accessed 5th August 2024].

[22] De Gheldere, A., Ndjoko, R., Docquier, P. L., Mousny, M. & Rombouts, J. J. (2006). "Orthopaedic complications associated with sickle-cell disease". *Acta Orthopaedica Belgica.* [Online]. Vol. 72, no. 6, pp. 741-747. Available from: http://www.actaorthopaedica.be/assets/1317/13-De_Gheldere.pdf [Accessed 6th August 2024].

[23] Ebong, W. W. (1986). "Acute osteomyelitis in Nigerians with sickle cell disease". *Annals of The Rheumatic Disease.* [Online]. Vol. 45, no. 11, pp. 911-915. Available from: doi: 10.1136/ard.45.11.911 [Accessed 11th August 2024].

[24] Emodi, J. I. & Okoye, I. J. (2001). "Vertebral bone collapse in sickle cell disease: a report of two cases". *East African Medical Journal.* [Online]. Vol. 78, no. 8, pp. 445-446. Available from: doi: 10.4314/eamj.v78i8.9000 [Accessed 11th August 2024].

[25] Eskiocak, Ö., Yılmaz, M. Ö. & İlhan, G. (2022). "Metabolic bone diseases in sickle cell anemia patients and evaluation of associated factors". *The American Journal of the Medical Sciences.* [Online]. Vol. 363, no. 6, pp. 490-494. Available from: doi: 10.1016/j.amjms.2021.07.002 [Accessed 30th July 2024].

[26] Formica, M., Zanirato, A., Cavagnaro, L., Basso, M., Divano, S., Formica, C. & Felli, L. (2018a). "What is the Current Evidence on Vertebral Body Osteonecrosis?: A Systematic Review of the Literature". *Asian Spine Journal.* [Online]. Vol. 12, no. 3, pp. 586-599. Available from: doi: 10.4184/asj.2018.12.3.586 [Accessed 1st August 2024].

[27] Formica, M., Zanirato, A., Cavagnaro, L., Basso, M., Divano, S., Lamartina, C., Berjano, P., Felli, L. & Formica, C. (2018b). "Vertebral body osteonecrosis: proposal of a treatment-oriented classification system". *European Spine Journal.* [Online]. Vol. 27, no. (Suppl 2), pp. 190-197. Available from: doi: 10.1007/s00586-018-5600-6 [Accessed 15th August 2024].

[28] Francine, S. B., Ritha, M. B., Paul, E. O., Pauline, M. F., Charlotte, E. E., Estelle, M. T., Romain, E. M. & Madeleine, S. N. (2024). ""FISH VERTEBRA" about 3 Sickle Cell Patients Followed at Laquintinie Hospital, Douala". *Open Journal of Rheumatology and Autoimmune Diseases.* [Online]. Vol. 14, no. 1. Available from: doi: 10.4236/ojra.2024.141003 [Accessed 8th August 2024].

[29] Frush, D. P., Heyneman, L. E., Ware, R. E. & Bissett, G. S. 3rd. (1999). "MR features of soft-tissue abnormalities due to acute marrow infarction in five children with sickle cell disease". *AJR American Journal of Roentgenology.* [Online]. Vol. 173, no. 4, pp. 989-993. Available from: doi: 10.2214/ajr.173.4.10511164 [Accessed 8th August 2024].

[30] Gauthier, M. & Winikoff, R. (2010). "Meningeal signs and facial edema in a child with sickle cell disease". *Canadian Medical Association Journal.* [Online]. Vol. 182, no. 10, pp. 1069-1072. Available from: doi: 10.1503/cmaj.091004 [Accessed 8th August 2024].

[31] Gowri, M., Manoj, K., Amudha, D. S., Kumaravel, K. S. & Sampathkumar, D. (2022). "A case of neglected chronic back pain in a girl with Sickle cell disease". *Open Journal of Clinical & Medical Case Reports.* [Online]. Vol. 8, no. 5. Available from: https://jclinmedcasereports.com/articles/OJCMCR-1847.pdf [Accessed 8th August 2024].

[32] Grimbly, C., Escagedo, P. D., Jaremko, J. L., Bruce, A., Alos, N., Robinson, M. E., Konji, V. N., Page, M., Scharke, M., Simpson, E., Pastore, Y. D., Girgis, R., Alexander, R. T. & Ward, L. M. (2022). "Sickle cell bone disease and response to intravenous bisphosphonates in children". *Osteoporosis International.* [Online]. Vol. 33, no. 11, pp. 2397-2408. Available from: doi: 10.1007/s00198-022-06455-2 [Accessed 1st August 2024].

[33] Hajnovic, L., Sefranek, V. & Schütz, L. (2018). "Influence of blood supply on fracture healing of vertebral bodies". *European Journal of Orthopaedic Surgery and Traumatology.* [Online]. Vol. 28, no. 3, pp. 373-380. Available from: doi: 10.1007/s00590-017-2069-7 [Accessed 15th August 2024].

[34] Hebbel, R. P., Vercellotti, G. & Nath, K. A. (2009). "A systems biology consideration of the vasculopathy of sickle cell anemia: the need for multi-modality chemo-prophylaxsis". *Cardiovascular & Hematological Disorders Drug Targets.* [Online]. Vol. 9, no. 4, pp. 271-292. Available from: doi: 10.2174/1871529x10909040271 [Accessed 5th August 2024].

[35] Hendrickse, R. G. (1960). "Sickle cell anaemia in Nigerian children". *Central African Journal of Medicine.* [Online]. Vol. 6, no. 2, pp. 45-57. Available from: https://hdl.handle.net/10520/AJA00089176_5810 [Accessed 8th August 2024].

[36] Hoffbrand, A. & Moss, P. (2016). *Essential Haematology*., 7th ed., Chichester: Wiley Blackwell. pp. 81-85.

[37] Huo, M. H., Friedlaender, G. E. & Marsh, J. S. (1990). "Orthopaedic manifestations of sickle-cell disease". *The Yale Journal of Biology and Medicine.* [Online]. Vol. 63, no. 3, pp. 195-207. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2589295/ [Accessed 26th July 2024].

[38] Jean-Baptiste, G. & De Ceulaer, K. (2000). "Osteoarticular disorders of haematological origin". *Bailliere's Best Practice & Research Clinical Rheumatology.* [Online]. Vol. 14, no. 2, pp. 307-323. Available from: doi: 10.1053/berh.2000.0067 [Accessed 12th August 2024].

[39] Kaklamanis, P. (1984). "Osteoarticular manifestations in sickle-cell disorders". *Clinical Rheumatology.* [Online]. Vol. 3, no. 4, pp. 419-434. Available from: https://doi.org/10.1007/BF02031264 [Accessed 29th July 2024].

[40] Kanis, J. A. (2008). *Assessment of osteoporosis at the primary health care level. Technical Report.* World Health Organization. Available from: https://frax.shef.ac.uk/FRAX/pdfs/WHO_Technical_Report.pdf [Accessed 13th August 2024].

[41] Kayle, M., Blewer, A., Pan, W., Rothman, J., Polick, C., Rivenbark, J., Fisher, E., Reyes, C., Strouse, J., Weeks, S., Desai, J., Snyder, A., Zhou, M., Sutaria, A., Valle, J., Horiuchi, S., Sontag, M., Miller, J., Singh, A. & Hulihan, M. (2024). "Birth Prevalence of Sickle Cell Disease and County-Level Social Vulnerability — Sickle Cell Data Collection Program, 11 States, 2016–2020". *MMWR. Morbidity and mortality weekly report.* [Online]. Vol. 73, no. 12, pp. 248-254. Available from: http://dx.doi.org/10.15585/mmwr.mm7312a1 [Accessed 6th July 2024].

[42] Keeley, K. & Buchanan, G. R. (1982). "Acute infarction of long bones in children with sickle cell anemia". *The Journal of Pediatrics.* [Online]. Vol. 101, no. 2, pp. 170-175. Available from: doi: 10.1016/s0022-3476(82)80111-x [Accessed 8th August 2024].

[43] Kim, S. K. & Miller, J. H. (2002). "Natural history and distribution of bone and bone marrow infarction in sickle hemoglobinopathies". *The Journal of Nuclear Medicine.* [Online]. Vol. 43, no. 7, pp. 896-900. Available from: https://jnm.snmjournals.org/content/43/7/896.long [Accessed 4th August 2024].

[44] Kooy, A., de Heide, L. J., ten Tije, A. J., Mulder, A. H., Tanghe, H. L., Kluytmans, J. A. & Michiels, J. J. (1996). "Vertebral bone destruction in sickle cell disease: infection, infarction or both". *Netherlands Journal of Medicine.* [Online]. Vol. 48, no. 6, pp. 227-231. Available from: doi: 10.1016/0300-2977(95)00075-5 [Accessed 11th August 2024].

[45] Kosaraju, V., Harwani, A., Partovi, S., Bhojwani, N., Garg, V., Ayyappan, S., Kosmas, C. & Robbin, M. (2017). "Imaging of musculoskeletal manifestations in sickle cell disease patients". *British Journal of Radiology.* [Online]. Vol. 90, no. 1073, pp. 20160130. Available from: doi: 10.1259/bjr.20160130 [Accessed 29th July 2024].

[46] Lafforgue, P. (2006). "Pathophysiology and natural history of avascular necrosis of bone". *Joint Bone Spine.* [Online]. Vol. 73, no. 5, pp. 500-507. Available from: doi: 10.1016/j.jbspin.2006.01.025 [Accessed 15th August 2024].

[47] Lal, A., Fung, E. B., Pakbaz, Z., Hackney-Stephens, E. & Vichinsky E. P. (2006). "Bone mineral density in children with sickle cell anemia". *Pediatric Blood & Cancer.* [Online]. Vol. 47, no. 7, pp. 901-906. Available from: doi: 10.1002/pbc.20681 [Accessed 12th August 2024].

[48] Mankad, V. N., Williams, J. P., Harpen, M. D., Manci, E., Longenecker, G., Moore, R. B., Shah, A., Yang, Y. M. & Brogdon, B. G. (1990). "Magnetic resonance imaging of bone marrow in sickle cell disease: clinical, hematologic, and pathologic correlations". *Blood.* [Online]. Vol. 75, no. 1, pp. 274-283. Available from: https://doi.org/10.1182/blood.V75.1.274.274 [Accessed 8th August 2024].

[49] Manwani, D. & Frenette, P. S. (2013). "Vaso-occlusion in sickle cell disease: pathophysiology and novel targeted therapies". *Blood.* [Online]. Vol. 122, no. 24, pp. 3892-3898. Available from: doi: 10.1182/blood-2013-05-498311 [Accessed 4th August 2024].

[50] Ma, R., Chow, R. & Shen, F. H. (2010). "Kummell's disease: delayed post-traumatic osteonecrosis of the vertebral body". *European Spine Journal.* [Online]. Vol. 19, no. 7, pp. 1065-1070. Available from: doi: 10.1007/s00586-009-1205-4 [Accessed 15th August 2024].

[51] Massart, A. & Allemeersch, G. J. (2023). "H-Shaped Vertebrae". *Journal of the Belgian Society of Radiology.* [Online]. Vol. 107, no. 1, pp. 73. Available from: doi: 10.5334/jbsr.3234 [Accessed 8th August 2024].

[52] Meeuwes, M., Souza de Carvalho, T. F., Cipolotti, R., Gurgel, R. Q., Ferrão, T. O., Peters, M. & Agyemang, C. (2013). "Bone mineral density, growth, pubertal development and other parameters in Brazilian children and young adults with sickle cell anaemia". *Tropical Medicine & International Health.* [Online]. Vol. 18, no. 12, pp. 1539-1546. Available from: doi: 10.1111/tmi.12211 [Accessed 13th August 2024].

[53] Miller, R. G., Segal, J. B., Ashar, B. H., Leung, S., Ahmed, S., Siddique, S., Rice, T. & Lanzkron, S. (2006). "High prevalence and correlates of low bone mineral density in young adults with sickle cell disease". *American Journal of Hematology.* [Online]. Vol. 81, no. 4, pp. 236-241. Available from: doi: 10.1002/ajh.20541 [Accessed 31st July 2024].

[54] Mohammed, S., Addae, S., Suleiman, S., Adzaku, F., Annobil, S., Kaddoumi, O. & Richards, J. (1993). "Serum calcium, parathyroid hormone, and vitamin D status in children and young adults with sickle cell disease". *Annals of Clinical Biochemistry.* [Online]. Vol. 30 (Pt 1), pp. 45-51. Available from: doi: 10.1177/000456329303000108 [Accessed 12th August 2024].

[55] Nagy, M. R. & Nabil, D. M. (2020). "Spinal Involvement in Adult Patients with Sickle Cell Disease". *The Egyptian Spine Journal.* [Online]. Vol. 34, no. 1, pp. 26-35. Available from: https://doi.org/10.21608/esj.2020.28739.1131 [Accessed 11th August 2024].

[56] Nelson, D. A., Rizvi, S., Bhattacharyya, T., Ortega, J., Lachant, N. & Swerdlow, P. (2003). "Trabecular and integral bone density in adults with sickle cell disease". *Journal of Clinical Densitometry.* [Online]. Vol. 6, no. 2, pp. 125-129. Available from: doi: 10.1385/jcd:6:2:125 [Accessed 31st July 2024].

[57] Ntagiopoulos, P. G., Moutzouris, D. A. & Manetas, S. (2009). "The "fish-vertebra" sign". *BMJ Case Reports.* [Online]. Vol. 2009. Available from: doi: 10.1136/bcr.09.2008.0900 [Accessed 4th August 2024].

[58] Ozoh, J. O., Onuigbo, M. A., Nwankwo, N., Ukabam, S. O., Umerah, B. C. & Emeruwa, C. C. (1990). ""Vanishing" of vertebra in a patient with sickle cell haemoglobinopathy". *British Medical Journal.* Vol. 301, no. 6765, pp. 1368-1369. Available from: doi: 10.1136/bmj.301.6765.1368 [Accessed 8th August 2024].

[59] Patil P. V. (2024). "Intervertebral Disc Vacuum Phenomenon With H-Shaped Vertebrae in an Adolescent With Sickle Cell Anemia". *Korean Journal of Radiology.* [Online]. Vol. 25, no. 2, pp. 210-211. Available from: doi: 10.3348/kjr.2023.1074 [Accessed 8th August 2024].

[60] Paulukonis, S., Eckman, J., Snyder, A., Hagar, W., Feuchtbaum, L., Zhou, M., Grant, A. & Hulihan, M. (2016). "Defining Sickle Cell Disease Mortality Using a Population-Based Surveillance System, 2004 through 2008". *Public Health Reports.* [Online]. Vol. 131, no. 2, pp. 367-375. Available from: doi: 10.1177/003335491613100221 [Accessed 6th July 2024].

[61] Rees, D. C., Williams, T. N. & Gladwin, M. T. (2010). "Sickle-cell disease". *The Lancet.* [Online]. Vol. 376, no. 9757, pp. 2018-2031. Available from: doi: 10.1016/S0140-6736(10)61029-X [Accessed 16th August 2024].

[62] Riebel, T., Kebelmann-Betzing, C., Götze, R. & Overberg, U. S. (2003). "Transcranial Doppler ultrasonography in neurologically asymptomatic children and young adults with sickle cell disease". *European Radiology.* [Online]. Vol. 13, no. 3, pp. 563-570. Available from: doi: 10.1007/s00330-002-1481-4 [Accessed 14th August 2024].

[63] Rudy, H. L., Yang, D., Nam, A. D. & Cho, W. (2019). "Review of Sickle Cell Disease and Spinal Pathology". *Global Spine Journal.* [Online]. Vol. 9, no. 7, pp. 761-766. Available from: doi: 10.1177/2192568218799074 [Accessed 29th July 2024].

[64] Sadat-Ali, M., Ammar, A., Corea, J. R., & Ibrahim, A. W. (1994). "The spine in sickle cell disease". *International Orthopaedics.* [Online]. Vol. 18, no. 3, pp. 154-156. Available from: doi: 10.1007/BF00192471 [Accessed 4th August 2024].

[65] Schwartz, A. M., Homer, M. J. & McCauley, R. G. (1979). ""Step-off" vertebral body: Gaucher's disease versus sickle cell hemoglobinopathy". *AJR American Journal of Roentgenology.* [Online]. Vol. 132, no. 1, pp. 81-85. Available from: doi: 10.2214/ajr.132.1.81 [Accessed 8th August 2024].

[66] Shah, K. N., Racine, J., Jones, L. C. & Aaron, R. K. (2015). "Pathophysiology and risk factors for osteonecrosis". *Current Reviews in Musculoskeletal Medicine.* [Online]. Vol. 8, no. 3, pp. 201-209. Available from: doi: 10.1007/s12178-015-9277-8 [Accessed 15th August 2024].

[67] Sidhu, P. S. & Rich, P. M. (1999). "Sonographic detection and characterization of musculoskeletal and subcutaneous tissue abnormalities in sickle cell disease". *The British Journal of Radiology.* [Online]. Vol. 72, no. 853, pp. 9-17. Available from: doi: 10.1259/bjr.72.853.10341683 [Accessed 14th August 2024].

[68] Smith, J. A. (1996). "Bone disorders in sickle cell disease". *Hematology Oncology Clinics of North America.* [Online]. Vol. 10, no. 6, pp. 1345-1356. Available from: doi: 10.1016/s0889-8588(05)70405-6 [Accessed 4th August 2024].

[69] Soliman, A. T., Bererhi, H., Darwish, A., Alzalabani, M. M., Wali, Y. & Ansari, B. (1998). "Decreased bone mineral density in prepubertal children with sickle cell disease: correlation with growth parameters, degree of siderosis and secretion of growth factors". *Journal of Tropical Pediatrics.* [Online]. Vol. 44, no. 4, pp. 194-198. Available from: doi: 10.1093/tropej/44.4.194 [Accessed 12th August 2024].

[70] Teitelbaum, S. L. (2007). "Osteoclasts: what do they do and how do they do it?". *The American Journal of Pathology.* [Online]. Vol. 170, no. 2, pp. 427-435. Available from: doi: 10.2353/ajpath.2007.060834 [Accessed 13th August 2024].

[71] Umans, H., Haramati, N. & Flusser, G. (2000). "The diagnostic role of gadolinium enhanced MRI in distinguishing between acute medullary bone infarct and osteomyelitis". *Magnetic Resonance Imaging.* [Online]. Vol. 18, no. 3, pp. 255-262. Available from: doi: 10.1016/s0730-725x(99)00137-x [Accessed 14th August 2024].

[72] UpToDate. (17th May, 2024a) *Acute and chronic bone complications of sickle cell disease.* [Online]. Available from: https://www-uptodate-com.proxy.library.rcsi.ie/contents/acute-and-chronic-bone-complications-of-sickle-cell-disease?search=sickle%20cell%20disease%20spine%20osteonecrosis&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1 [Accessed 19th August 2024].

[73] UpToDate. (2nd July, 2024b) *Vertebral osteomyelitis in adults: Clinical manifestations and diagnosis.* [Online]. Available from: https://www-uptodate-com.proxy.library.rcsi.ie/contents/vertebral-osteomyelitis-in-adults-clinical-manifestations-and-

diagnosis?search=complications%20of%20spinal%20osteomyelitis&source=search_result&selectedTitle=1~65&usage_type=default&display_rank=1 [Accessed 13th August 2024].

[74] Vaishya, R., Agarwal, A. K., Edomwonyi, E. O. & Vijay, V. (2015). "Musculoskeletal Manifestations of Sickle Cell Disease: A Review". *Cureus.* [Online]. Vol. 7, no. 10, pp. e358. Available from: doi: 10.7759/cureus.358 [Accessed 6th August 2024].

[75] Vanderhave, K. L., Perkins, C. A., Scannell, B. & Brighton, B. K. (2018). "Orthopaedic Manifestations of Sickle Cell Disease". *Journal of the American Academy of Orthopaedic Surgeons.* [Online]. Vol. 26, no. 3, pp. 94-101. Available from: doi: 10.5435/JAAOS-D-16-00255 [Accessed 26th July 2024].

[76] VanderJagt, D. J., Bonnett, C., Okolo, S. N. & Glew, R. H. (2002). "Assessment of the bone status of Nigerian children and adolescents with sickle cell disease using calcaneal ultrasound and serum markers of bone metabolism". *Calcified Tissue International.* [Online]. Vol. 71, no. 2, pp. 133-140. Available from: doi: 10.1007/s00223-001-1107-x [Accessed 12th August 2024].

[77] Wautier, J. L. & Wautier, M. P. (2020). "Cellular and Molecular Aspects of Blood Cell-Endothelium Interactions in Vascular Disorders". *International Journal of Molecular Sciences.* [Online]. Vol. 21, no. 15. Available from: doi: 10.3390/ijms21155315 [Accessed 6th August 2024].

[78] William, R. R., Hussein, S. S., Jeans, W. D., Wali, Y. A. & Lamki, Z. A. (2000). "A prospective study of soft-tissue ultrasonography in sickle cell disease patients with suspected osteomyelitis". *Clinical Radiology.* [Online]. Vol. 55, no. 4, pp. 307-310. Available from: doi: 10.1053/crad.1999.0377 [Accessed 13th August 2024].

[79] Williams, H. J., Davies, A. M. & Chapman, S. (2004). "Bone within a bone". *Clinical Radiology.* [Online]. Vol. 59, no. 2, pp. 132-144. Available from: doi: 10.1016/s0009-9260(03)00337-4 [Accessed 8th August 2024].

[80] Young, W. F., Brown, D., Kendler, A. & Clements, D. (2002). "Delayed post-traumatic osteonecrosis of a vertebral body (Kummell's disease)". *Acta Orthopaedica Belgica.* [Online]. Vol. 68, no. 1, pp. 13-19. Available from: http://actaorthopaedica.be/assets/89/02-young-clements-.pdf [Accessed 15th August 2024].