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Evidence-based dental management in the new era of sickle cell disease

A scoping review

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ABSTRACT

Background. Sickle cell disease (SCD) is an emerging global health issue with rapid progress in therapy especially since 2017. However, systematic reviews found no clinical trials on dental treatment of SCD.

Types of Studies Reviewed. Using a scoping review approach, the authors examined citations from 13 national SCD guidelines and 10 books spanning 4 decades. The authors also searched the following databases: PubMed, Cumulative Index to Nursing and Allied Health Literature, ScienceDirect, Scientific Electronic Library Online, and GoogleScholar. Eligibility criteria included SCD, oral health care and dental treatment, related to oral and systemic health, original data, or observations.

Results. Systemic treatment of SCD might have opposing effects on caries, perhaps explaining the conflicting results published. Malocclusion correlates with marrow expansion. Other unusual orofacial findings reflect ischemia. Of 86 full-text articles examined, only 1, a Brazilian esthetic dentistry study, was a randomized clinical trial. No disease-specific data were found on risk of developing bacterial endocarditis, safety of inhaled nitrous oxide, safety of epinephrine with local anesthetic, or the benefit of comprehensive oral health care.

Practical Implications. In SCD, oral health and systemic health could be strongly linked. Penicillin, vaccines, and hydroxyurea might impact caries and bone. The interaction of SCD treatments and oral health merit study.

Key Words. Sickle cell; systemic health; evidence-based dentistry; caries risk; malocclusion; pulp necrosis; ischemia; osteomyelitis; mental nerve neuropathy; guidelines.

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Sickle cell disease (SCD) is a rare disease in the United States but is the most common single-gene sequence variation disease in the world.[1,2] Practical guidelines for the oral health care of this special care group[3-8] are based on the natural history (that is, untreated SCD). Progress in therapeutics is accelerating rapidly,[2] and all health care professionals need to be aware of best practices and evidence-based treatment.

SCD is an inherited disorder of red blood cells,[9] with the following major systemic manifestations: complex pain syndrome, chronic hemolytic anemia, immune deficiency from functional asplenia, and multisystem organ damage.[2,10] SCD disproportionately affects minorities (1 in 365 African-American births and 1 in 16,300 Hispanic-American births).[11] When the standard of care is followed (that is, diagnosis by means of newborn screening, vaccinations against *Streptococcus pneumoniae*, prophylactic penicillin through at least 5 years, stroke screening, and offer of hydroxyurea), life expectancy is middle-aged adulthood.[2,11] All types of SCD cause complications with potential dental implications.[10]

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PATHOPHYSIOLOGY OF SICKLE CELL DISEASE

SCD pathophysiology has expanded[2] beyond the classical focus on hemoglobin S polymerization. A new understanding of SCD pathophysiology recognizes the role of erythrocyte hemolysis (that is,

Table 1. Sickle cell disease (SCD) oral health and systemic health interactions: topics with the largest evidence base.

HIGHER-RISK SCD*	TYPE OF EVIDENCE CITED IN GUIDELINES	SUMMARY OF RESULTS	LEVEL OF EVIDENCE
Caries (n = 19)	7 case-control 2 cohort 9 cross-sectional 1 case report	Mixed results whether SCD raises risk of developing caries. Penicillin, vaccination, salivary flow, and access to care are cofactors.	Low to moderate
Periodontal Disease (n = 13)	6 case-control 1 cohort 5 cross-sectional 1 case series	Mixed results whether SCD is associated with greater periodontal disease.	Low to moderate
Malocclusion (n = 13)	5 case control 1 cohort 6 cross-sectional 1 case series	SCD is associated with higher incidence of malocclusion, but not every person has it. Genotype and disease-modifying treatment could be cofactors.	Moderate
Radiographic Changes (n = 12)	4 case control 2 cross-sectional 4 case series 2 case reports	Bony trabecular spacing, absence of bony canal. Some features are shared with other severe anemias.	Moderate
Mandibular Neuropathy (n = 8)	1 cross-sectional 2 case series 5 case reports	SCD is among the causes of neuropathy, notably the mental nerve.	Low
Osteomyelitis of Mandible (n = 7)	4 case series 3 case reports	SCD can be complicated by osteomyelitis of mandible or maxilla. Poor access to care, delayed recognition, and infection of devitalized bone could be cofactors.	Low
Aseptic Pulpal Necrosis (n = 7)	2 case control 1 cohort 1 cross-sectional 1 case series 2 case report	SCD can cause pulpal necrosis with no infectious cause, associated with low oxygen saturation.	Moderate
Other Findings	See eTable, available online at the end of this article		

* In order of estimated incidence.

leading to oxidant stress, inflammation, prothrombotic state, endothelial dysfunction with depleted nitric oxide, and abnormal vasoconstriction). According to SCD pathophysiology, blood flow is slowed by abnormally high adhesion between erythrocytes and leukocytes and endothelial cells.

Besides episodic intense vaso-occlusive pain, the other leading acute complication in SCD is acute chest syndrome, an "amplified pneumonia" with potential for overnight deterioration to life-threatening respiratory failure. Asthma and atelectasis can also trigger potentially fatal acute chest syndrome, which occurs as often as 27% of the time after surgery.[12] Therefore, general anesthesia for oral surgery in SCD carries high risk of developing postoperative complications.

Chronic ischemia and hemolytic anemia cause chronic organ damage throughout the body, including bone,[13,14] specifically avascular necrosis and susceptibility to osteomyelitis.[15] Cortical bone weakening and collapse are common in thoracolumbar vertebrae. Bone marrow infarction can cause bone pain and inflammation without infection. Marrow expansion can distort bones with loss of trabeculae, maxillary hyperplasia, malocclusion, and frontal bossing.[16]

SCD causes multiple other systemic complications that need heightened caution by the dentist.[2,17] Chronic renal failure makes ibuprofen contraindicated, and longer dosing intervals are required for some drugs. Collaboration with the medical team can reduce adverse outcomes from immunocompromise or select medications to avoid cardiac arrhythmias. Renal tubular dysfunction creates vulnerability to dehydration when fluid intake is restricted for oral surgery. Finally, the complex and heterogeneous pathophysiology makes the disease course of any person hard to predict.

Progress in medical management of SCD has accelerated. For 20 years, hydroxyurea was the only medication used to reduce severity and change the natural history of SCD. The following new medications used to decrease the severity of SCD became available from 2017 through 2019: glutamine (reduces oxidant stress in the erythrocyte), crizanlizumab (inhibits abnormal adhesion with P-selectin), and voxelotor (blocks sickle polymerization). In 2020, the clinical trial pipeline has more than a dozen other pharmaceutical candidates.[18] Bone marrow hematopoietic stem cell

ABBREVIATION KEY

SCD: Sickle cell disease.

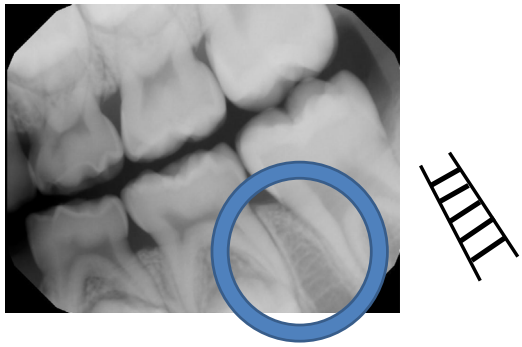

Figure 1. Bone trabeculae in sickle cell disease can have an abnormal distribution and decreased density (circled), with a radiographic pattern described as a "stepladder" (diagram on the right). Radiograph provided courtesy of Dr. Sahar M. Alrayyes, Department of Pediatric Dentistry, University of Illinois at Chicago, Chicago, Illinois.

transplant from HLA-identical sibling donors has cured (that is, normal blood counts and no new SCD complications) SCD in more than 1,200 people, and alternative-donor transplants hold promise. Gene therapy with lentiviral gene transfer or gene editing techniques, like clustered regularly interspaced short palindromic repeats, are having early success in clinical trials.[19]

The natural history of SCD can include specific patterns of orofacial complications (Table 1).[4,5,20] Ischemic and inflammatory dental problems reported in SCD have some unique and recognizable patterns or damage to enamel structure, gingiva, and mandibular and maxillary bone. Nerve compression by inflamed or infarcted bone can cause paresthesia. Acute ischemia can cause a syndrome of tooth pain without caries or infections. Bone marrow expansion as a response to high erythropoietic drive in SCD, like thalassemia, can lead to maxillary hyperplasia that causes malocclusion. Marrow expansion also causes decreased density of bony trabeculae, which appear as a stepladder pattern on mandibular radiographs (Figure 1). Investigators have documented that oral health in patients with SCD is important for quality of life.[21]

Practical guidelines for the dentist and oral surgeon caring for a person with SCD are available.[3-8] However, there is a lack of uniformity in the treatment[22,23] described in the literature of oral health care in SCD, and investigators of the most current systematic review in 2019 found no rigorous evidence in 9 databases to guide the oral health care of people with SCD,[10] leaving expert consensus as the next choice to guide dentists in clinical practice.[24] In the past 10 years, several countries have developed expert guidelines for overall health care standards for SCD that include new pathophysiology and new therapies.

We hypothesized that a scoping review of new guidelines and articles about SCD might uncover new evidence on SCD dental treatment and information about how the new systemic treatments interact with oral health in SCD. The term *dental treatment* will be used to encompass a variety of therapeutics: restorative, periodontic, endodontic, prosthodontic, orthodontic, and oral surgery. The following research questions were structured based on the patient, intervention, comparison, and outcome format:

- Are there evidence-based dental treatments specific for people with sickle cell disease?
- Are there evidence-based dental treatments that specifically improve the health of people with SCD?
- Do standard dental treatment plans need to be modified to avoid harm for people with SCD?
- Do dental treatments need to be adjusted for SCD treatments?

METHODS

Because approaching the literature with the systematic review methodology had minimal yield,[10] we conducted a scoping review using a standard framework.[25,26] The goal of our scoping review was to identify evidence gaps and to provide recommendations for future SCD research.

Eligibility

The inclusion criteria for studies in our review were the following: related to oral health care in SCD, original data, and in English or translated to English. We retrieved full-text versions of all

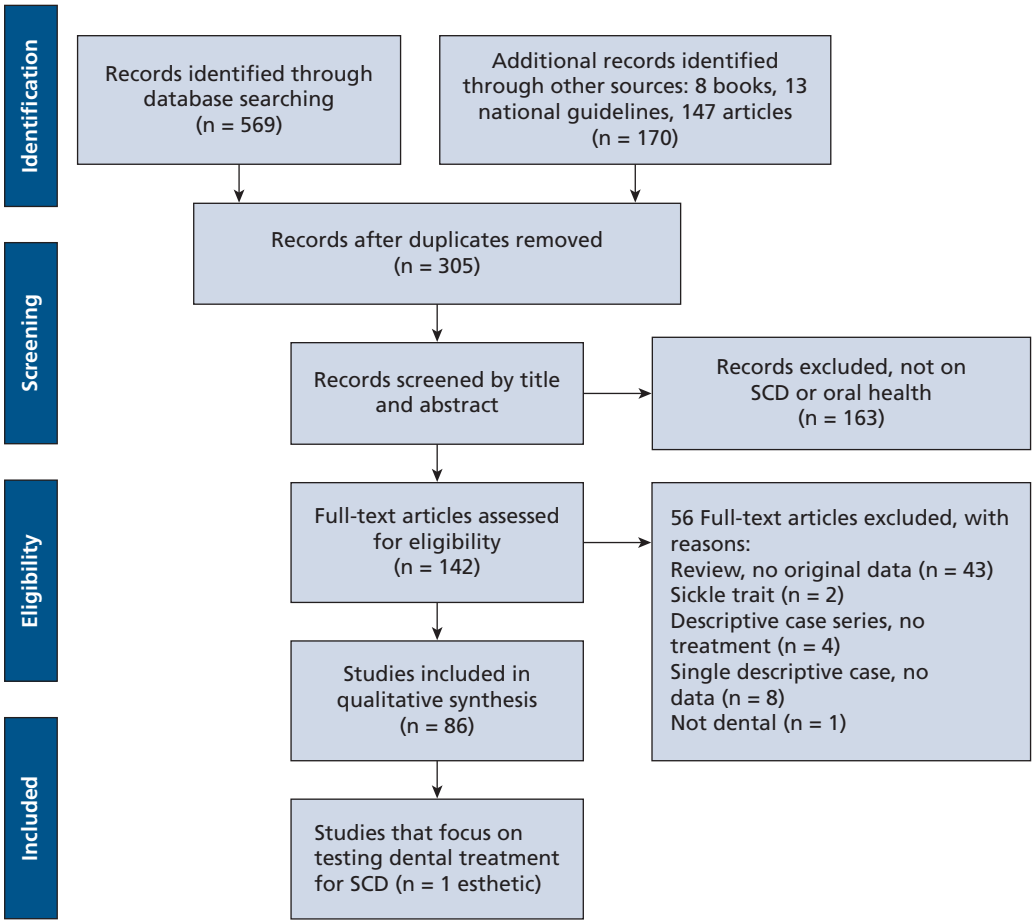

Figure 2. Preferred Reporting Items for Systemic Reviews and Meta-Analyses flow diagram.[28]

potentially relevant studies for review, either electronic or hard copy, through the University of Illinois at Chicago Health Sciences Library. The following 3 major concepts were used to select key words for the literature search, drawing from reviews from 2018 and 2019[5,10,20,27]: sickle cell (*sickle*, *sickle cell anemia*, *sickle cell disease*), oral health (*oral health*, *dental needs*, *caries*, *dental caries*, *periodontal disease*, *endodontic disease*, *root canal*, *neuropathy*, *pulpal necrosis*, *pulp necrosis*, *osteomyelitis*, *mandibular*, *maxillary*, *endocarditis prophylaxis*, *antibiotic prophylaxis*, *local anesthesia*, *dental anesthesia*, *trabeculation*, *orofacial*, *mental nerve*, *malocclusion*, *craniofacial*, *gingivitis*, *dentin*, *enamel*, *oral surgery*, *hypocalcification of dentin*, *interglobular dentin*, *dental implant*), and clinical research (*randomized clinical trial*, *case-control*, *cohort*, *control group*, *incidence*, *guidelines*).

Study screening and structure

In our scoping review, we used a 2-pronged search process according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis[28] (Figure 2): a key word search of several databases (that is, PubMed, Cumulative Index to Nursing and Allied Health Literature, ScienceDirect, Scientific Electronic Library Online to access Brazilian literature, and Google Scholar) and a manual search. The manual search was designed to ensure that regional knowledge bases were accessed by examining the references cited for oral health in SCD in all available global national guidelines for SCD care and all available comprehensive medical books on SCD management. We acquired national guidelines and books on SCD. We have been trained in evidence-based practice and independently examined the literature to determine articles that were eligible for analysis. Disagreements were resolved through discussion or, if required, consultation with a third person. In the first screening of articles, we only examined the title and abstract for eligibility criteria (Figure 2). The second examination included the full text. We used translations of French and Brazilian guidelines to confirm the concepts for oral health care.

Charting the data

After examining the articles, we abstracted the main research outcomes of each study and organized them using the following information: study author and year of publication, title, study design, and comments on methodology (eTable, available online at the end of this article). A summary table was constructed for the topics with the most original data (Table 1). The last step in eligibility was selection of rigorous studies of oral health treatment in SCD.

RESULTS

Summary of the main findings

The database search and manual search identified 739 articles, which became 305 after duplicates were removed (Figure 2). When screening the titles and abstracts, we found that 163 did not meet the eligibility criteria, largely because key words were sometimes used in a context other than oral health (for example, *antibiotic prophylaxis*, *neuropathy*, *local anesthesia*, and *trabeculation*). On review of 142 full-text articles, we found that only 1 met all of the eligibility criteria: a randomized controlled trial from Brazil on whether people with SCD have greater sensitivity to dental bleaching.[54] However, that single study on treatment focused on the esthetic dentistry bleaching procedure only. No other topics had high-quality evidence because none of the studies were randomized or prospective (Table 1 and eTable, available online at the end of this article). Investigators examined the possible impact of systemic treatments for SCD on oral health in only 4 retrospective studies.[30,36,37,44]

The answer to the research question "Are there evidence-based dental treatments specific for people with sickle cell disease?" is no. Evidence for dental treatments specific for SCD is limited and composed of case-control studies, case series, and expert opinion. The answer to all of the subquestions is "no high-quality evidence."

Caries have high prevalence in some SCD populations, but studies conflict on whether the rate of caries is higher in participants with SCD than in non-SCD control participants. Investigators using the larger outcome measure of decayed, missing, and filled teeth scores did not consistently find a correlation with SCD.

Periodontal disease has high prevalence, and results are mixed about whether SCD is associated with greater periodontal disease. Sociobehavioral factors might be more important than SCD.

Malocclusion due to orofacial bone marrow hyperplasia can cause functional and esthetic problems, although not in every person with SCD. A few studies noted that skeletal and dental radiographic abnormalities correlate with anemia severity in SCD subtypes.[46,49,50]

Radiographic changes in SCD include bony trabecular spacing in a stepladder pattern and absence of the bony canal, which are shared with other severe anemias. Enamel and dentin hypomineralization are frequent in SCD.[29,47,52]

Neuropathy involving the mental nerve and osteomyelitis of the mandible are unusual findings in SCD that are shared with other diseases. They are linked to ischemic damage of the mandible but occur so rarely that they are only described in case series.

"Aseptic" pulpal necrosis from ischemia has a moderately strong association with SCD. Necrosis due to ischemia, without infection, occurs in multiple bones in SCD and so ischemic necrosis of dental pulp is completely expected as a complication of SCD. Investigators in 1 mechanistic study reported that mild hypoxia could be measured in the pulp.[51]

Evidence gaps

Studies on the overall interaction between oral health and overall systemic SCD health have mixed findings, which are summarized in Table 1 (a detailed list of studies is provided in eTable, available online at the end of this article). Dental infection increases the risk of there being hospital admissions in a large database of emergency encounters by people with SCD, although the study lacked control participants and investigators did not provide details on dental problems.[34] In 1 study, investigators correlated high rates of caries in SCD with poor access to dental services, not SCD itself.[32] Investigators in a follow-up study found that SCD adults with free access to basic dental services had fewer hospitalizations,[53] but it lacked a control group.

Investigators in the oral health care studies rarely remarked on systemic SCD therapies, apparently assuming that there would be no impact on oral health. This assumption has not been tested.

Table 2. Overview of oral health care recommendations in national guidelines for sickle cell disease.

YEAR	COUNTRY	PREVENTIVE ORAL HEALTH CARE	SUBACUTE BACTERIAL ENDOCARDITIS PROPHYLAXIS	ACUTE ORAL HEALTH CARE*
2010	United Kingdom	No mention	No mention	No mention
2013	Italy, pediatric	No mention	No mention	No mention
2014	Brazil	Yes	Yes	Yes
2014	United States (National Institutes of Health)	Yes	No mention	No mention
2014	Nigeria	No mention	No mention	No mention
2014	South Africa	No mention	No mention	No mention
2015	Canada	No mention	No mention	No mention
2015	France	Yes	Yes	Yes
2015	Saudi Arabia	No mention	No mention	No mention
2016	Uganda	No mention	No mention	No mention
2019	United Kingdom, pediatric	Yes	No mention	No mention
2019	United States (American Society of Hematology)	No mention	No mention	No mention
2019	Italy	No mention	No mention	No mention

* Acute oral health care precautions (for example, vasoconstrictors, nitrous oxide, oxygenation, and hydration).

For example, none of the study investigators examined whether pulp oxygen levels are improved by means of SCD therapy or what patterns of hypoxia correlate with pulp necrosis. To our knowledge, no investigators have examined whether systemic therapy for SCD ameliorates the orofacial abnormalities and malocclusion.

Variation in attention to oral health in national guidelines

We found a total of 13 national SCD guidelines from Brazil,[55] the United States,[56,57] the United Kingdom,[58,59] France,[60] Nigeria,[61] Uganda,[62] South Africa,[63] Italy,[7,64] Saudi Arabia,[65] and Canada[66] (Table 2). All guidelines used the McMaster Grading of Recommendations, Assessment, Development and Evaluation criteria with panels of experts.[67]

Brazil provides the only national oral health guideline (2005, updated 2013) for SCD, citing case-control studies, case series, and anecdotal reports. Brazil dominates this research field, contributing 31 of the 86 articles in the qualitative synthesis and several studies with more than 100 children with SCD. Some reports highlighted vulnerability to bacteremia, abscesses, bone infarction, ischemia of tooth pulp and mandible, and poor tolerance of hypoxia during inhalation anesthesia. The guidelines recommend heightened attention to regular comprehensive oral health care to prevent SCD complications.

French, UK, and Canadian guidelines recommend routine oral health care for people with SCD, with little mention of specific concerns or any evidence base. French adult guidelines recommend preoperative antibiotic prophylaxis against subacute bacterial endocarditis, citing French anesthesiology guidelines and oral surgery experience and no mention of an evidence base. The only recommendation in US guidelines is to supplement fluoride, as in other children. Other national SCD guidelines do not mention oral health.

Books on SCD clinical management spanning 40 years and multiple perspectives were also found. Two books were from sub-Saharan Africa,[68,69] 2 were from Jamaica,[70,71] 1 had editors in Brazil,[72] and others were from the United States.[73-77] Manual search of the bibliographies of these books led to several articles that were missed in the database search. These books contained a few expert opinions on oral health care, but no new rigorous evidence base and no mention of the interaction of SCD therapy with oral health.

Impact of SCD therapy

Two categories of SCD systemic therapy (anti-infection and hydroxyurea) are evidence-based recommendations in all of the national SCD guidelines. Limited evidence suggests

they could have an impact on oral health and could merit attention from dentists and researchers.

All SCD guidelines recommend anti-infection therapy for young children with SCD (that is, antibiotic prophylaxis [at least 5 years of penicillin] and pneumococcal vaccination to reduce the risk of developing sepsis from *S pneumoniae)*. Investigators in the United States, Brazil, and India have reported that penicillin prophylaxis is associated with less *Streptococcus mutans* and perhaps less caries or lower decayed, missing, and filled teeth scores.[30,37,44] A study in India suggested that adding pneumococcal vaccination was associated with further reduction in *S mutans* and caries rates. Pneumococcal vaccination might also help change the oral microbiome and reduce caries risk,[44] which has intriguing implications for the long search for a vaccine against caries. Penicillin prophylaxis might also lead to more *Candida albicans* in the mouth for children with SCD.[36] However, many environmental and medical factors can affect the oral microbiome, suggesting that multicenter studies with multivariate analysis could be valuable for validation.

All global SCD guidelines recommend offering daily hydroxyurea to reduce the severity of SCD. Investigators in only 2 studies examined whether hydroxyurea affects oral health outcome measures. In 1 study, investigators linked hydroxyurea with decreased salivary flow and decreased salivary buffering in 33 children receiving hydroxyurea compared with 28 children not receiving hydroxyurea.[40] Hydroxyurea had an effect on the *Candida* species in the mouth but no clinical impact.[78] We did not find any studies on the long-term effects of hydroxyurea on oral health in SCD.

CONCLUSIONS

Oral health standards of care are stated in a few national SCD guidelines, based on moderate evidence and without randomized clinical trials. Attention to oral health in SCD has regional variation, ranging from extensive SCD oral health guidelines in Brazil to some from the United Kingdom to little or no mention of oral health in other national SCD guidelines.

A positive link between systemic and oral health is that the standard medical care for preventing *S pneumoniae* bacterial sepsis in children with SCD might also protect them against caries.[30,37,44] These findings could explain why several single-institution studies had conflicting results on whether the rate of caries is higher in participants with SCD than in control participants without SCD,[21,28,31,33,35,38-43] because investigators in those studies did not track penicillin prophylaxis or pneumococcal vaccination as potential confounding factors.

Several negative links between oral health in SCD and systemic treatment of SCD have been reported. Caries can trigger more serious complications as well as systemic infection, sickle cell vaso-occlusive pain, abscess, or osteomyelitis.[34,45,48,79,80] Other negative interactions between oral health care and SCD systemic health could occur if prolonged dental anesthesia or dental procedures trigger SCD respiratory, ischemic, thrombotic, or infectious complications. One implication is that good access to oral health care might be as important for SCD as it is for diabetes mellitus, but more research is needed. The wide range of opinions (with no data) about what precautions to use for invasive oral surgical procedures in SCD (for example, endocarditis prophylaxis, nitrous oxide, and vasoconstrictor epinephrine for local anesthesia) also highlights the need for more research evidence.

Agreement with results from similar reviews

Similar findings about the dearth of rigorous evidence about dental treatment in SCD have been reported in previous systematic reviews.[10,81] Investigators of other reviews pointed out unusual oral complications with untreated SCD and provided expert opinion on oral health care and SCD.[5,20,22,82-87]

In thalassemia, international guidelines use the orofacial findings of thalassemic facies as a measure of abnormal marrow expansion to make clinical long-term transfusion therapy decisions.[88,89] However, investigators of a systematic review found no high-quality evidence for the impact of dental care management in thalassemia.[90]

Implications for dental practice

- SCD dental guidelines are based on old low-quality evidence and natural history of oral health complications, but the face of SCD is being changed by means of new treatments and new understanding of SCD pathophysiology.

Box. Potential Research Questions on Oral Health Care in Sickle Cell Disease

Pathophysiological Links Between Systemic and Oral Health

- Will multicenter studies confirm that antibiotic prophylaxis and pneumococcal vaccination protect people with sickle cell disease (SCD) from caries? Randomization of antibiotic prophylaxis might not be ethical but some people with SCD do have longer periods of antibiotic prophylaxis than others due to surgical splenectomy or variation in the policy of the center. What is the magnitude of this protective benefit compared with other factors that affect caries rates, such as fluoridated water, household educational level, and good hygiene habits?
- Will systemic therapy for people with SCD (for example, hydroxyurea, glutamine, crizanlizumab, voxelotor, chronic transfusions, transplantation, and gene therapy) reduce the changes to teeth and bones, such as pulp necrosis, bony trabeculation, and malocclusion? Will the level of therapy that reduces acute systemic complications also affect these chronic orofacial changes?
- Can multicenter studies validate the single-center findings that dental radiographic abnormalities correlate with skeletal changes and anemia in people SCD? Can the ischemic changes to bone density from SCD be used as a model for other bone changes in other diseases?
- Can physiological measurements in the mouth, such as dental pulp oxygen levels or trabeculation density, serve as markers for avascular necrosis in the femoral head that is anatomically less accessible for measurement?
- Do chronic medications used to treat SCD, such as hydroxyurea or opioids, have measurable adverse impact on salivary flow and oral health that merits counseling for patients?
- Oral reduction of nitrate to nitrite is dependent on the oral microbiome. Can nitric oxide depletion in people with SCD be affected by enhancement of oral nitrogen-converting bacteria?

ORAL HEALTH CARE IMPACT ON SYSTEMIC HEALTH

- Can excellent comprehensive preventive oral health care for people with SCD as described in the Brazilian guidelines have a measurable long-term health benefit? Is it cost-effective?
- Is antibiotic prophylaxis necessary against subacute bacterial endocarditis in people with SCD? In any subgroups of SCD?
- What is the best anesthetic for oral surgery for people with SCD?
- Is epinephrine in local anesthetic safe and useful for people with SCD?

- Moderately strong evidence supports associations between SCD and aseptic pulpal necrosis. The dental practitioner should be aware that SCD ischemia can cause oral pain and tooth damage without infectious etiology.
- The complications of SCD could cause poor outcomes, so interprofessional planning for oral surgery in collaboration with a hematologist is prudent.
- Many guidelines for oral health care for SCD patients are based on the assumption of untreated disease and low quality of evidence. When there are no evidence-based clinical guidelines, wide practice variations may result.
- New insights from SCD studies, like potential pneumococcal vaccine benefit for reducing caries, could help advance oral health care for everyone.

Future research

The lack of national guidelines on oral health care for patients with SCD reveals major gaps in evidence on oral health treatments in SCD and on the interaction between oral health and systemic health care in SCD. We found a small body of evidence on interactions between oral health and systemic health in SCD. Few investigators captured the oral health impact of differences in

genotypes of SCD, the effects of hydroxyurea treatment or penicillin prophylaxis, and access to oral health care. Will systemic antisickling therapy reduce the incidence of orofacial abnormalities that are consequences of ischemia or marrow expansion? Future directions could include more data on oral health care in SCD and evidence-based guidelines using the McMaster Grading of Recommendations, Assessment, Development and Evaluation system (Box). ■

SUPPLEMENTAL DATA

Supplemental data related to this article can be found at https://doi.org/10.1016/j.adaj.2020.05.023.

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Dr. Michael R. Hsu was available as a third reviewer to resolve discrepancies.

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eTable. Studies with original data on oral health in sickle cell disease.

STUDY, BY TOPIC	TITLE	TYPE OF STUDY	PATIENTS, NO.	AGE, Y	FINDINGS	LEVEL OF EVIDENCE
Caries						
Okafor and colleagues,[28] 1986	Oral and dental complications of sickle cell disease in Nigerians	Case-control	37 SCD* (HbSS†) 24 control participants	14-33	Less caries in HbSS (35% versus 54%) of controls because sickle cell patients "avoid sweets because of the widespread belief that it might weaken their blood." No mention whether examiner was blinded to the medical diagnosis of the patients.	Low
Taylor and colleagues,[29] 1995	Sickle cell anemia: a review of the dental concerns and retrospective study of dental and bony changes	Case report	21 SCD	8-31	Chart review, no control, poor study design, 24% of patients had hypomineralization, radiographic trabeculae stepladder pattern, overjet of 3-10 millimeters (56%), overbite of 30-80%, and calcified canal (5%).	Low
Fukuda and colleagues,[30] 2005	Acquisition of mutans streptococci and caries prevalence in pediatric sickle cell anemia patients receiving long-term antibiotic therapy	Case-control	60 SCD, 60 control participants	3-12	Patients with SCD receiving prophylactic penicillin have significantly lower rates of caries than matched control participants ($P < .01$), and no *Streptococcus mutans* ($P < .01$). Discontinuation of prophylactic penicillin in patients with sickle cell anemia results in detectable levels of *S mutans* and caries rates approaching those of untreated controls after approximately 4 y. Weakness: examiners not blinded to patients' history.	Moderate
Laurence and colleagues,[31] 2006	The association between sickle cell disease and dental caries in African Americans	Retrospective cohort	102 SCD, 103 control participants	18-70	Significantly more carious surfaces ($P < .001$) and fewer restorations ($P < .001$) in patients with SCD in hematology clinic compared with control participants from Howard University dental clinic. Confounding factors of poverty and access to care. Weak study with groups starting from different points of oral health.	Low to moderate
Laurence and colleagues,[32] 2006	Self-perceived loss of control in untreated dental decay in African-American adults with and without sickle cell disease	Cross-sectional	102 SCD (81 HbSS, 16 HbSC,‡ 5 SB Thal§), 103 control participants	18-59	Study investigators found that higher dental external locus of control is associated with increased untreated caries, for both African Americans with and without SCD.	Low
Passos and colleagues,[33] 2012	Sickle cell disease does not predispose to caries or periodontal disease	Case-control	99 SCD (50% HbSS; 50% HbSC) 91 control	16-68	Dental examiner is blinded to clinical history. No statistical association between a history of clinical systemic severity of the disease and the DMFT¶ index or CPI#.	Moderate
Laurence and colleagues,[34] 2013	Dental infections increase the likelihood of hospital admissions among adult patients with sickle cell disease	Cross-sectional chart review	1,572 encounters of SCD with dental infection 549,045 encounters of SCD without dental infection	Not reported	Review of nationwide emergency department data (2006-2008) found higher chance of admission in those patients with SCD with dental infections than those without dental infections (65.7% versus 40%).	Low to moderate
Singh and colleagues,[35] 2013	Dental and periodontal dental health status of beta thalassemia major and sickle cell anemic patients a comparative study	Case-control	250 SCD, 250 control participants, 250 thalassemia	3-15	Comparative descriptive study found significant difference in DMFT and plaque index between SCD and control participants ($P < .0001$) in India. No mention examiners were blinded.	Low to moderate
Brighenti and colleagues,[36] 2014	Evaluation of caries-associated virulence of biofilm from *Candida albicans* isolated from saliva of pediatric patients with sickle-cell anemia	Cross-sectional	25 SCD, 25 control participants	4-6	Significantly higher acid production ($P = .025$), polysaccharides ($P = .025$), and protein ($P = .047$) with *Candida albicans* biofilm in children with SCD than in control participants.	Moderate
de Matos and colleagues,[37] 2014	Oral microbial colonization in children with sickle cell anaemia under long-term prophylaxis with penicillin	Cross-sectional	40 SCD and 40 control participants	4-11	Evaluated DMFT and salivary. Although no significant differences between cariogenic microorganism counts, there were significantly higher oral levels of yeast in the SCD group. Control participants had lower salivary flow and buffering capacity. Pediatric patients with SCD had significantly higher oral level of yeast. No mention of blinded examiners.	Low to moderate

* SCD: Sickle cell disease. † HbSS: Sickle cell disease, SS type. ‡ HbSC: Sickle cell disease, SC type. § SB Thal: Sickle-β-thalassemia. ¶ DMFT: Decayed, missing, and filled teeth. # CPI: Community Periodontal Index. ** BTM: β-thalassemia major. †† SCT: Sickle cell trait. ‡‡ HbAA: Normal hemoglobin.

eTable. Continued

STUDY, BY TOPIC	TITLE	TYPE OF STUDY	PATIENTS, NO.	AGE, Y	FINDINGS	LEVEL OF EVIDENCE
Ralstrom and colleagues,[21] 2014	The impact of sickle cell disease an oral health-related quality of life	Case-control	54 SCD, 52 control participants	SCD mean 14, control participants mean 16	No statistical significant difference between the 2 groups, except in subset SC had fewer cavities than healthy peers ($P < .02$). No mention of blinded examiners or how many examiners.	Low to moderate
Al-Alawi and colleagues,[38] 2015	The association between dental and periodontal diseases and sickle cell disease: a pilot case-control	Case-control	33 SCD, 33 control participants	18-38	Significantly more carious teeth in participants with SCD compared with control group ($P = .036$) due to oral hygiene negligence. The mean number of restored teeth was significantly lower in participants with SCD (in Saudi Arabia) compared with the control group ($P = .015$).	Low to moderate
Fernandes and colleagues,[e1] 2015	Caries prevalence and impact on oral health-related quality of life in children with sickle cell disease: cross-sectional study	Cross-sectional	106 SCD	8-14	Younger children with SCD had lower caries experience compared with healthy peers ($P = .03$). Teen with SCD had caries score similar to healthy peers ($P > .05$). No control participants. No mention of blinded examiners.	Low
Soares and colleagues,[39] 2016	Maternal risk behavior and caries incidence in children with sickle cell disease	Cohort	295 SCD	0.5-5	A 16-mo study found an association between the incidence of caries and maternal behavior (that is, alcohol abuse and maternal depression). Positive association between SCD severity and caries incidence.	Moderate
Brandão and colleagues,[40] 2018	Association between sickle cell disease and the oral health condition of children and adolescents	Cross-sectional	61 SCD, 63 control participants	5-18	Bahia, Brazil. Significant higher DMFT in children and adolescents with SCD than control participants ($P = .013$). Lower salivary buffer than control participants ($P = .006$). Those on hydroxyurea had higher DMFT and lower salivary flow.	Moderate
Kalbassi and colleagues,[41] 2018	Comparative evaluation of oral and dental maxillofacial manifestation of patients with sickle cell diseases and beta thalassemia major	Cross-sectional	55 SCD, 100 control participants, 120 BTM**	16-23	Higher carious teeth, CPI, and DMFT rate higher in SCD than control participants ($P < .05$). No mention of blinded examiners to medical history.	Low to moderate
Luna and colleagues,[42] 2018	Perception of treatment needs and use of dental services for children and adolescents with sickle cell disease	Cross-sectional	250 SCD (child—parent dyads)	3-18	47.2% caries and 14.0% periodontal problem in children and teen with SCD in Recife, Brazil. Mothers' schooling was only variable significantly associated with caries rate. Perception of need was influenced by caries, periodontal problems, and history of toothache in past 6 mo.	Moderate
Medeiros and colleagues,[43] 2018	Analysis of oral health conditions and risk factors for dental caries in patients with sickle cell disease	Cross-sectional	43 SCD	6-44	Higher DMFT correlated with lower buffer capacity in children aged 6-12 y. Graphs and table are missing in article. Poor study. No treatment rendered.	Low to moderate
Hanumanta and colleagues,[44] 2019	Acquisition of *Streptococcus mutans* and dental caries experience in pediatric sickle cell anaemia patients under various prophylactic therapies	Case-control	160 SCD (4 groups), 40 control participants	4-10	Significant decrease in DMFT ($P < .05$) and *S mutans* count ($P = .016$) in children with SCD receiving prophylactic penicillin, pneumococcal vaccine, and both penicillin and pneumococcal vaccine, compared with children who did not receive any antibiotics or vaccine, and healthy control participants. The maximum reduction was in the group receiving both antibiotics and vaccine.	Moderate
Periodontal Disease						
Rada and colleagues,[45] 1987	Sickle cell crisis precipitated by periodontal infection: report of two cases	Case series	2	25, 17	Periodontal infections precipitate sickle crisis possibly caused by third molar operculum and a popcorn kernel.	Low
Crawford,[e2] 1988	Periodontal disease in sickle cell subjects	Case-control	45 HbSS, 19 HbSC, 46 control participants	18-60	Blind examiners used clinical and radiographic indices and found that SCD is not associated with increased levels of gingivitis or periodontitis.	Moderate to strong
Arowojolu and Savage,[e3] 1997	Alveolar bone patterns in sickle cell anemia and non-sickle cell anemia adolescent Nigerians: a comparative study	Case-control	50 SCD, 50 control participants	11-19	No significant difference in the radiographic alveolar bone level measurements between SCD and control adolescents groups, in Nigeria. Blinded examiner.	Moderate

eTable. Continued

STUDY, BY TOPIC	TITLE	TYPE OF STUDY	PATIENTS, NO.	AGE, Y	FINDINGS	LEVEL OF EVIDENCE
Arowojulo,[e4] 1999	Periodontal probing depths of adolescent sickle cell anaemia (SCA) Nigerians	Case-control	50 SCD, 50 control participants	11-19	Probing depth was significantly higher for SCD than control participants (2.68 versus 2.24 mm). But overall none had periodontal disease. Female patient with SCD had highest periodontal pockets. Blinded examiner.	Moderate
Guzeldemir and colleagues,[e5] 2011	Dental and periodontal health status of subjects with sickle cell disease	Case-control	55 SCD, 41 control participants	21-41	Higher plaque index, gingival index, and probing depth in patients with SCD (no description of type of SCD). No mention of blinded examiners	Low to moderate
Passos and colleagues,[33] 2012	Sickle cell disease does not predispose to caries or periodontal disease	Case-control	99 SCD (50% HbSS; 50% HbSC) and 91 control participants	16-68	No statistical association between history of clinical systemic severity of the SCD and CPI, in Bahia, Brazil.	Moderate
Singh and colleagues,[35] 2013	Dental and periodontal dental health status of beta thalassemia major and sickle cell anemic patients: a comparative study	Cross-sectional	250 SCD, 250 control participants, (250 BTM)	3-15	Significant difference between SCD and control participants in DMFT and plaque index ($P < .0001$), in Bilaspar, India. No mention of blinded examiners or details of examiners' consistency.	Low to moderate
Veiga and colleagues,[e6] 2013	Serum cytokine profile among Brazilian children of African descent with periodontal inflammation and sickle cell anaemia	Cross-sectional	10 SCD, 15 control participants	6-12	Children were examined for periodontal health. SCD group had increased interferon gamma, tumor necrosis alpha ($P < .05$). No relationship between SCD and periodontal inflammation, in Bahia, Brazil.	Low to moderate
Al-Alawi and colleagues,[38] 2015	The association between dental and periodontal diseases and sickle cell disease: a pilot case-control study	Case-control	33 SCD, 33 control participants	18-38	DMFT, CPI, and plaque index systems did not differ significantly between the patients with SCD and the control group. Not blinded, single examiner.	Low to moderate
de Carvalho and colleagues,[e7] 2016	Are sickle cell anaemia and sickle cell trait predictive factors for periodontal disease? A cohort study	Cohort	123 SCD, 123 control participants (and 123 SCT[††])	17-55	Evaluated plaque index, gingival index, CPD, BOP, bone loss, and furcation involvement by 1 blinded examiner. Study found no association between SCD and periodontal disease.	Moderate to strong
Brandão and colleagues,[40] 2018	Association between sickle cell disease and the oral health condition of children and adolescents	Cross-sectional	61 SCD, 63 control participants	5-18	Significant higher DMFT in SCD group than control participants ($P = .013$), and lower salivary buffer than control participants ($P = .006$). Those on hydroxyurea had higher DMFT and lower salivary flow, in Bahia, Brazil. No mention of blinded examiners to medical history.	Moderate
Kalbassi and colleagues,[41] 2018	Comparative evaluation of oral and dental maxillofacial manifestation of patients with sickle cell diseases and beta thalassemia major	Cross-sectional	55SCD, 100 control participants, (55 BTM)	16-23	Higher caries, CPI, and DMFT in SCD than normal ($P < .05$). No mention of blinded examiners.	Low to moderate
Tonguç and colleagues,[e8] 2018	Gingival enlargement in children with sickle cell disease	Cross-sectional	49 SCD, 39 control participants	5-18	Higher gingival enlargement in children with SCD (55%) than control participants (15%), $P < .001$. No mention of blinded or number of examiner.	Low to moderate
Malocclusions						
Brown and colleagues,[e9] 1986	Sickle cell gnathopathy: radiologic assessment	Case-control	50 SCD, 25 control participants	15-60	Lateral skull radiographs showed palate-alveolar ridge angle was statistically significant ($P < .01$).	Low to moderate
Okafor and colleagues,[28] 1986	Oral and dental complications of sickle cell disease in Nigerians	Case-control	37 SCD, 24 control participants	14-33	Malocclusion in 35% of HbSS versus 16.6% of control participants. No mention if examiner was blinded to the medical diagnosis.	Low
Taylor and colleagues,[29] 1995	Sickle cell anemia: a review of the dental concerns and retrospective study of dental and bony changes	Case-series	22 SCD	8-31	High incidence of overjet (65%), overbite (50%), in Columbus, OH. Lack control participants.	Very low
Oredugba and Savage,[e10] 2002	Anthropometric finding in Nigerian children with sickle cell disease	Case-control	177 SCD, 122 control participants	1-18	Class 2 malocclusion in 21% of SCD versus 2% of control participants ($P < .05$), in Lagos, Nigeria.	Moderately strong

eTable. Continued

STUDY, BY TOPIC	TITLE	TYPE OF STUDY	PATIENTS, NO.	AGE, Y	FINDINGS	LEVEL OF EVIDENCE
da Costa and colleagues,[e11] 2005	Occlusal features of sickle cell anemia patients in Lagos, Nigeria	Descriptive cross-sectional	104 SCD	10-45	88.5% of patients seen had Angle class II malocclusion. Increased overjet was 48.2%, and overbite was 2 mm. No control participants.	Low
Licciardello and colleagues,[e12] 2007	Craniofacial morphology in patients with sickle cell disease: a cephalometric analysis	Cross-sectional	36 SCD (mixture of Hb), 36 control participants	19-43	Posterior rotation of the mandible and a tendency toward a vertical pattern with lower ($P = .000$) and total ($P = .002$) face heights increased in comparison with the control maxillary incisor proclination than in the control group.	Low to moderate
Onyeaso and colleagues,[e13] 2009	Dental aesthetics assessed against orthodontic treatment complexity and need in Nigerian patients with sickle-cell anemia	Descriptive cross-sectional	176 SCD	10-36	No control participants. Did not separate the types of SCD; 50% of the participants had poor dental esthetics and this correlated with their high orthodontic treatment complexity and need.	Low to moderate
Gonçalves Maia and colleagues,[e14] 2011	Facial features of patients with sickle cell anemia	Descriptive cross-sectional	50 SCD (not specify Hb type)	18-43	Blinded examiners found 26% esthetically unpleasant, 10% esthetically pleasing, 64% acceptable pleasing; 69% of patients had no compensatory maxillary protrusion, in Minas Gerais, Brazil.	Low to moderate
Pithon,[e15] 2011	Orthodontic treatment in a patient with sickle cell anemia	Case report	1 SCD	12	Orthodontic corrections treating child with SCD from class 2 to class 1.	Low
Alves e Luna and colleagues,[e16] 2014	Malocclusion and treatment need in children and adolescents with sickle cell disease	Descriptive cross-sectional	71 SCD	5-18	Study found 100% malocclusion in adolescent population; 62.9% of 5-year-old had very severe and disabling malocclusion, in Brazil.	Low to moderate
Costa and colleagues,[e17] 2015	Is sickle cell anemia a risk factor for severe dental malocclusion?	Cohort	93 SCD, 186 control participants	16-60	SCD was associated with moderate (relative risk, 1.36) and very severe malocclusion (relative risk, 8.0).	Moderate
Basyouni and colleagues,[e18] 2018	Malocclusion and craniofacial characteristics in Saudi adolescents with sickle cell disease	Cross-sectional	112 SCD, 124 control participants	12-18	Higher prevalence of SCD teens with malocclusion in Saudi Arabia. Maxillary misalignment was statistically significant ($P < .05$), open bite ($P = .001$) and posterior cross bite ($P = .0001$). No mention of blinded examiner.	Moderate
Pashine and colleagues,[e19] 2019	Craniofacial and occlusal features of children with sickle cell disease compared to normal standards: a clinical and radiographic study of 50 pediatric patients	Case-control	50 SCD, 50 control participants	10-18	Children with SCD had significant higher incidence of class II malocclusion ($P < .05$): 24% SCD versus 4% of control participants. SCD had significantly more incisal crowding and maxillary overjet ($P < .001$). No mention of blinded examiners.	Moderate
Radiographic Changes						
Prowler and colleagues,[46] 1955	Dental bone changes occurring in sickle-cell disease and abnormal hemoglobin traits	Case series	23 SCD: 12 (HbSS), 11 (HbSC),	Not reported	Radiographic changes in patients with SCD: loss of trabeculation and possible radiopacity suggesting infarction; 7 of 23 had SCD had severe bone changes. No control participants.	Low to moderate
Soni,[47] 1966	Microradiographic study of dental tissues in sickle cell anemia	Case series	5 SCD, 6 teeth	10-15	4 permanent and 2 primary teeth had radiographic changes of trabecular pattern in varying degrees of osteoporosis, radiolucent, and radiopaque incremental lines, diffused hypomineralized zones and accentuation of striae of Retzius in enamel, wide areas of interglobular dentine with scattered globules, unusual inclusions in dentinal tubules, and calcified bodies in pulp.	Low to moderate
Sanger and colleagues,[48] 1977	Differential diagnosis of some simple osseous lesions associated with sickle-cell anemia	Case series	16 SCD	4-10	Excellent review with descriptions of radiographic studies on patients with SCD up through 1977; 56% of children with SCD had severe bony changes and 44% had moderate bony changes.	Moderate
Sears and colleagues,[e20] 1981	The effects of sickle cell disease dental in skeletal maturation	Case-control	33 SCD, 30 control participants	3-18	Children with SCD had normal tooth maturation, without delayed eruption (but skeletal maturation hand/wrist radiograph was delayed). No mention of blinded observer.	Low to moderate

eTable. Continued

STUDY, BY TOPIC	TITLE	TYPE OF STUDY	PATIENTS, NO.	AGE, Y	FINDINGS	LEVEL OF EVIDENCE
Cherry-Peppers and colleagues,[e21] 1992	Sickle-cell anemia: a case report and literature review	Case report	1 SCD	34	A 10-y radiographic record showing radiolucent sclerotic mandible around tooth no. 18 with thinning of cortical plate to area, changing to radiolucent opaque bodies. Patient had pain in left mandible and aseptic pulpal necrosis and neuropathy.	Low
Faber and colleagues,[e22] 2002	Fourier analysis reveals increased Trabecular spacing in sickle cell anemia	Case-control	18 SCD and 18 control participants	Mean 20.8	Increase intertrabecular distance in sickle cell patients than control participants. Fourier analysis of dental radiographs found 94% sensitivity and specificity.	Moderate
Gillis and colleagues,[e23] 2004	Sickle cell disease and trait: an increase in trabecular spacing, a case study	Case report	1 SCT	25	SC trait person with bony trabeculation.	Very low
Neves and colleagues,[49] 2011	Radiographic changes of the jaws in HBSS and HBSC genotypes of sickle cell disease	Case-control	71 SCD (36 HbSS and 35 HbSC), 52 control participants	18-67	No statistically significant between the groups with HbSS and HbSC, except for more trabecular spacing in HbSS ($P < .001$). Decreased bone density in 58.3% in HbSS, 22.9% in HbSC, and 11.5% in control participants.	Moderate
Neves and colleagues,[50] 2012	Correlation between maxillofacial radiographic features in systemic severity as sickle cell disease severity predictor	Descriptive cross-sectional	71 SCD	18-61	Increased bony trabeculae spacing was statistically associated with absence of corticalization of mandibular canal ($P < .01$) and horizontal arrangement of bony trabeculae ($P = .04$). Statistically significant association between history of clinical jaundice and presence of increased spacing of bony trabeculae ($P = .02$), and between history of stroke and presence of horizontal arrangement of bony trabeculae ($P = .04$).	Low to moderate
Neves and colleagues,[e24] 2012	Evaluation of panoramic radiomorphometric indices related to low bone density in sickle cell disease	Cross-sectional	44 SCD, 44 control participants	22-56	Increased trabecular spacing was significantly more frequent in the sickle cell groups (58% HbSS, 23% HbSC, 16% control participants) compared with control participants ($P < .001$), and absence of mandibular canal corticalization (39% HbSS, 29% HbSC) compared with control participants, 4% ($P < .001$).	Moderate
Elias and colleagues,[e25] 2013	Quantitative MRI analysis of craniofacial bone marrow in patients with sickle cell disease	Case-control	14 SCD and 17 control participants	20-48	Study investigators found the craniofacial bone marrow of patients with SCD showed significant differences in T1 relaxation time, T2 and secular T2 relaxation time ($P < .001$). Larger bone marrow volume is also found in SCD group.	Moderate
Watanabe and colleagues,[e26] 2013	Craniofacial bone infarct in sickle cell disease: clinical and radiological manifestations	Case series	85 SCD	1-56	Head and neck magnetic resonance imaging (MRI) reviewed found marrow and subperiosteal hematoma; 6 of 40 with headache or facial pain, had acute bone infarct identified by MRI. Acute craniofacial bone infarcts were found in 7% of patients with SCD who underwent MRI and in 15% of patients with SCD who have pain.	Low to moderate
Mandibular Neuropathy						
Konotey-Ahulu,[e27] 1972	Mental-nerve neuropathy: a complication of sickle-cell crisis	Case series	5 SCD	21-33	First report of mental nerve neuropathy after pain in mandible.	Low
Kirson and colleagues,[e28] 1979	Mental nerve paresthesia secondary to sickle cell crisis	Case series	2 (SC and SB Thal)	18, 29	First case patient underwent biopsy under general anesthesia to rule out tumor on radiolucent mass in mandible. Second case resolved in a few days without treatment. Both were in Cleveland, OH.	Low
Friedlander and colleagues,[e29] 1980	Mental nerve neuropathy: a complication of sickle cell crisis	Case report	1	40	Case report on patient with SCD with right mandibular and mental nerve neuropathy.	Low
Hammerseley,[e30] 1984	Mandibular infarction occurring during a sickle cell crisis	Case report	1	29	Mandibular infarct causing pain, sensory changes, and unique location, female patient.	Low

eTable. Continued

STUDY, BY TOPIC	TITLE	TYPE OF STUDY	PATIENTS, NO.	AGE, Y	FINDINGS	LEVEL OF EVIDENCE
Gregory and Olujohungbe,[e31] 1994	Mandibular nerve neuropathy in sickle cell disease	Case report	1 SCD	25	Mandibular neuropathy after endodontically treated molar owing to gross caries. Patient was aged 25 y with HbSS and glucose-6-phosphate dehydrogenase deficiency.	Low
Bishop and colleagues,[e32] 1995	Sickle cell disease: a diagnostic dilemma	Case report	1	44	Ghanaian man in the United Kingdom has inferior dental nerve paresthesia and aseptic pulpal necrosis in sound mandibular premolars and molars. Root canal therapy completed in affected teeth and eliminated pain.	Low
Mendes and colleagues,[e33] 2011	Orofacial manifestations in patients with sickle cell anemia	Cross-sectional	165 SCD, 165 control participants	0.5-60	SCD group had a significantly higher prevalence of previous mental nerve neuropathy ($P = .000$) and delayed tooth eruption ($P = .006$) than control participants. Not blinded examiner.	Moderate
Hamdoun and colleagues,[e34] 2012	Bilateral mental nerve neuropathy in an adolescent during sickle cell crises	Case report	1	15	First reported bilateral mental nerve neuropathy	Low
Aseptic Pulpal Necrosis						
Andrews and colleagues,[e35] 1983	Sickle cell anemia: an etiological factor in pulpal necrosis	Case series	22 SCD	12-37	23% of patients with SCD had periapical radiographic changes, and 63% had noncariogenic and nontraumatic teeth.	Low
Cox and Soni,[e36] 1984	Pathological effects of sickle cell anemia on the pulp	Case-control	18 SCD, 20 control participants	7-28	Extracted noncarious premolars examined by 2 blinded examiners. Qualitative findings of significant pathological findings in pulp and dentin.	Moderate
Bishop and colleagues,[e32] 1995	Sickle cell disease: a diagnostic dilemma	Case report	1	44	Ghanaian man in the United Kingdom with inferior dental nerve paresthesia and aseptic pulpal necrosis in sound mandibular premolars and molars. Root canal therapy completed in affected teeth eliminated pain.	Low
Kelleher and colleagues,[e37] 1996	Oral complications associated with sickle cell anemia	Case report	1 SCD	41	Bone healing and pain resolution after root canal therapies for 4 noncariogenic and nontraumatized necrotic teeth in the United Kingdom. Patient was from Ghana.	Low
Demirbaş and colleagues,[e38] 2004	Pulpal necrosis with sickle cell anaemia	Case-control	36 SCD, 36 control participants	16-40	Statistically significant difference between the SCD and control groups ($P < .05$) in pulpal sensitivity and radiologic finding in Turkey.	Low to moderate
Costa and colleagues,[e39] 2013	Association between sickle cell anemia and pulp necrosis	Cohort	113 SCD, 226 control participants	Median 26, > 16	Incidence of aseptic pulpal necrosis of clinically intact permanent teeth is 8.33 more prevalent in SCD group than control participants in age $\geq$ 16 y ($P <$ .001), in Maranhao, Brazil.	Moderate
Souza and colleagues,[51] 2017	Healthy dental pulp oxygen saturation rates in subjects with homozygous sickle cell anemia: a cross-sectional study nested in a cohort	Cross-sectional	133 SCD, 246 control participants	17-41	Study investigators found that patients with HbSS has lower oxygen saturation rate on all maxillary teeth, except canines, compared with those with normal HbAA[‡‡] ($P < .05$); 2,543 teeth were evaluated in Maranhao, Brazil.	Moderate to high
Temporomandibular Joint						
Caracas and colleagues,[e40] 2013	Temporomandibular joint arthritis in sickle cell disease: a case report	1 case report	1	22	1 case report of aseptic left temporomandibular joint arthritis in 1 female with SCD 18 wk of pregnancy. Did not give antibiotics, rather imaged and watched. Recovered after a few days.	Low
Pathologic Findings						
Cox and Soni,[e36] 1984	Pathological effects of sickle cell anemia on the pulp	Case-control	18 SCD, 20 control participants	7-28	Extracted noncarious premolars examined by 2 blinded examiners. Qualitative findings of significant pathologic findings in pulp and dentin.	Moderately strong
Hammerseley,[e30] 1984	Mandibular infarction occurring during a sickle cell crisis	Case-control	1 SCD	29	Mandibular infarct causing pain, sensory changes, and unique location.	Low

eTable. Continued

STUDY, BY TOPIC	TITLE	TYPE OF STUDY	PATIENTS, NO.	AGE, Y	FINDINGS	LEVEL OF EVIDENCE
Taylor and colleagues,[29] 1995	Sickle cell anemia: a review of the dental concerns and retrospective study of dental and bony changes	Chart review	21 SCD	8-31	Found incidence of stepladder trabeculae pattern (70%), enamel hypomineralization (24%), calcified canals (5%), increased overbite (30-80%), and increased overjet (56%), in Children's Hospital Dental Clinic, Columbus, OH.	Low to moderate
Souza and colleagues,[51] 2017	Healthy dental pulp oxygen saturation rates in subjects with homozygous sickle cell anemia: a cross-sectional study nested in a cohort	Cross-sectional	133 SCD, 246 control participants	17-41	Study investigators found that patients with HbSS has lower oxygen saturation rate on all maxillary teeth, except canine, compared with those with normal HbAA ($P < .05$); 2,543 teeth were evaluated in Maranhao, Brazil.	Moderate to high
Lopes and colleagues,[52] 2018	Enamel defects in tooth eruption disturbances in children with sickle cell anemia	Cross-sectional	56 SCD	6-12	Prevalence dentoenamel defect in children with SCD in Recife, Brazil, was 58.2% ($P > .05$). Tooth eruption was delayed in 32.1% of children with SCD ($P < .05$). No control participants.	Low
Souza and colleagues,[e41] 2018	Association of sickle cell haemoglobinopathies with dental and jaw bone abnormalities	Cohort	123 SCD, (123 SCT), 123 control participants	4-55	Patients with SCD had higher changes of trabeculae in maxillary and mandibular than control participants and SCT ($P < .001$). SCD also had higher prevalence (prevalence ratio, 8.31) and number of teeth (prevalence ratio, 13.40) with external resorption; 2 blinded examiners.	Moderate
Orafacial Pain						
Cox,[e42] 1984	A study of oral pain experience in sickle cell patients	Case-control	25 SCD, 25 control participants	Not reported	SCD had 36% (9×) more idiopathic orofacial pain than control participants.	Very low
O'Rourke and colleagues,[e43] 1990	Orofacial pain in patients with sickle cell disease	Case series	19 SCD, 21 control participants	2-24	Interviews of 19 children with SCD, 19 sickle trait, 21 normal for pain locations. Found a lot of tooth pain symptoms but two-thirds of patients with SCD had no corresponding dental pathology. Not a blinded study. Patients coming to dental clinic for routine oral health care.	Low to moderate
O'Rourke and colleagues,[e44] 1998	Sickle cell disorder and orofacial pain in Jamaican patients	Case-control	51 SCD, 51 control participants	13-45	49% of SCD group had mandible or maxillary pain (68% without dental origin), and 8% of control participants had pain, but all had dental origin. Convenience sample in sickle cell clinic in Jamaica. Blinded investigators.	Moderate
Quality of Life						
da Matta Felisberto Fernandes and colleagues,[e45] 2016	The impact of the oral condition of children with sickle cell disease and family quality of life	Cross-sectional	106 SCD (child—parent dyad)	8-14	Results of dental examinations and surveys found that caries correlated to poor quality of life ($P < .05$), and severe malocclusion was associated with negative impact in adolescents ($P < .05$). SCD severity was associated with impact on parents of younger children, overall $P < .05$.	Low to moderate
da Matta Felisberto Fernandes and colleagues,[e46] 2016	Oral health-related quality of life of children and teens with sickle cell disease	Case-control	106 SCD, 385 control participants	8-14	Significant negative impact of malocclusion on teens with SCD. Oral symptoms and functional limitations has greater negative impact on the quality of life of teens with SCD ($P < .001$ and $P < .01$, respectively).	Moderate
Whiteman and colleagues,[53] 2016	Effects of free dental services on individuals with sickle cell disease	Retrospective cohort	55 SCD	19-59	Free basic oral health care for patients with SCD and found decrease in hospital admission and total days hospitalized ($P = .03$), if dental work was completed. But free basic oral health care did not alter acute care visits ($P = .4$).	Moderate
General Anesthesia						
Demas and colleagues,[e47] 1988	Use of general anesthesia in dental care of the child with sickle cell anemia: a case report	Case report	1 SCD	3	Review and descriptive of dental management including general anesthesia.	Low
Facial Swelling						
Scipio and colleagues,[e48] 2001	Facial swelling and gingival enlargement in a patient with sickle cell disease	Case report	1 SCD	14	1 case of facial swelling without caries etiology and gingival enlargement in a boy with SCD in Caribbean. Biopsied.	Low

eTable. Continued

STUDY, BY TOPIC	TITLE	TYPE OF STUDY	PATIENTS, NO.	AGE, Y	FINDINGS	LEVEL OF EVIDENCE
Moghe and colleagues,[e49] 2012	Idiopathic facial swelling secondary to sickle cell anemia	Case report	1 SCD	20	Facial swelling in absence of infection in 1 unverified patient with SCD in India. Treated with amoxicillin 500 milligrams 4 times a day for 7 days.	Very low
Ferreira and colleagues,[e50] 2016	Sickle cell anemia in Brazil: personal, medical, and endodontic patterns	Descriptive cross sectional	108 SCD	5-59	SCD group has 10.2% incidence rate of needing endodontic therapy. Significant difference in eosinophil ($P = .045$) counts and atypical lymphocyte counts ($P = .036$) between SCD and control participants regardless of the need for endodontic treatment.	Low
Antibiotics Use						
Tate and colleagues,[23] 2006	Antibiotic prophylaxis for children with sickle cell disease: a survey of pediatric dentistry residency program directors in pediatric hematologist	Cross-sectional survey	37 SCD	NA	Varied perceptions among pediatric hematologists (n = 17) and pediatric dental residency directors (n = 20) for antibiotic prophylaxis need for children with SCD undergoing dental treatment; 71% of program directors recommended additional antibiotic for oral surgical procedure versus 38% of pediatric hematologists ($P = .001$); 86% dental residency program directors chose amoxicillin for prophylaxis versus 62% of pediatric hematologists ($P < .05$).	Moderate
Endodontic Need						
Kelleher and colleagues,[e37] 1996	Oral complications associated with sickle cell anemia: review and case report	Case report	1 SCD	41	Bone healing and pain resolution after root canal therapies of 4 noncariogenic, nontraumatized necrotic teeth.	Low
Ferreira and colleagues,[e50] 2016	Sickle cell anemia in Brazil: personal, medical, and endodontic patterns	Descriptive cross-sectional	108 SCD	5-59	10.2% of patients with SCD need endodontic treatment.	Low
Bleaching						
Lisboa and colleagues,[54] 2016	Post-bleaching sensitivity in patients with sickle cell disease	Randomized clinical trial	40 SCD, 40 control participants	18-45	Study analyzed effectiveness of bleaching and tooth sensitivity after in-office bleaching in patients with SCD. Participants were randomly assigned to 4 groups of 10 (5 with SCD and 5 control participants) and treated using in-office bleaching with 35% hydrogen peroxide and different light activation protocols. No statistically significant difference was observed with tooth sensitivity, with or without use of a source of light for peroxide activation, and all bleaching therapies were effective, regardless of the technique used and the presence or absence of SCD.	Moderate to high
Perioperative						
Stanley and colleagues,[22] 2013	Sickle cell disease in perioperative considerations review: in retrospective report	Case series	21 SCD	Not reported	33 case reviews among 21 patients in Memphis, TN. Found no consistent protocol in treatment.	Low
Systemic Complications/ Odontogenic in Origin						
Sarma,[e51] 2007	*Klebsiella ozaenae* splenic abscess following odontogenic infection in a girl with sickle cell disease	Case report	1 SCD (SB Thal)	16	Odontogenic abscess was treated and got better, but 6 d later the patient returned with fever and a large abscess in spleen with the same bacteria.	Low

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