Revista Eletrônica
Acervo Saúde
Electronic Journal Collection Health ISSN 2178-2091

Orofacial manifestations associated with sickle cell anemia

Manifestações orofaciais associadas à anemia falciforme

Manifestaciones orofaciales asociadas a la anemia falciforme

Adriana Gomes Rocha Bastos[1], Karina Mara Martins da Costa Pinto[1], Cíntia Gonçalves Vimercati Ferreira Pinto[1], Patrícia Rebouças de Souza Barros[1], Marco Orsini[2], Dennis de Carvalho Ferreira[1,3], Vera Lúcia Duarte da Costa Mendes[4], Luciana Armada Dias[1,2].

ABSTRACT

Objective: Review the main orofacial manifestations commonly associated with Sickle Cell Anemia (SCA), emphasizing the clinical and radiographic characteristics of these changes, their pathophysiology, and their relationship with systemic complications**. Bibliographic review:** Sickle cell disease (SCD) is a term used to describe a group of hereditary hematological disorders characterized by sickling of the erythrocytes. Several factors associated with the disease increase susceptibility to changes in oral tissues. This study aimed to review the main orofacial manifestations commonly associated with Sickle Cell Anemia (SCA), emphasizing the clinical and radiographic characteristics of these changes, their pathophysiology, and their relationship with systemic complications. **Final considerations:** It is concluded that several factors associated with SCA can influence the development of some oral manifestations, directly impacting oral health and quality of life. Therefore, it is essential that the dentist knows these clinical, pathophysiological and radiographic characteristics for the correct management and approach of patients with sickle cell anemia.

Keywords: Hemolysis, Orofacial manifestations, Sickle cell anemia, Vaso-occlusive crisis.

RESUMO

Objetivo: Revisar as principais manifestações orofaciais comumente associadas à anemia falciforme (AF), enfatizando as características clínicas e radiográficas dessas alterações, sua fisiopatologia e sua relação com complicações sistêmicas. **Revisão Bibliográfica:** A doença falciforme (DF) é um termo usado para descrever um grupo de distúrbios hematológicos hereditários caracterizados pela falcização dos eritrócitos. Vários fatores associados à doença aumentam a suscetibilidade a alterações nos tecidos orais. **Considerações Finais:** Conclui-se que vários fatores associados à AF podem influenciar no desenvolvimento de algumas manifestações orais, impactando diretamente na saúde bucal e na qualidade de vida. Assim, é fundamental que o cirurgião-dentista conheça essas características clínicas, fisiopatológicas e radiográficas para o correto manejo e abordagem do paciente com anemia falciforme.

Palavras-chave: Hemólise, Manifestações orofaciais, Anemia falciforme, Crise vaso-oclusiva.

RESUMEN

Objetivo: Revisar las principales manifestaciones orofaciales comúnmente asociadas con la anemia falciforme (AF), enfatizando las características clínicas y radiográficas de estos cambios, su fisiopatología y

[1] Programa de Pós-graduação em Odontologia, Universidade Estácio de Sá, Rio de Janeiro- RJ.
[2] Programa de Pós-graduação em Vigilância em Saúde, Universidade Iguaçu, Nova Iguaçu- RJ.
[3] Faculdade de Enfermagem, Universidade Estadual do Rio de Janeiro, Rio de Janeiro- RJ.
[4] Hemorio, Rio de Janeiro- RJ.

SUBMETIDO EM: 2/2025 | ACEITO EM: 2/2025 | PUBLICADO EM: 5/2025

su relación con las complicaciones sistémicas. **Revisión bibliográfica:** La enfermedad falciforme (EF) es un término utilizado para describir un grupo de trastornos hematológicos hereditarios caracterizados por la falcización de los eritrocitos. Varios factores asociados con la enfermedad aumentan la susceptibilidad a cambios en los tejidos orales. Este estudio tuvo como objetivo revisar las principales manifestaciones orofaciales comúnmente asociadas con la anemia falciforme (AF), enfatizando las características clínicas y radiográficas de estos cambios, su fisiopatología y su relación con las complicaciones sistémicas. **Consideraciones finales:** Se concluye que varios factores asociados a la anemia falciforme pueden influir en el desarrollo de ciertas manifestaciones orales, impactando directamente la salud bucal y la calidad de vida. Por lo tanto, es fundamental que el odontólogo conozca estas características clínicas, fisiopatológicas y radiográficas para el manejo y abordaje adecuado de los pacientes con anemia falciforme.

Palabras clave: Hemólisis, Manifestaciones orofaciales, Anemia falciforme, Crisis vaso-oclusiva.

INTRODUCTION

Sickle cell disease (SCD) is a term used to describe a group of hereditary hematological disorders characterized by sickling of the erythrocytes. The pathophysiology of the disease consists of a genetic mutation of the Hemoglobin (Hb) molecule that leads to the production of a modified Hb, called S (MANDAL AK, et al., 2020; CHEKROUN M, et al., 2019)

According to the World Health Organization (WHO), approximately 300,000 to 500,000 children are born with SCD annually (MCCAVIT TL,2012). In Brazil, the distribution of this disorder by region is not homogeneous. According to data from the Ministry of Health (2014), the North and Northeast regions have a prevalence of 6% to 10%, while in the South and Southeast, this rate varies from 2% to 3%, with greater evidence in the states of Salvador, Rio de Janeiro, Minas Gerais, and São Paulo (MINISTÉRIO DA SAÚDE DO BRASIL, 2014). Given the above, SCD is treated as a public health issue in Brazil, due to its high prevalence in the population and morbidity and mortality (MINISTÉRIO DA SAÚDE DO BRASIL, 2015).

Sickle cell anemia (SCA) is characterized by homozygosity of HbS (HbSS) and is the most severe and prevalent form of the SCD group. It results from a genetic mutation in the β chain of normal hemoglobin (HbA) due to the substitution of glutamic acid for valine that leads to the production of modified hemoglobin (HbS) (COSTA SA, et al., 2023; SOUZA SFC, et al.,2018). Under hypoxic conditions, biochemical changes in the Hb molecule trigger changes in the red blood cells, giving rise to sickle-shaped cells. Consequently, these sickle cells become less flexible and more adherent to the vascular endothelium, blocking the capillaries and restricting blood flow to various organs and systems. These vaso-occlusive events result in ischemia, infarction, and tissue damage, which can lead to significant systemic complications, such as changes in various organs, pain crises, stroke, acute chest syndrome, splenic sequestration, avascular bone necrosis, osteoporosis, and high susceptibility to infections (SOUZA SFC, et al.,2018).

Various factors associated with SCA increase susceptibility to changes in oral tissues (COSTA SA, et al., 2023). The most frequent oral manifestations are not pathognomonic signs of the disease but may suggest it. Orofacial complications are directly influenced by socioeconomic status (REES DC, et al.,2022), oral hygiene, and eating habits (KAWAR N, et al., 2018; JAVED F, et al.,2013).

Sickle cell anemia is a genetic disease that particularly requires complex treatment. The dental surgeon must understand the most important aspects of the disease since SCA patients require specific care and regular monitoring (CHEKROUN M, et al., 2019).

This study aimed to review the main orofacial manifestations commonly associated with SCA, emphasizing the clinical and radiographic characteristics of these changes, their pathophysiology, and their relationship with systemic complications.

BIBLIOGRAPHIC REVIEW

Soft tissue manifestations: oral mucosa and tongue

According to some studies, the most common intraoral manifestation associated with SCA is mucosal pallor (KAKKAR M, et al., 2021; KAWAR N, et al.,2018) resulting from the premature destruction of erythrocytes in

the spleen and, consequently, the low number of these cells in the blood vessels, leading to hemolytic anemia and hyperbilirubinemia (KAKKAR M, et al., 2021). The oral mucosa is pale and yellowish due to reduced oxygen saturation (KAKKAR M, et al., 2021; KAWAR N, et al., 2018). This is seen on the buccal mucosa, lips, and gums (KAKKAR M, et al., 2021; KAWAR N, et al., 2018). These patients also have changes in the surface cells of the tongue (JAVED F, et al.,2013), such as papillary atrophy, which can cause changes in taste (CHEKROUN M, et al.,2019). Another change is pale glossitis (MENDES PHC, et al., 2011).

Dental alterations

Late tooth eruption has been reported in sickle cell anemia patients (GIRGIS S, et al., 2021; KAWAR N, et al., 2018; MENDES PHC, et al., 2011). Patients with these hematological disorders can develop some dental anomalies, such as agenesis (GIRGIS S, et al., 2021); hypomineralization, and hypomaturation of enamel and dentin are common (KAKKAR M, et al., 2021; KAWAR N, et al., 2018; LOPES CMI, et al., 2018; TAYLOR LB, et al., 1995).

The study conducted by Fukuda JT, et al. (2005) compared the prevalence of Streptococcus mutans and dental caries in SCA patients undergoing long-term prophylactic treatment with penicillin and healthy individuals. However, this benefit only occurs during the active administration of the drug (FUKUDA JT, et al., 2005).

Studies on the prevalence of dental caries in SCA patients are conflicting. However, Kawar N, et al. (2018) added that the oral health care is more significant for developing of dental caries than factors related to SCA (KAWAR N, et al., 2018).

Dental radiographic changes involving the pulp cavity and root surface have also been commonly observed in sickle cell patients. These include pulp calcification (COSTA SA, et al., 2023; COSTA CPS, et al., 2021; SOUZA SFC, et al., 2018; SONI NN et al., 1996; TAYLOR LB, et al.,1995), hypotaurodontism, (CARVALHO HLCC, et al.,2017), hypercementosis (COSTA CPS, et al.,2021; SONI NN et al., 1996), and external root resorption (SOUZA SFC, et al., 2018).

The vaso-occlusive crises observed in SCA are considered the main risk factors for developing these pulp changes (COSTA SA, et al.,2023). These results in tissue hypoxia and, consequently, may occur the differentiation of dental pulp cells into the odontoblastic layer, and the deposition of mineralized tissue (SOUZA SFC, et al.,2017; LI L, et al.,2011). Through periapical radiographs, Souza SFC, et al. (2018) showed that SCA individuals had a higher frequency of calcified dental pulp. Literature also reported that the development of tooth resorption is related to a greater propensity to infections in sickle cell individuals and favors inflammatory mechanisms associated with the destruction of dental tissues by biochemical factors (SOUZA SFC, et al., 2018).

Pulp Necrosis

Several studies have reported the occurrence of pulp necrosis in clinically intact permanent teeth in SCA patients (KAKKAR M, et al., 2021; COSTA CPS, et al., 2021; GIRGIS S, et al., 2021; COSTA CPS, et al., 2020; CHEKROUN M, et al., 2019; JAVED F, et al., 2013; ANDREWS CH, et al., 1983). The narrative review by Kakkar M, et al. (2021) reports that pulp tissue necrosis can be symptomatic or asymptomatic, without any signs of odontogenic pathology in an apparently healthy tooth (KAKKAR M, et al., 2021). The probable etiology refers to the formation of microthrombi made up of sickle cells that block the microcirculation of the pulp, which leads to the development of tissue ischemia and hypoxia. This condition can cause avascular necrosis with the possible development of periapical disease (COSTA CPS, et al., 2020; CHEKROUN M, et al., 2019; COSTA CPS, et al., 2013; JAVED F, et al., 2013; ANDREWS CH, et al., 1983).

In their study, Kaya AD, et al. (2004) noted that after applying pulp sensitivity tests to 827 teeth of 36 patients with this disorder, pulp necrosis occurred in 6% of the sample. The authors also reported that 83% of these patients had orofacial or dental pain with no apparent cause (KAYA AD, et al., 2004). Also, the descriptive, cross-sectional study by Ferreira SBP, et al. (2016), evaluating the relationship between SCA and endodontic diseases based on clinical and radiographic criteria, detected a 10.2% rate of necrotic teeth in these patients (FERREIRA SBP, et al., 2016).

The biological plausibility of the increase in intercurrences may lie in the propensity of the pro-inflammatory profile, as seen in the evaluation of IFN-γ, TNF-α, and IL-1β of sickle cell patients in the presence of apical periodontitis (FERREIRA SBP, et al., 2015). A significant difference was also seen in the count of eosinophils and atypical lymphocytes when the sickle cell patient needed endodontic treatment (FERREIRA SBP, et al., 2016). The systemic impact was assessed through the recurrence of hospitalizations of sickle cell patients with or without the need for endodontic or periodontal treatment.

Periodontal disease

Studies on periodontal disease (PD) in patients with SCA are controversial. Some studies point to a greater susceptibility to periodontal inflammatory conditions in sickle cell patients (JAVED F, et al.,2013; MAHMOUD MO, et al., 2013). SCD patients often show an exacerbated inflammatory response, which intensifies the reaction of periodontal tissues to the minimal amount of dental plaque, making them more likely to develop gingivitis and PD (KAWAR N, et al., 2018). The study by Mahmoud MO, et al. (2013), when investigating the association between periodontal disease and SCA, showed a significantly higher prevalence of inflamed periodontium in SCA children compared to a population without the disease. They also showed a significant association between the intensity of gingival inflammation and the severity of SCA (MAHMOUD MO, et al., 2013).

On the other hand, some studies show no association between PD and SCA. In the study carried out by Arowojolu MO and SavageKO (1997), the authors measured the alveolar bone level of patients with and without PD using periapical radiographs. The results showed that there was no significantly greater bone loss in the group with the disease (AROWOJOLU MO andSAVAGE KO,1997). Passos CP, et al. (2012) studied sickle cell patients and reported greater pocket depth due to the patient's advanced age and lack of daily flossing, highlighting that these factors are more aggravating to PD than SCA (PASSOS CP, et al., 2012).

CarvalhoHLCC, et al. (2016) investigated the association between SCA and PD by evaluating some clinical and radiographic exams. They showed that none of the periodontal parameters evaluated were associated with SCA (CARVALHO HLCC, et al.,2016). Fernandes MLMF et al. (2015) reported that SCD adolescents had more gingival bleeding when compared to adolescents without the disease. However, this finding was associated with poor hygiene habits (FERNANDES MLMF, et al.,2015). According to the results of the works by KawarN, et al. (2018) and HsuLL and Fan-hsu J (2020), socio-behavioral factors are more relevant to the severity of PD than PD itself (HSU LL and FAN-HSU J, 2020; KAWAR N, et al., 2018).

Bone alterations

Bone involvement is the most common oral manifestation associated with sickle cell hemoglobinopathy (SOUZA SFC, et al., 2018). It has a multifactorial etiology including compensatory bone marrow hyperplasia in response to chronic hemolysis, vaso-occlusive phenomena, nutritional deficiencies of vitamin D, calcium, zinc, and iron overload (COSTA SA, et al., 2023). There is also an association with the maxillary expansion and protrusion commonly found in these patients (MENKA KF, et al., 2021; HSU LL and FAN-HSU J,2020; CARVALHO HLCC, et al., 2017).

In general, the main bone manifestations observed in the mandible of SCA patients can be classified as osteomyelitis due to infections; radiopaque lesions associated with previous vaso-occlusive phenomena and infarcts; and regions with a generalized osteoporotic appearance due to bone marrow hyperplasia (CHEKROUN M, et al.,2019).

According to the literature, intravascular sickling may trigger obstruction of blood flow. Vascular involvement can lead to ischemic infarction and consequently bone necrosis, favoring the creation of an environment conducive to bacterial proliferation, resulting in tissue that is particularly susceptible to infection, thus characterizing the development of osteomyelitis (CHEKROUN M, et al., 2019; KAWAR N, et al., 2018; COSTA CPS, et al., 2013; PATTON LL, et al., 1990; ANDREWS CH, et al., 1983). Initially, the radiographic appearance of a bone infarction due to vaso-occlusive phenomena is similar to osteomyelitis. Therefore, the differential diagnosis cannot be made using conventional radiographs alone but must be associated with clinical and laboratory evidence (CHEKROUN M, et al., 2019; KAVADIA-TSATALA S, et al., 2004).

The clinical characteristics of a bone infarction are associated with symptoms of varying severity and the absence of edema or marked erythema. On the other hand, a patient with osteomyelitis usually shows typical signs of infection, such as pain, edema, fever, leukocytosis, suppuration, and exposure of the alveolar bone (KAWAR N, et al., 2018; JAVED F, et al., 2013; KAVADIA-TSATALA S, et al., 2004). These osteomyelitis lesions are commonly found in the mandible, due to its relatively precarious blood supply (KAWAR N, et al., 2018; JAVED F, et al., 2013; KAYA AD, et al., 2004; TAYLOR LB, et al., 1995; SHROYER JV, et al., 1991; PATTON LL, et al., 1990; ANDREWS CH, et al., 1983), particularly involving its posterior region (TAYLOR LB, et al., 1995). The radiographic evaluation shows lesions with large bone sequestrations (JAVED F, et al.,2013). The studies by PattonLL, et al. (1990) and Shroyer JV, et al. (1991) report that osteomyelitis is hundreds of times more frequent in patients with SCA than in the rest of the population (SHROYER JV, et al., 1991; PATTON LL, et al., 1990).

PattonLL, et al. (1990) described a case of mandibular osteomyelitis in a SCA patient, with subsequent development of paresthesia of the mentual nerve. They also added that this infection can potentially precipitate a sickle cell crisis.

The study by Kavadia-tsatala S, et al. (2004) through the radiographic evaluation of patients with SCA observed radiopaque lesions located in the posterior region of the mandible, preferably along the vascular canals or apical regions of the teeth. According to the authors, these radiopacities are related to the formation of sclerotic bone, which characterizes the healing of a previous vaso-occlusive event. The Acharya S (2015) study, using radiographs, confirmed a higher prevalence of osteopathic regions characterized by increased medullary spaces and decreased bone density in SCA patients. Radiographically, these changes appear as radiolucent lesions usually seen between the apices of the posterior teeth and the lower mandibular margin.

The studies by TaylorLB, et al. (1995), Kavadia-tsatala S, et al. (2004), Kaya AD, et al. (2004), Acharya S (2015), Carvalho HLCC et al. (2017), Souza SFC, et al. (2018), and Costa et al. (2023) reported a high prevalence of "ladder-like" trabecular changes in SCA individuals.

These changes may present as prominent horizontal rows, generally located in the body of the mandible between the apical regions of the teeth and the alveolar bone crest (SOUZA SFC, et al., 2018; ACHARYA S, 2015; KAYA AD, et al., 2004; KAVADIA-TSATALA S, et al., 2004; TAYLOR LB, et al., 1995).

Extramedullary hematopoiesis has been documented in various chronic anemia conditions, including SCA. It is seen as a compensatory mechanism in the face of a need to increase blood production, commonly occurring in the liver and spleen. However, it has been documented in the paranasal sinuses, particularly the maxillae (SAITO N, et al., 2010; COLLINS WO et al., 2005).

FINAL CONSIDERATIONS

Several factors associated with SCA, such as erythrocyte sickling, hyperhemolysis, and vaso-occlusive episodes, may influence the development of some oral manifestations. Therefore, it is strongly suggested that sickle cell individuals are more susceptible to changes in oral tissues, particularly pulp and bone. Given the peculiarities of this disease, the dental surgeon needs to know the clinical and radiographic characteristics of these changes, the understanding of their pathophysiology, and the relationship with systemic complications, broadening the contribution of dentistry in the approach to patients with sickle cell disease. Analyzing this possible correlation can help professionals establish a prognosis and influence treatment decisions since oral health status can have a major impact on the general health and quality of life of these individuals.

REFERÊNCIAS

1. ACHARYA S, et al. Oral and dental considerations in the management of sickle cell anemia. Int J Clin Pediatr Dent. 2015;8(2):141-144.
2. ANDREWS CH, et al. Sickle cell anemia: an etiological factor in pulpal necrosis. J Endod. 1983;9(6):249-252.
3. AROWOJOLU MO, SAVAGE KO. Alveolar bone patterns in sickle cell anemia and non-sickle cell anemia adolescent Nigerians: a comparative study. J Periodontol. 1997;68(3): 225-228.

4. CARVALHO HLCC, et al. Are sickle cell anaemia and sickle cell trait predictive factors for periodontal disease? A cohortstudy. J Periodontal Res. 2016;51(5):622-629.
5. CARVALHO HLCC, et al. Are dental and jaw changes more prevalent in a Brazilian population with sickle cell anemia? Oral Surg Oral Med Oral Pathol Oral Radiol. 2017;124(1):76-84.
6. CHEKROUN M, et al. Oral manifestations of sickle cell disease. Br Dent J. 2019;226(1):27-31.
7. COLLINS WO, et al. Extramedullary hematopoiesis of the paranasal sinuses in sickle cell disease. Otolaryngol Head Neck Surg 2005;132(6):954–956.
8. COSTA CPS, et al. Association between sickle cell anemia and pulp necrosis. J Endod. 2013;39(2):177–181.
9. COSTA CPS, et al. Biological factors associating pulp necrosis and sickle cell anemia. Oral Dis. 2020;26(7):1558-1565.
10. COSTA CPS, et al. Is there bacterial infection in the intact crowns of teeth with pulp necrosis of sickle cell anaemia patients? A case series study nested in a cohort. Int Endod J. 2021;54(6):817-825.
11. COSTA SA, et al. Mechanisms underlying the adaptive pulp and jaw bone trabecular changes in sickle cell anemia. Oral Dis. 2023;29(2):786-795.
12. FERNANDES MLMF, et al. Caries prevalence and impact on oral health-related quality of life in children with sickle cell disease: cross-sectional study. BMC Oral Health. 2015;18:15:68.
13. FERREIRA SBP, et al. Periapical cytokine expression in sickle cell disease. J Endod. 2015;41(3):358-362.
14. FERREIRA SBP, et al. Sickle cell anemia in Brazil: personal, medical and endodontic patterns. Braz Oral Res. 2016;30(1):S1806-83242016000100255.
15. FUKUDA JT, et al. Acquisition of mutans streptococci and caries prevalence in pediatric sickle cell anemia patients receiving long-term antibiotic therapy. Pediatr Dent. 2005;27(3):186-190.
16. GIRGIS S, et al. Orofacial manifestations of sickle cell disease: implications for dental clinicians. Br Dent J. 2021;230(3):143-147.
17. HONG L, et al. Association between enamel hypoplasia and dental caries in primary second molars: a cohort study. Caries Res. 2009;43:345-353.
18. HSU LL, FAN-HSU J. Evidence-based dental management in the new era of sickle cell disease: A scoping review. J AmDent Assoc. 2020;151(9):668-677.
19. ITO K, et al. Hypoxic condition promotes differentiation and mineralization of dental pulp cells in vivo. Int Endod J. 2014;48(2):115-123.
20. JAVED F, et al. Orofacial manifestations in patients with sickle cell disease. Am J Med Sci 2013;345(3):234–237.
21. KAKKAR M, et al. Orofacial manifestation and dental management of sickle cell disease: A scoping review. Anemia. 2021:5556708.
22. KAVADIA-TSATALA S, et al. Mandibular lesions of vasoclusive origin in sickle cell hemoglobinopathy. Odontology. 2004;92(1):68-72.
23. KAWAR N, et al. Sickle cell disease: An overview of orofacial and dental manifestations. Dis Mon. 2018;64(6):290-295.
24. KAYA AD, et al. Pupal necrosis witch sickle cell anaemia. Int Endod J. 2004;37(9): 602-606.
25. KELLEHER M, et al. Oral complications associated with sickle cell anemia: a review and case report. Oral Surg Oral Med Oral Pathol Oral RadiolEndod. 1996;82(2):225-228.
26. LI L, et al. Hypoxia promotes mineralization of human dental pulp cells. J Endod. 2011;37(6):799–802.
27. LOPES CMI, et al. Enamel defects and tooth eruption disturbances in children with sickle cell anemia. Braz Oral Res. 2018;13;32:e87.
28. LOPES CMI, et al. Occlusal disorders in patients with sickle cell disease: Critical literature review. J Clin Pediatr Dent. 2021;45(2):117-122.
29. MAHMOUD MO, et al. Associations between sickle cell anemia and periodontal diseases among 12- to 16-year-old Sudanese children. Oral Health Prev Dent. 2013;11(4):375–381.
30. MANDAL AK, et al. Sickle cell hemoglobin. SubcellBiochem. 2020;94:297-322.
31. MCCAVIT, TL. Sickle cell disease. Pediatr Rev. 2012;33(5):195-206.
32. MENDES PHC, et al. Orofacial manifestations in patients with sickle cell anaemia. Quintessence Int. 2011;42(8):701-709.
33. MENKA K, et al. Analyzing effects of sickle cell disease on morphometric and cranial growth in Indian population. J Pharm Bioallied Sci. 2021;13(Suppl 2):S1402-S1405.
34. BRASIL. Manual doMinistério da Saúde Doença falciforme: saúde bucal: prevenção e cuidado. 2014. Disponível em:https://bvsms.saude.gov.br/bvs/publicacoes/doenca_falciforme_saude_bucal_prevencao.pdf
35. BRASIL. Manual do Ministério da Saúde Doença falciforme: conhecer para cuidar. 2015. Disponível em:https://bvsms.saude.gov.br/bvs/publicacoes/caderno_informacao_sangue_hemoderivados_5ed.pdf

36. PASSOS CP, et al. Sickle cell disease does not predispose to caries or periodontal disease. SpecCareDentist. 2012;32(2):55-60.
37. PATTON LL, et al. Mandibular osteomyelitis in a patient with sickle cell anemia: report of case. J Am Dent Assoc. 1990;121(5):602-604.
38. REES DC, et al. Determinants of severity in sickle cell disease. Blood Rev. 2022;56:100983
39. SAITO N, et al. Clinical and radiographic manifestations of sickle cell disease in the head and neck. RadioGraphics. 2010;30(4):1021-1034.]
40. SHROYER JV, et al. Osteomyelitis of the mandible as a result of sickle cell disease. Oral Surg Oral Med Oral Pathol. 1991;72(1):25-28.
41. SONI NN. Microradiographic study of dental tissues in sickle-cell anaemia. Arch Oral Biol. 1966;11(6):561-564
42. SOUZA SFC, et al. Association of sickle cell haemoglobinopathies with dental and jaw bone abnormalities. Oral Dis 2018;24(3):393-403.
43. SOUZA SFC, et al. Healthy dental pulp oxygen saturation rates in subjects with homozygous sickle cell anemia: A cross-sectional study nested in a cohort. J Endod. 2017;43(12):1997-2000.
44. TAYLOR LB, et al. Casamassimo PS. Sickle cell anemia: A review of the dental concerns and a retrospective study of dental and bony changes. Spec Care Dentist. 1995:15(1):38-42.
45. ZHANG D, et al. Neutrophils, platelets, and inflammatory pathways at the nexus of sickle cell disease pathophysiology. Blood. 2016;127(7):801-810.