

## Review Article

# Osteoarticular disorders in sickle cell disease

Syed Asif Hasan<sup>1\*</sup>, Mahmood Ahmad Boeisa<sup>2</sup>, Yazid Taha Alandunesi<sup>3</sup>,  
Abdulkarim Thumayl Alshammari<sup>4</sup>, Diyaa Hisham Calcattawi<sup>5</sup>, Hamed Arif Hejazi<sup>6</sup>,  
Nasser Mubarak Alshahrani<sup>7</sup>, Abdullah Saeed Alahmari<sup>8</sup>, Malak Hussain Alkishi<sup>9</sup>,  
Yussif Mohammed Alnawar<sup>10</sup>, Roaa Ali Alkanderi<sup>11</sup>

<sup>1</sup>Department of Orthopaedics, Sameera Medical Center, Jeddah, Saudi Arabia

<sup>2</sup>Department of Obstetrics and Gynecology, Maternity and Children Hospital, Mubarratz, Saudi Arabia

<sup>3</sup>College of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

<sup>4</sup>College of Medicine, Almaarefa Colleges, Riyadh, Saudi Arabia

<sup>5</sup>Department of Intensive Care Unit, Al Noor Specialist Hospital, Mecca, Saudi Arabia

<sup>6</sup>Department of Orthopaedics, Al Noor Specialist Hospital, Mecca, Saudi Arabia

<sup>7</sup>College of Medicine, King Khalid University, Abha, Saudi Arabia

<sup>8</sup>College of Medicine, Bisha University, Bisha, Saudi Arabia

<sup>9</sup>College of Medicine, Medical University of Lodz, Lodz, Poland

<sup>10</sup>Primary Healthcare Center, Ministry of Health, Medina, Saudi Arabia

<sup>11</sup>College of Medicine, Arabian Gulf University, Manama, Bahrain

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### \*Correspondence:

Dr. Syed Asif Hasan,

E-mail: [drasifhh@gmail.com](mailto:drasifhh@gmail.com)

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## ABSTRACT

Different organs can be affected secondary to sickle cell disease, including the central nervous system, kidneys, gastrointestinal tract, respiratory system, cardiovascular system, bone, and joints. This can lead to increased morbidity and mortality events among the affected patients. Osteoarticular complications represent a severe set of events for patients with sickle cell disease. These complications might include gouty, septic, juvenile, and erosive arthritis, dactylitis, bone infarction, and osteomyelitis. These are the most common complications reported in the literature, and some case reports even reported other types of complications that develop secondary to the previously mentioned ones. Adequate diagnosis might be challenging in some cases. Therefore, clinicians must be crucial in determining the appropriate clinical and radiographic manifestations. Treating these cases is also challenging. Consequently, clinicians should be aware of these complications to enhance the prognosis of the affected patients. Further research is needed for the standardization of the diagnostic and management approaches in these events.

**Keywords:** Osteoarticular, Arthritis, Septic, Sickle cell disease, Osteomyelitis, Bone infarction

## INTRODUCTION

Sickle cell disease is an inherited genetic disorder that is characterized by being autosomal recessive. Estimates from the United States indicate that it is the most commonly reported blood disorder, as it usually affects 90000 to 100000 patients across the country. Estimates also suggest that the condition's prevalence is higher

among African Americans, with an estimated incidence of 1 in 500. Hemoglobin S is characteristically present in up to 40% of cases with sickle cell trait (also known as carrier state or heterozygous form).<sup>1,2</sup>

On the other hand, reduced oxygen levels in the homozygous states of the disease significantly lead to the formation of sickle-shaped red blood cells. Accordingly,

the affected blood cells do not function at the standard needed quality, reducing oxygenation and tissue perfusion. This can affect normal body functions and lead to the development of various complications. Different organs can be affected, including the central nervous system, kidneys, gastrointestinal tract, respiratory system, cardiovascular system, bone, and joints.<sup>3</sup> This can lead to increased morbidity and mortality events among the affected patients. The present literature review aims to discuss the different osteoarticular complications that affect patients with sickle cell disease.

## LITERATURE REVIEW

This literature review is based on an extensive literature search in Medline, Cochrane, and EMBASE databases which was performed on 27<sup>th</sup> October 2021 using the medical subject headings (MeSH) or a combination of all possible related terms, according to the database. To avoid missing potential studies, a further manual search for papers was done through Google Scholar while the reference lists of the initially included papers. Papers discussing clinical features, diagnosis, and types of optic neuritis were screened for useful information. No limitations were posed on date, language, age of participants, or publication type.

## DISCUSSION

Different osteoarticular disorders were reported to occur in patients with sickle cell disease frequently. In the following section, we will discuss the most commonly reported forms of osteoarticular complications among patients with sickle cell disease, based on evidence from the relevant studies in the literature. Hospital admission is indicated for patients with sickle cell disease for different reasons, most commonly due to acute vaso-occlusive pain.<sup>4</sup> This has been demonstrated in the different young age groups. As a result of this hospital admission, patients usually receive various pain killers and opioids.<sup>5</sup>

### Arthritis

#### Overview

Estimates indicate that arthritis is a common condition in this setting. The disorder usually manifests in several forms, including inflammatory and non-inflammatory. Some of these manifestations might include osteomyelitis, gout, hyperuricemia, and bone infarction. These events can further progress into other more severe disorders, including bone erosions and the destruction of vital joint components.<sup>6</sup> Among patients with sickle cell disease, evidence also shows that synovitis might manifest together with joint destruction and evidence of plasma infiltration.<sup>7</sup> In such events, evidenced arthritis is characterized by being symmetrical in 60% of patients and polyarticular in 80% of the cases.<sup>8</sup> Besides, evidence shows that the condition usually lasts for >1 week, and larger joints of lower extremities are the most commonly

affected. Moreover, imaging might play a vital role in diagnosis since these modalities can detect remarkable findings. Some of potential findings include joint space narrowing, synovitis, bone erosions, and osteopenia.

#### Gouty arthritis

Although gouty arthritis has been reported in the literature, evidence shows that the incidence of this disorder is not common among patients with sickle cell disease. Different explanations were reported for the low frequency of gout among patients with sickle cell disease. One of these might be the thrombosis and congestion of the blood vessels secondary to sickling of the red blood cells. These events will intervene against the chemotactic function of leukocytes at the affected joints following the deposition of the pathological crystals. Furthermore, evidence indicates that the development of gouty attacks necessitates the presence of abundant amounts of polymorphonuclear cells.<sup>9</sup>

#### Septic arthritis

Estimates also indicate that although septic arthritis might manifest among patients with sickle cell disease, the incidence of these events is rare. If present, it is usually observed as monoarthritis.<sup>10</sup> In around 20% of the cases suffering from acute attacks, synovial effusion usually manifests. These events might be attributed to the reactions of synovial ischemia and bone infarcts secondary to sickle cell disease. Estimates also show that among pediatric patients with sickle cell disease, the prevalence of septic arthritis is 5%. However, it should be noted that the complication is less common among affected adults, with an estimated incidence of 0.3%. A previous retrospective investigation demonstrated that the prevalence of septic arthritis among their 2000 population with sickle cell disease was 3% only. Among these patients, most infections (61%) affected the hip joint, and 96% of the cases had positive cultures. Gram-negative bacteria and *Staphylococcus aureus* were the most commonly detected pathogens. Finally, 29% of these cases had a history of osteonecrosis.<sup>5</sup>

#### Erosive arthritis

Another rare complication reported among patients with sickle cell disease is erosive arthritis. It has been associated with the activation of phospholipase A2 and neutrophils. Furthermore, the pathology of the disorders influences the vascular endothelium, leading to the release of many adhesion molecules. Some of the reported factors include E-selectin and tissue factors, intercellular adhesion molecules, and vascular cell adhesion molecules.<sup>6</sup>

#### Juvenile arthritis

Finally, evidence shows that patients with sickle cell disease might develop attacks of juvenile arthritis that can

be diagnosed clinically and laboratory with positive antinuclear factors. However, this association is not adequately reported and comprehended among studies in literature.<sup>11</sup>

### **Dactylitis**

This condition is characterized by edema and pain to the dorsum of feet and hands or both. Therefore, it is usually called the hand-foot syndrome (Figure 1). Besides, it is generally associated with local erythema and increased temperature.<sup>12,13</sup> On histological examination, it has been evidenced that periosteal bone formation together with multiple areas of bone infarction is associated.<sup>12</sup> A previous retrospective investigation in the United States demonstrated that dactylitis was the first observed clinical manifestation for 55% of 16 children who have sickle cell disease. The authors furtherly estimated that the incidence of dactylitis among the included children was 12%.<sup>14</sup> The condition is usually self-limited and can last for 2 weeks. However, recurrence of the disease was reported. Leukocytosis and fever might be associated in severe cases. However, joint sequela is rarely observed. Therefore, clinicians must establish a differential diagnosis between dactylitis and similar conditions, including osteomyelitis and juvenile arthritis.<sup>13</sup>



**Figure 1: X-ray of hand-foot syndrome secondary to sickle cell disease.**

### **Bone infarction**

Estimates show that the prevalence of osteonecrosis among patients with sickle cell disease might be up to 10%.<sup>15,16</sup> In addition, the pathology of this condition has been reported to involve the entire epiphysis. This is unlike other causes of osteonecrosis, which usually cause focal pathological changes. Therefore, growth disturbances and proximal femoral deformities might be characteristics of osteonecrosis in affected children. This

has been furtherly associated with limb length discrepancies, coxa plana, coxa Magna, and short femoral neck.<sup>17,18</sup> Furthermore, no sufficient evidence was reported in the literature regarding the validity of a treatment modality that can prevent the progression of the disease.<sup>4</sup> Therefore, it is critical to detect osteonecrosis among these patients to intervene in the development of these complications adequately. In this context, a previous investigation suggested that elevated hemoglobin-to-hematocrit ratio might predict the disorder in asymptomatic patients with sickle cell disease.<sup>18</sup>

### **Osteomyelitis**

The incidence of osteomyelitis is low among patients with sickle cell disease. However, estimates indicate that the condition is still more prevalent in this population than in general. In addition, the development of osteomyelitis among patients with sickle cell disease has been reported more frequently than in other patients from the general population. This has been attributed to the potential disruption of the blood flow, resulting from the occlusion of small blood vessels. This can lead to the development of ischemic areas that support bacterial contamination and growth, in addition to the poor immune response secondary to these events. Multifocal infections can also be a characteristic of osteomyelitis in patients with sickle cell disease.<sup>4</sup> Complications of osteomyelitis were also reported to be common among adults. Some of these complications include chronicity, pathological fractures, osteonecrosis, and adhesive pericapsulitis.<sup>19</sup> Therefore, these cases should be early and promptly managed to enhance the prognosis.

Accordingly, the management of osteomyelitis should be initially aimed to fix these conditions and enhance immune response. In addition, parenteral antibiotic therapy is indicated for up to 8 weeks following surgical decompression of the abscess. Besides, the management of sickle cell disease is vital to intervene in the development of future episodes. Therefore, a multidisciplinary team should conduct the management to provide the necessary care and achieve optimal management. Coordinated care is also recommended in these events to perform surgical interventions, bone aspiration, and imaging modalities required for treatment and follow-up of these cases. In cases of resistance to the routine management approaches, imaging and cultures should be conducted. In most cases, cultures are positive for *Salmonella* and *Staphylococcus aureus*.<sup>19</sup>

### **Differentiating osteomyelitis from bone infarction**

It should be noted that clinicians might find it difficult to differentiate between acute osteomyelitis and bone infarction because of the similar clinical presentations of these conditions for patients with sickle cell diseases. Acute musculoskeletal pain might be a unique characteristic of bone infarction among children.<sup>20</sup> Estimates show that the likelihood of having this

condition in this regard is 20 times higher than being diagnosed with osteomyelitis.<sup>21</sup> Bone infarction develops in patients with sickle cell disease due to vessel occlusion by sickled red blood cells.<sup>21,22</sup> The onset of the manifestations is usually acute, which might be associated with pain and swelling of the affected extremities. Reduced mobility, local erythema, and warmth might also be associated manifestations.

Many approaches have been proposed in the literature to differentiate between osteomyelitis and bone infarctions. Besides, the treatment of both of these conditions is remarkably different. Therefore, efforts should be integrated to establish a proper diagnosis to achieve the best prognosis. Furthermore, fever is not a common manifestation in cases of bone infarction, and inflammatory mediators are rarely elevated in the affected patients. In general, evidence shows that patients with osteomyelitis are more severely ill than patients with bone infarction. A thorough clinical and physical examination can remarkably distinguish between the two conditions necessary to decide the proper treatment plan. A previous investigation aimed to differentiate between osteomyelitis and bone infarction using different clinical parameters. The authors demonstrated that having a fever >38.2°C and longer pain duration were indicators of osteomyelitis.<sup>23</sup> Infection was also indicated when patients reported pain at multiple regions in their bodies. Radiographic findings are not well-established in both conditions, and therefore, they are of limited value for differentiating between them. Plain radiographs usually show swelling to the underlying soft tissues during the early phases. After 2 weeks, periosteal reactions can be detected. However, modality is still of limited value and can poorly differentiate between infarction and osteomyelitis.<sup>24</sup> As result, conducting gallium Ga-67 citrate scintigraphy and Tc-99m can add to diagnostic value when clinical parameters fail to indicate diagnosis. It might also be difficult to differentiate osteomyelitis from medullary infarcts in acute attacks (Figure 2).<sup>25,26</sup>



**Figure 2: Posteroanterior chest radiograph of the effects of intramedullary hyperplasia and stage II avascular necrosis.<sup>31</sup>**

Recent investigations support that bone scan should be combined with radionuclide bone marrow scanning to differentiate between osteomyelitis and bone infarction.<sup>27</sup> For a proper diagnosis of osteomyelitis, evidence indicates that gadolinium-enhanced MRI is preferably used in these settings.<sup>25</sup> This has been indicated in a previous investigation that included 35 patients with sickle cell disease. It has been estimated that the sensitivity and specificity of MRI were 92% and 96%, respectively.<sup>28</sup> Another investigation also indicated that contrast material MRI could effectively differentiate osteomyelitis from bone infarction.<sup>29</sup> Supportive management is the treatment of choice for bone infarctions, aiming to achieve adequate hydration and good analgesia. However, it should be noted that the administration of antibiotics can be indicated in cases until osteomyelitis has been excluded.<sup>30</sup>

## CONCLUSION

Osteoarticular complications represent a severe set of events for patients with sickle cell disease. These complications might include gouty, septic, juvenile, and erosive arthritis, dactylitis, bone infarction, and osteomyelitis. Adequate diagnosis might be challenging in some cases. Therefore, clinicians must be crucial in determining the appropriate clinical and radiographic manifestations. Treating these cases is also challenging. Consequently, clinicians should be aware of these complications to enhance the prognosis of the affected patients. Further research is needed for the standardization of the diagnostic and management approaches in these events.

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