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SICKLE CELL ANEMIA AND ITS IMPACT ON THE ORAL CAVITY: INTEGRATIVE REVIEW

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Introduction: Sickle cell anemia, a hereditary disease, results from a mutation in the β-globin coding gene that makes up hemoglobin, leading to the deformation of erythrocytes. Numerous oral manifestations result from this disease; however, some may not be specific.

Objectives: This study's objective is to recognize these clinical manifestations of the disease to be able to manage oral health in sickle cell anemia patients.

Methods: this integrative review analyzes scientific literature on the impact of sickle cell anemia on oral cavity. A bibliographic search was performed in PubMed, ScienceDirect, CINAHL Plus (via EBSCO host), Web of Science and Google Scholar databases using several combined keywords. The research question was: "What is the impact of sickle cell anemia on the oral cavity and dental treatments?".

Results: By applying the inclusion and exclusion criteria, 11 articles were included in this review.

Conclusions: Studies show that the most common oral manifestations in these patients are periodontal disease and caries, although this association is not well understood.

Keywords: Sickle cell disease, Oral manifestations, Dental treatments, Oral health, Correlation.

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The authors declare no conflicts of interest.

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LA DREPANOCYTOSE ET SON IMPACT SUR LA CAVITE ORALE: REVUE INTEGRATIVE

Introduction: La drépanocytose, maladie héréditaire, résulte d'une mutation du gène codant pour la β-globine qui compose l'hémoglobine, entraînant la déformation des érythrocytes. De nombreuses manifestations bucco-dentaires résultent de cette maladie, mais certaines peuvent ne pas être spécifiques.

Objectifs: Cette étude a pour but de reconnaître ces manifestations cliniques de la maladie pour pouvoir gérer la santé bucco-dentaire des patients atteints de drépanocytose.

Méthodes: cette revue intégrative analyse la littérature scientifique sur l'impact de la drépanocytose sur la cavité buccale. Une recherche bibliographique a été effectuée dans les bases de données PubMed, ScienceDirect, CINAHL Plus (via EBSCO host), Web of Science et Google Scholar, en utilisant plusieurs mots-clés combinés. La question de recherche était la suivante: "Quel est l'impact de la drépanocytose sur la cavité buccale et les traitements dentaires?

Résultats: En appliquant les critères d'inclusion et d'exclusion, 11 articles ont été inclus dans cette revue.

Conclusions: Les études montrent que les manifestations bucco-dentaires les plus courantes chez ces patients sont les maladies parodontales et les caries, bien que cette association ne soit pas bien comprise.

Mots-clés: Drépanocytose, Manifestations buccales, Traitements dentaires, Santé bucco-dentaire, Corrélation.

Introduction

Sickle cell anemia is defined as a chronic hematological disease of congenital origin that affects the entire body. It is characterized by several episodes of acute crises, caused by the constriction of blood vessels by thrombi [1].

Sickle cell anemia is caused by an alteration in the gene encoding the β-globin protein, a component of hemoglobin (Hb). This alteration leads to the formation of unstable and atypical Hb molecules, jeopardizing the transport of oxygen to the tissues. The presence of altered Hb also leads to an increase in blood viscosity [2].

In addition to the increase in blood viscosity, there is cellular polymerization capable of changing the original biconcave shape of the red blood cells into a sickle shape. These physical and functional aspects of the HbS molecules (S for Sickle) favor vaso-occlusive events in the body, which are capable of reducing blood flow. The organs and tissues most affected are those located at the extremities of the body or those that already have low blood nutrition, such as the spleen, feet and hands. So, considering that the whole body is vulnerable to the repercussions caused by the disease, the oral cavity can also be affected [3].

Numerous oral manifestations have been reported in patients with sickle cell anemia, and therefore it is important to be able to recognize these clinical manifestations and have a good knowledge of this pathology to help manage sickle cell anemia from an oral health perspective [4].

The attitude of neglecting oral health is frequent in individuals with sickle cell anemia. Medical communities, as well as patients, may not understand or be aware of the impact that poor oral health can have on hematological diseases. Thus, there is a tendency to prioritize other healthcare needs to the detriment of oral health [5]. Consequently, if the patient neglects their oral health, they are at greater risk of cavities and infections which can lead to the need for more complicated dental treatment and consequently a greater likelihood of a sickle cell crisis and emergency hospitalization.

The aim of this integrative review is therefore to analyze the existing scientific literature from the last eight years on the impact that sickle cell anemia has on the oral cavity, through the most common oral manifestations.

Sickle cell disease

Characterization

Sickle cell anemia is one of a group of haemoglobinopathies that result from mutations in the gene that codes for the ß-globin protein, a subunit of Hb. The first description of the disorder 'similar' to sickle cell anemia was provided by Dr Africanus Horton in his book 'The Disease of Tropical Climates and their Treatment'. However, it wasn't until 1910 that Dr James B Herrick and Dr Ernest Irons reported noticing sickle-shaped red blood cells in a dental student [6].

Sickle cell anemia, or drepanocytosis, is characterized by a point mutation, missense, in the HBB gene that determines the replacement of glutamic acid (Glu) in the sixth position of the β-globin chain with a valine (Val). The substitution of a hydrophilic Glu residue for a hydrophobic Val residue leads to the formation of a mutant Hb (HbS) (α2β2s) in erythrocytes with this condition [2, 7-9].

The detection of HbS and the diagnosis of sickle cell anemia depend on laboratory tests, which include a combination of biochemical and molecular tests to detect the HbS hemoglobin and confirm the diagnosis [10].

The diagnosis of sickle cell anemia is based on the analysis of the Hb molecule using various methods, which analyze the presence or absence of HbS, as well as the percentage of adult Hb (HbA), fetal Hb (HbF) and HbA2 that the erythrocytes have [11]. Currently, the methods used include blood count, HbS solubility testing, Hb electrophoresis, isoelectric focusing, high-performance liquid chromatography (HPLC) and genetic testing [10, 12].

Newborn screening programs are in place not only in several European countries, but also in the United States of America, India, Africa and Brazil [13]. In Portugal, in May 2021, the Instituto Nacional de Saúde Doutor Ricardo Jorge (INSA) began a pilot study for sickle cell anemia screening in Lisbon and Setúbal, which identified a prevalence of 1 positive case per 944 newborns. In February 2022, the INSA extended the pilot study to all health units in the country, with a view to assessing the real need to include sickle cell anemia in the National Neonatal Screening Program. In this way, it will be possible to compare the prevalence of sickle cell anemia at birth across the country [14].

Epidemiology and prevalence

Sickle cell anemia is a hematological disease that is estimated to affect around 3.2 million people all over the world. Every year, 176,000 people die from complications associated with this condition [2].

Every year, around 2,300,000 children are born with sickle cell anemia in sub-Saharan Africa, around 2,600 and 1,300 children in the United States of America and Europe respectively, and around 2,500 children in India. In the United States of America, France and the United Kingdom, more than 94% of children born with sickle cell anemia survive to adulthood. However, in sub-Saharan Africa, 50 to 90 per cent of children can die within the first five years of life [15].

Symptoms and clinical manifestations

The clinical manifestations of sickle cell anemia are very diverse.

Some patients live an almost normal life without crises, but others have severe crises, even in childhood. Generally, children with sickle cell anemia are asymptomatic until they are six months old, due to the presence of HbF [15, 16].

Painful vaso-occlusive crises are the most frequent clinical manifestations in patients with sickle cell anemia and occur due to the aforementioned vaso-occlusion phenomena. These crises can be sporadic and unpredictable or precipitated by infection, acidosis, dehydration or deoxygenation (such as changes in altitude, surgery or sudden physical exercise) [15].

In babies, the pain is associated with dactylitis, a diffuse edema of the fingers and/or toes resulting from vaso-occlusion. However, in older children and adults, the pain appears in the long bones of the extremities (humerus, tibia and femur), as well as in the chest and back [7,16]. There can be up to six episodes of painful vaso-occlusive crises per year, which persist for around five days [1, 12].

Acute thoracic syndrome (ATS) is characterized by fever and chest pain and the presence of pulmonary infiltrates on a chest X-ray. Hematologically, there is a sudden decrease in Hb and an increase in the number of platelets and leukocytes [12, 16]. ATS is often triggered by infections, embolic events and/or pulmonary vaso-occlusion [7].

Patients with sickle cell anemia are more likely to contract infections with *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Haemophilus influenzae*. Acute infections are the most common cause of hospitalizations in the first three years of life. Bacterial blood infections (septicemias) are exacerbated by the effect of auto splenectomy, as the spleen loses its ability to function as a secondary lymphoid tissue to eliminate microorganisms from the blood [12].

Hemolytic crises are common clinical manifestations in sickle cell anemia. These crises arise due to the sudden acceleration of the hemolytic process and a decrease in Hb, accompanied by an increase in reticulocytes and jaundice [12, 16, 17].

Aplastic crises are crises in which the bone marrow is temporarily suppressed. These crises are characterized by an abrupt drop in Hb and reticulocytes due to *Parvovirus* infection or folic acid deficiency [17]. Most aplastic crises are short-lived and do not require therapy, but if the anemia is severe and the bone marrow remains aplastic, transfusion will be necessary [12].

The risk of having a stroke is 10% in the first 20 years of life, with a peak incidence between 4 and 8 years of age. Most of these strokes are ischemic in nature, while hemorrhagic strokes account for less than 10% of all strokes that occur [9]. Risk factors include the homozygous HbSS genotype, previous transient ischemic attacks, low Hb concentrations, high white blood cell counts, increased systolic blood pressure and previous ATS [6].

Strokes can also occur, as can ulcers on the lower legs due to vascular stasis. In childhood, the spleen may suffer splenomegaly. Pulmonary hypertension is common. Proliferative retinopathy, priapism, liver and kidney damage are complications that can also occur in sickle cell anemia [17].

Impact on oral health

There are different oral manifestations of sickle cell anemia. However, most are not specific to the disease and can also be seen in other haemoglobinopathies. One of the most common manifestations of this pathology in the oral cavity is a consequence of chronic hemolytic anemia, which can present in the oral cavity as pallor and jaundice of the mucous membrane. Although most patients present with a generalized pallor of the entire mucosa of the oral cavity, some sites, such as the gums and the buccal and labial mucosa, are more noticeable than others [5, 18].

Changes in teeth eruption and dental anomalies

Delayed tooth eruption has been observed in children and adolescents with sickle cell anemia [19]. A 1.7% higher risk of delayed tooth eruption was found in children with sickle cell anemia compared to the healthy population [20]. The study by Pashine et al. [21] suggested that this delay in tooth eruption may be a consequence of disturbed bone formation and resorption patterns or may be attributable to systemic disorders and bone marrow hyperplasia.

Patients with sickle cell anemia appear to be at greater risk of dental malocclusion and skeletal anomalies. Malocclusion can lead to masticatory, swallowing, phonation and respiratory disorders, affecting patients' self-esteem and quality of life [22].

Some studies have reported dental anomalies in children and adolescents with sickle cell anemia, including enamel hypoplasia, enamel and dentin hypomineralization and hypercementosis [5, 23, 24]. These alterations are not pathognomonic for sickle cell anemia but have also been observed in other chronic diseases. Amelogenesis is a highly regulated process that can be influenced by pathological conditions such as fever, infection, changes in oxygen saturation or antibiotics [19].

Periodontal problems and oral infections

There is little information available on periodontal disease and, although a high incidence has been reported in patients with sickle cell anemia, the results are inconclusive as to whether there is an association [18]. However, this association seems to exist due to the fact that the density of trabecular bone is reduced by the pathology in heterozygous individuals, making them more susceptible to the consequences of periodontitis [25].

Infection is the most common triggering event for periodontitis in patients with sickle cell anemia, and

this infection can lead to subsequent worsening of periodontitis. Therefore, any dental infection must be eliminated and prevented, especially in these patients [8].

Dental infections can trigger a vaso-occlusive crisis, leading to a greater likelihood that the patient will require additional hospitalization to deal with the related complications [8, 22].

Materials and methods

A research protocol was established according to the Joanna Briggs Institute (JBI) model [26-28], which led to the formulation of the following question: What is the impact of sickle cell anemia on the oral cavity and dental treatments? Thus, the PICO acronym is described in Table 1.

To prepare this integrative review, a bibliographic search was carried out in PubMed, ScienceDirect, CINAHL Plus (via EBSCO host), Web of Science and Google Scholar databases with the aim of finding studies relating sickle cell anemia to changes in the oral cavity. The search was carried out using the following keywords: "*sickle cell disease*", "*anemia falciforme*", "*oral health*", "*oral cavity*", "*dental health*", "*stomatology*", "*dental care*", "*dental treatment*" and "*medical-dental management*", using Boolean operators "AND" e "OR".

The articles were selected using Rayyan after being retrieved from the aforementioned databases. For the final review, the items identified in the reports designed to guide systematic reviews and extend meta-analyses (PRISMA-ScR) were used. This protocol was registered with the OSF (https://osf.io/uwtch/).

Table 1. PICO strategy (Population, Intervention, Comparison, Outcome)

Population	Patients with sickle cell anemia
Intervention	Oral manifestations or disorders related to sickle cell anemia
Comparison	Patients without sickle cell anemia or without oral manifestations
Outcome	Impact on dental treatment outcomes and oral health status

Inclusion and exclusion criteria

Inclusion criteria: studies addressing the topic of this thesis carried out on humans; articles in English, French or Portuguese.

Exclusion criteria: articles that after reading the abstract did not present scientific content relevant to this review and articles in animals.

Search strategy

The search strategy was planned by two reviewers and revised by a third reviewer considering the Peer Review of Electronic Search Strategies (PRESS) checklist [29].

Table 2. Bibliographical research strategy

Database	Keyword articulation	Number of articles
PubMed	("sickle cell disease"[All Fields] OR "anemia falciforme"[All Fields]) AND ("Oral Health"[MeSH Terms] OR "oral cavity"[All Fields] OR "dental health"[All Fields] OR "stomatology"[All Fields]) AND ("Dental Care"[MeSH Terms] OR "dental treatment"[All Fields] OR "medical-dental management"[All Fields])	4
Science Direct	("sickle cell disease"[All Fields] OR "anemia falciforme"[All Fields]) AND ("Oral Health"[MeSH Terms] OR "oral cavity"[All Fields] OR "dental health"[All Fields] OR "stomatology"[All Fields]) AND ("Dental Care"[MeSH Terms] OR "dental treatment"[All Fields] OR "medical-dental management"[All Fields])	25
CINAHL Plus (via EBSCO host)	TI sickle cell disease OR AB sickle cell disease OR SU sickle cell disease OR TI anemia falciforme OR AB anemia falciforme OR SU anemia falciforme AND TI dental care OR AB dental care OR SU dental care OR TI dental treatment OR AB dental treatment OR SU dental treatment OR TI medical-dental management OR AB medical-dental management OR SU medical-dental management AND TI oral health OR AB oral health OR SU oral health OR TI oral cavity OR AB oral cavity OR SU oral cavity OR TI dental health OR AB dental health OR SU dental health OR TI stomatology OR AB stomatology OR SU stomatology	7
Web of Science	("sickle cell disease" OR "anemia falciforme") AND ("Oral Health" OR "oral cavity" OR "dental health" OR "stomatology") AND ("Dental Care" OR "dental treatment" OR "medical-dental management")	7
Google Scholar	("sickle cell disease" OR "anemia falciforme") AND ("Oral Health" OR "oral cavity" OR "dental health" OR "stomatology") AND ("Dental Care" OR "dental treatment" OR "medical-dental management")	1090

In this integrative review, the search was carried out in the following databases: PubMed, ScienceDirect, CINAHL Plus (via EBSCO host), Web of Science and Google Scholar. The search strategy recommended by JBI was implemented.

A preliminary search enabled the identification of keywords used in publications on this topic. This allowed the search strategy to be developed for each database (Table 2). This search was carried out on 25 February 2025.

The list of bibliographies of all the articles included was reviewed for the possibility of including additional articles.

After the search, the articles identified were deposited in the ENDNOTE program. The results of the electronic search were exported to Rayyan® [30] and duplicates eliminated. The software developer is Rayyan Systems Inc. of Cambridge, MA, USA. No AI-based software was used to select the articles. The Rayyan software was used as a support tool, only to collate all the articles found in the different databases described above and identify duplicates.

Selection, analysis and studies presentation

Two reviewers independently collated data from the articles to decide on their inclusion in this integrative review. Doubts and conflicts were discussed with a third reviewer according to the Peer Review of the Electronic Search Strategies (PRESS) checklist [29].

Each article to be included in this review was first analyzed by reading the title and abstract, and then by reading each article in its entirety. This methodology is represented in the Prisma Flowchart (Figure 1).

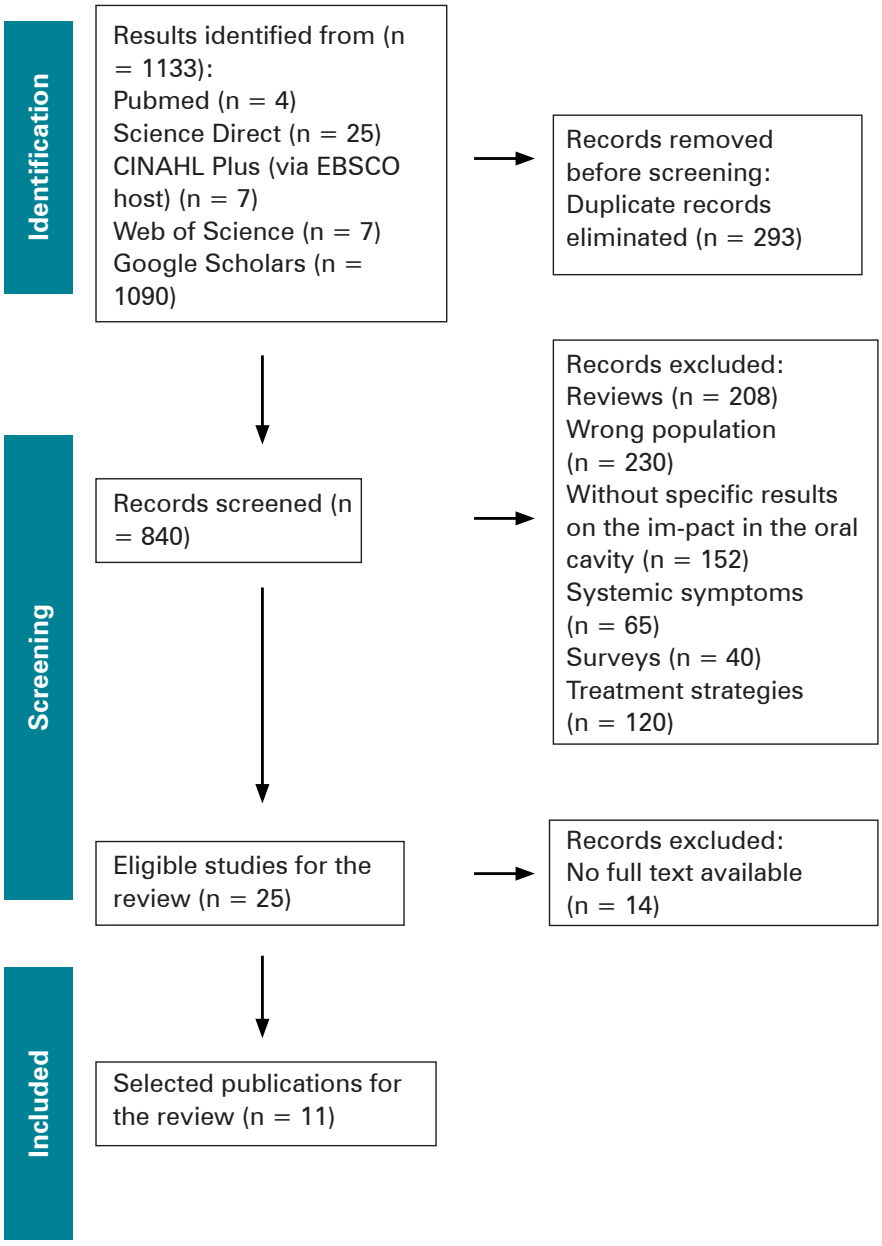

Figure 1. Graphical representation of the PRISMA diagram adapted from PRISMA 2000 flow diagram [31]

In the first phase, filters were applied to the search and full articles available online, resulting in a total of 1133 articles. Of these, 293 duplicates were identified and eliminated. The 840 articles obtained were initially screened only by reading the title and abstract, which led to the exclusion of 815. A total of 25 articles were selected for full reading, 14 of which were eliminated because no full text was available. At the end of this selection process, 11 articles were included in this integrative review (Figure 1).

Analysing Methodological Quality and Risk of Bias

The methodological quality of the studies included in this review was assessed using the JBI tool [32]. The JBI tool uses 4 domains, each of which can have between 8 and 11 questions.

The 4 domains assessed in the JBI tool are as follows:

1. Bias related to selection and allocation
2. Bias related to administration of intervention/exposure
3. Bias related to assessment, detection, and measurement of the outcome
4. Bias related to participant retention

The JBI tool was developed with the aim of assessing the methodological quality of scientific studies used in systematic and integrative reviews, ensuring the reliability and validity of the evidence. It consists of specific checklists tailored to different study designs, such as qualitative studies, quantitative studies (cohort, case-control, clinical trials, among others), mixed-methods studies, and case reports. These checklists guide the critical appraisal process, helping to identify potential risks of bias and assist in selecting robust evidence for clinical practice. In this way, the JBI tool makes a significant contribution to strengthening evidence-based practice in the healthcare field. This tool incorporates logical algorithms that directly link the answers to the signalling questions to standardised assessments, facilitating a systematic, reproducible and transparent application of the instrument. These answers are processed by an internal logic, which leads to a classification of the risk of bias in each domain. The possible judgements are low risk of bias; moderate and high risk of bias. The final synthesis follows these rules: If all the domains present low risk, the overall risk will be low risk of bias; if there is at least one domain with some concerns, the overall risk will be some concerns; if a single domain presents high risk or if there are multiple domains with some concerns, the overall risk will be high risk of bias.

Results

Eleven articles were included, 8 of which were cross-sectional studies (CSS), 1 cohort study (CS) and 2 case-control studies (CCS) (Tables 3 and 4).

Table 3. General information on the included studies

Author (year)	Title	Type of study	Journal
Makolo et al.	Dental tissues of sickle cell anemia and their impact on the quality of life related to oral health.	CS	*Hematology*
Ahmad et al.	The association between dental caries and salivary buffering capacity in Syrian patients diagnosed with sickle cell disease.	CCS	*Cureus*
Tonguç et al.	Investigation of the relationship between periodontal and systemic inflammation in children with sickle cell disease: A case-control study.	CCS	*Cytokine*
Minja et al.	Dental Caries in Children with Sickle Cell Disease and Its Association with the Use of Hydroxyurea and Penicillin Prophylaxis in Dar Es Salaam.	CSS	*Pediatric health, medicine and therapeutics*
Sari et al.	Association between periodontal inflamed surface area and serum acute phase biomarkers in patients with sickle cell anemia.	CSS	*Archives of Oral Biology*
Kowe et al.	Oral Health Status of Children with sickle Cells in Kinshasa	CSS	*Romanian Journal of Oral Rehabilitation*
Davidopoulou et al.	Aggravated Dental and Periodontal Status in Patients with Sickle Cell Disease and Its Association with Serum Ferritin.	CSS	*The journal of contemporary dental practice*
Pashine et al.	Craniofacial and occlusal features of children with sickle cell disease compared to normal standards: a clinical and radiographic study of 50 pediatric patients.	CSS	*European Archives of Paediatric Dentistry*
Kalbassi et al.	Comparative evaluation of oral and dento-maxillofacial manifestation of patients with sickle cell diseases and beta thalassemia major.	CSS	*Hematology*
Brandão et al.	Association between sickle cell disease and the oral health condition of children and adolescents.	CSS	*BMC oral health*
Basyouni et al.	Malocclusion and craniofacial characteristics in Saudi adolescents with sickle cell disease.	CSS	*Saudi Journal of Medicine & Medical Sciences*

CS: cohort study; CCS: case-control study; CSS: cross-sectional study

Table 4. General characteristics of the included studies (Continued)

Author (year)	Sample (Np/Nc) [age]	Results
Kowe et al.	194/ N/A [2 – 17]	- The prevalence of dental caries in patients with sickle cell anemia was 58.8% with a mean DMFT index of 2.39 ± 3.12, while 73.2% had moderate gingival inflammation. - The average plaque index was 1.46 ± 0.89. - 14.4% had hypoplastic dental anomalies, 7.2% had glossitis and 1.5% had anterior tooth fractures.
Davidopoulou et al.	37/30 N/A	- 38% and 27% of sickle cell patients had gingivitis and periodontitis, respectively. The corresponding proportion for controls was 10 per cent for each condition. - Patients with sickle cell anemia showed a significantly higher DMFT index ($p = 0.003$), which was mainly reflected by increased caries activity ($p = 0.005$) and high tooth loss resulting from caries ($p = 0.003$).
Pashine et al.	50/50 [10 – 18]	- Children with sickle cell anemia showed delayed tooth eruption, a tendency towards a Class II molar relationship, increased crowding in the anteroinferior region, increased overjet and open bite when compared to normal children.
Kalbassi et al.	55/ 120 N/A	- Significantly ($p < 0.05$) higher number of decayed teeth in patients with sickle cell anemia (6.10 ± 3.620) compared to healthy individuals (2.33 ± 1.221). - Significantly increased mean DMFT value compared to healthy individuals ($p < 0.05$).
Kowe et al.	194/ N/A [2 – 17]	- The prevalence of dental caries in patients with sickle cell anemia was 58.8% with a mean DMFT index of 2.39 ± 3.12, while 73.2% had moderate gingival inflammation. - The average plaque index was 1.46 ± 0.89. - 14.4% had hypoplastic dental anomalies, 7.2% had glossitis and 1.5% had anterior tooth fractures.
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Kalbassi et al.	55/ 120 N/A	- Significantly ($p < 0.05$) higher number of decayed teeth in patients with sickle cell anemia (6.10 ± 3.620) compared to healthy individuals (2.33 ± 1.221). - Significantly increased mean DMFT value compared to healthy individuals ($p < 0.05$).
Makolo et al.	68/86 [6 – 64]	- DMFT index of 2.9 in the sickle cell group compared to 1.2 in the control group. - Significant association between caries and negative impact on the quality of life of patients with sickle cell anemia.
Ahmad et al.	341/411 [20 – 50]	- Mean DMFT index of 6.39 in the sickle cell group compared to 5.20 in the control group. - Significantly lower salivary buffer capacity in the sickle cell group than in the control group (6.47 vs 6.88, $p=0.022$).

Tonguç et al.	43/43 [5 – 17]	- Most participants in the sickle cell (n=38, 88.4%) and control (n=37, 86%) groups had bleeding gums, oedema and inflammation and were diagnosed with gingivitis. There were no participants in either group diagnosed with periodontitis. - Periodontal parameters were not significantly different between the two groups (p > 0.05). - The salivary flow rates of the two groups were also similar (p > 0.05).
Minja et al.	77/16 [2,5 – 5]	- Delayed tooth eruption (3 teeth had not yet erupted in the sickle cell group). - Lower prevalence of caries in the sickle cell group (2%) than in the control group (6.6%).
Sari et al.	80/80 [18 – 59]	- In the sickle cell anemia group, the presence of periodontitis was more frequent than periodontal health (p < 0.001). - All clinical periodontal records and periodontal inflamed surface area values were higher in the sickle cell anemia group compared to the control group (p < 0.001).

DMFT: Decayed, missing or filled teeth; N/A: not applicable; Nc: Number of controls; Np: Number of patients with sickle

Table 5 presents the assessment of the risk of bias of the studies selected for this integrative review, according to the criteria of the JBI tool.

Regarding the cohort study [33], all applicable criteria were met (8 out of 8), demonstrating good methodological quality. Criteria Q4, Q5, and Q10 were not relevant for this design, which limited the evaluation to specific aspects. Thus, the study presents a low risk of bias related to selection, measurement, and outcome reporting.

For the case-control studies [34, 35], both met all relevant criteria (6 out of 6). Items Q5, Q6, Q7, and Q9 were not applicable in these studies. Therefore, within the evaluated criteria, these studies also demonstrate good methodological quality and a low risk of bias, particularly regarding the definition of cases and controls and the conduct of analytical procedures.

Finally, the eight cross-sectional studies all complied fully with the applicable criteria (5 out of 5), while criteria Q3, Q5, and Q6 were considered not applicable to this design. This indicates adequate methodological quality in terms of population description, objective definition, and outcome measurement methods, minimizing the risk of relevant bias within the scope possible for cross-sectional studies.

In summary, considering only applicable criteria, the included cohort, case-control, and cross-sectional studies demonstrate good adherence to recommended methodological standards, reflecting a low risk of bias in

Table 5. Methodological evaluation of articles using the JBI tool

Cohort studies (CS)											
Author (year)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11
Makolo et al.	√	√	√	.	.	√	√	√	√	.	√
Case-control studies (CCS)											
Author (year)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	
Ahmad et al.	√	√	√	√	.	.	.	√	.	√	
Tonguç et al.	√	√	√	√	.	.	.	√	.	√	
Cross-sectional studies (CSS)											
Author (year)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8			
Minja et al.	√	√	.	√	.	.	√	√			
Sari et al.	√	√	.	√	.	.	√	√			
Kowe et al.	√	√	.	√	.	.	√	√			
Davidopoulou et al.	√	√	.	√	.	.	√	√			
Pashine et al.	√	√	.	√	.	.	√	√			
Kalbassi et al.	√	√	.	√	.	.	√	√			
Brandão et al.	√	√	.	√	.	.	√	√			
Basyouni et al.	√	√	.	√	.	.	√	√			

. not applicable

the assessed areas. However, the non-applicability of certain criteria limits the comprehensive evaluation of bias risk, warranting cautious interpretation of the results and recognition of the inherent limitations of each study design.

Discussion

Sickle cell anemia is a genetic disease with autosomal recessive transmission resulting from a mutation replacing a thymine with an adenine in the *HBB* gene on chromosome 11. This substitution causes an exchange of Glu for Val in position six of the β-globin chain, leading to an alteration in the three-dimensional structure of this protein, which is one of the components of Hb. HbS, an abnormal hemoglobin, is thus formed. This results in a change in the morphology of the erythrocyte, which changes from a biconcave shape to a sickle shape [3].

The blood supply that occurs in these patients can have harmful consequences for the whole body, with the oral cavity also being affected [43].

In this integrative review, only the studies by Minja et al. [36] and Pashine et al. [21] reported delayed tooth eruption. This delay in tooth eruption may be associated with tissue hypoxia, endocrine dysfunction and nutritional deficiency.

On the other hand, of the 11 studies included, enamel changes were only reported in one of the studies [38]. These changes can result from damage to the matrix formation during enamel development, leading to enamel hypoplasia, or damage during the mineralization and maturation phases which can lead to increased enamel translucency or opacity.

However, the most common oral manifestations found in the selected studies were periodontal diseases (gingivitis and periodontitis) and caries. In the studies by Tonguç et al. [35] and Kalbassi et al. [40], the majority of participants had gum inflammation and were diagnosed with gingivitis. Gingivitis is gum inflammation that occurs in response to microbial dental plaque that accumulates around the teeth. It is clinically characterized by erythema, oedema and bleeding at the gingival margin. In gingivitis, only the gingival epithelium and connective tissue are affected by the disease and there is no alveolar bone loss. The levels of gingival index and bleeding were slightly, but not significantly, higher among the entire sickle cell anemia group, as well as in the age subgroups, compared to the healthy groups. The plaque index levels of the groups were similar [35, 40].

Few studies have been found in the literature investigating the periodontal health status of individuals with sickle cell anemia, and their results are not very concordant [37, 39, 41]. While two of the studies that assessed periodontitis suggested that patients with sickle cell anemia had a higher prevalence of this disease [37, 39], the other did not support this result, reporting that no differences in gingival bleeding were observed between both groups [41]. The reason for these differences may be the use of different periodontal disease criteria in studies carried out in different populations and different age groups. In addition, patients with sickle cell anemia regularly use penicillin, folic acid, chelating agents and hydroxyurea according to the severity of their medical condition. The effects of these drugs on periodontal inflammation may also be involved in this difference. For example, hydroxyurea is an effective therapy for patients with sickle cell anemia because it increases HbF levels, in addition to other beneficial effects such as increasing red cell hydration and decreasing red cell adhesion to the vascular endothelium [44]. However, there are studies that report a decrease in salivary function in patients taking this therapy, which may influence the incidence of manifestations [41].

The study by Davidopoulou et al. [39] revealed a worsening of dental and periodontal health in adult patients with sickle cell anemia (average age over 40 years) compared to healthy individuals. While the higher occurrence of gingival inflammation is in line with previous findings [40], the higher prevalence of periodontitis demonstrated in this group of middle-aged adults with sickle cell anemia is a new observation. This significant finding confirms some previous indications of compromised periodontal health in sickle cell patients [40]. However, the prevalence or severity of periodontitis may depend on the age of the populations examined [35], since it probably takes longer for a chronic disease such as sickle cell anemia and comorbidities to affect periodontal condition.

Another fact from the study by Davidopoulou et al. [39] is the increase in the Decayed, Missing, Filled Teeth (DMFT) index and decayed teeth scores of these sickle cell patients. Previous findings in children [41] and adults [40], as well as in more recent studies [33, 34], support the results of this study [39]. Possibly, the age of the participants may explain the discrepancies in the incidence of caries reported, as previously suggested also for periodontitis. In addition, dentists may be more reluctant to provide treatment due to fear of post-operative complications in patients with sickle cell anemia [22].

In contrast to these results is the recent study by Minja and his team [36], which reported a lower prevalence of caries in patients with sickle cell anemia compared to the control group.

Regarding orofacial changes, two studies [21, 42] reached identical conclusions, where individuals with sickle cell anemia showed a tendency towards Class II molar relationship and open bite when compared to normal individuals. The increased destruction and reduced lifespan of red blood cells

that occur in patients with sickle cell anemia leads to hyperplasia and expansion of bone marrow. These changes in bone structure can lead to the development of dental malocclusion and other orofacial changes [8].

This integrative review highlights that the most common oral manifestations in patients with sickle cell anemia are periodontal disease and caries. However, the analyzed studies present contradictory results regarding the prevalence and severity of these conditions when compared to healthy individuals. The main inconsistency lies in the fact that some studies point to a higher incidence and severity of oral problems, while others suggest a similar or even lower prevalence.

The main hypotheses to justify these discrepancies, as discussed in the article, are:

- Age of Participants: Age appears to be a determining factor. The article suggests that the prevalence or severity of periodontitis may depend on the age of the populations examined, as a chronic disease like sickle cell anemia and its comorbidities take longer to affect the periodontal condition4. The study by Davidopoulou et al. [39], which found worse dental and periodontal health, was conducted in an adult population over 40 years old. In contrast, studies with children and adolescents show less consistent results.

- Treatment Regimens: Treatments for sickle cell anemia, such as the use of penicillin, folic acid, chelating agents, and especially hydroxyurea, can influence the results. Hydroxyurea, although effective in treating disease, may decrease salivary function. A lower salivary buffering capacity was observed in patients with sickle cell anemia in some studies, which could increase the risk of caries.

- Methodological Differences: The article points out that the use of different criteria to diagnose periodontal disease in studies conducted in different populations and age groups may be a cause for the differences in the results.

This synthesis demonstrate that the inconsistencies found in the literature can be largely attributed to differences in the age of the patients and their treatment regimens, such as the use of hydroxyurea and prophylactic antibiotics, which modulate the oral environment.

Despite the generally good methodological quality observed across the included studies, several limitations related to risk of bias should be acknowledged. The evaluation was restricted to criteria applicable to each study design, meaning that some potentially relevant aspects could not be assessed due to the non-applicability of certain criteria. This limitation reduces the comprehensiveness of the bias assessment. In the cohort study, the exclusion of criteria such as follow-up procedures and statistical analysis limits the ability to fully assess risks related to attrition or analytical bias. For the case-control studies, the absence of applicable criteria related to confounding control and matching may overlook potential residual confounding or selection biases. Similarly, for cross-sectional studies, inherent limitations in design and the absence of assessment for some quality domains restrict the evaluation of causality and control of confounders, increasing the possibility of information and selection biases. Therefore, while the studies met all applicable quality criteria, the restricted scope of assessment and inherent design limitations highlight a need for cautious interpretation of the findings due to potential unmeasured biases.

Conclusions

Sickle cell anemia is a common disease worldwide, and dental infections can trigger painful crises in patients. This integrative review highlights the scarcity of information on sickle cell anemia in the field of dentistry.

The oral manifestations most commonly found are periodontal disease and caries, but the studies found present contradictory results with regard to these two conditions, with studies reporting a higher incidence of these manifestations and others reporting a lower incidence.

Assessing the oral health of patients with sickle cell anemia is crucial, since sickle cell anemia increases the risk of dental caries and causes changes in salivary composition. In addition, as shown in this integrative review, there are more cases of periodontal disease in these patients, although an association between the two diseases has not been proven.

Preventive dental care and non-invasive dental procedures are the main focus for patients with sickle cell anemia to avoid possible subsequent complications.

Therefore, when there is a need to carry out a surgical procedure in the oral cavity, the dentist should request complementary blood tests in order to favor the safety of the procedure and the patient. In addition, susceptibility to infection should be taken into account and antibiotic prophylaxis can be included in the treatment to prevent bacteremia and other complications.

Therefore, the inclusion of dentistry in the multidisciplinary treatment of patients with sickle cell anemia is essential for the prevention of acute crises caused by oral infectious foci and in the management of oral manifestations resulting from the disease itself. Therefore, through promotion, prevention and removal of infectious foci, acute crises can be reversed or minimized, and manifestations can be controlled.

Hydroxyurea is the main treatment for sickle cell anemia and helps to reduce the symptoms of the disease. However, it can have a negative effect on saliva, and further studies may help to elucidate the impact of hydroxyurea on saliva and the oral health of sickle cell patients.

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