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ABSTRACT

This study used panoramic radiographs to evaluate the presence of radiographic changes in the jaws of a population who had sickle cell disease (SCD). The authors compared the frequency of findings between subjects with and without SCD. Panoramic radiographs of 71 subjects with SCD (36 with HbSS and 35 with HbSC) and 52 healthy controls (HbAA) were evaluated for the presence of the following radiographic alterations: radiopaque areas, increased spacing of bony trabeculae, horizontal arrangement of bony trabeculae, and absence of mandibular canal corticalization. The control group had a significantly smaller number of all the radiographic features evaluated. Differences were not statistically significant between the groups with HbSS and HbSC, except for more trabecular spacing in the molar region in the HbSS genotype, suggesting a possible correlation between radiographic findings and disease presentation.

KEY WORDS: sickle cell anemia, hemoglobin SC disease, sickle cell disease, osteoporosis, bone

Radiographic changes of the jaws in HbSS and HbSC genotypes of sickle cell disease

Frederico Sampaio Neves, DDS, MSc;[1,2]* Dayane Araújo de Almeida, DDS;[2] Christiano Oliveira-Santos, DDS, MSc, PhD;[2,3] Jean Nunes dos Santos, DDS, MSc, PhD;[4] Maria Betânia Pereira Toralles, MD, PhD;[5] Maria Christina Bahiana Olympio da Silva, BSBIO;[6] Maria Isabela Guimarães Campos, DDS, MSc, PhD;[6] Iêda Crusoé-Rebello, DDS, MSc, PhD[2]

[1]Department of Oral Diagnosis, Division of Oral Radiology, Piracicaba Dental School, University of Campinas, Piracicaba, São Paulo, Brazil; [2]Department of Oral and Maxillofacial Radiology, School of Dentistry, Federal University of Bahia, Salvador, Bahia, Brazil; [3]Department of Stomatology, Bauru Dental School, University of São Paulo, Bauru, Bahia, Brazil; [4]Department of Oral Pathology, School of Dentistry, Federal University of Bahia, Salvador, Bahia, Brazil; [5]Department of Pediatrics, School of Medicine, Federal University of Bahia, Salvador, Bahia, Brazil; [6]Department of Biomorphology, Institute of Health Sciences, Federal University of Bahia, Salvador, Bahia, Brazil.
*Corresponding author e-mail: fredsampaio@yahoo.com.br

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Introduction

Sickle cell disease (SCD) is a genetic hematologic disorder, in which polymerization of abnormal hemoglobin (HbS) leads to morphologic alterations in erythrocytes.[1-3] Sickle cell anemia (SCA) is the most common and severe form of the disease, and is characterized by HbS homozygosis (HbSS genotype).[1] SC disease (HbSC genotype) is a milder clinical presentation of SCD, in which abnormal HbC induces erythrocyte dehydration, facilitating HbS polymerization.[4] In SC trace, heterozygosis for genes of normal hemoglobin (HbA) and mutant (HbS) hemoglobin (HbAS genotype) do not exhibit clinical symptoms under physiological conditions.[4,5]

SCD is one of the most widespread genetic disorders worldwide, with marked predilection for Africans and their descendants around the globe.[6] In the U.S., the population with SCD is estimated to be 100,000.[7] In Brazil, it is estimated that more than 2 million people carry the HbS gene, with more than 8,000 affected with the homozygotic form (HbSS). Nearly 1,000 people each year are born with SCD, which makes this disease a public health issue.[8]

Sickle erythrocytes have less flexibility and higher adherence to endothelium, which can cause vaso-occlusion of the microcirculation, which results in tissue ischemia and infarction.[1] Premature destruction of altered red blood cells may lead to chronic anemia and compensatory hyperplasia of bone marrow, resulting in increased marrow spaces.[9]

Systemic manifestations of SCD may vary among individuals and may include impaired function of liver, kidneys, and lungs; priapism; leg ulcerations; stroke; vaso-occlusive pain crisis; acute chest syndrome; and bony changes such as osteonecrosis, osteomyelitis, osteopenia, and osteoporosis.[2,3,6,10,11]

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Oral manifestations have been reported in subjects with SCD, including: pallor of the mucosa, gingival enlargement and excessive bleeding,[12] calcified root canals, enamel hypomineralization and/or hypomaturation, increased overjet and overbite,[13] asymptomatic pulp necrosis,[14] and inferior alveolar nerve paresthesia.[15,16]

Only a few studies[14,17-20] have dealt with radiographic features in the maxillofacial region of patients with SCD. Analysis of radiographic findings and their possible correlation to systemic severity of the disease may help to establish the prognosis and influence decisions on treatment of systemic and oral complications.

The aim of this study was to use panoramic radiographs to investigate the radiographic features in the oral and maxillofacial region in a Brazilian population with SCD, and compare those findings with matched healthy control subjects. Differences between the HbSS and HbSC genotypes of disease were also evaluated.

Materials and methods

The Research Ethics Committee of Federal University of Bahia School of Dentistry, Bahia, Brazil, approved this study. All volunteers signed an informed consent document explaining the study.

One hundred and twenty-three Brazilian subjects took part in this study and were subdivided into two groups: the study group, consisting of 71 patients with SCD (36 HbSS and 35 HbSC subjects), and a matched control group comprising 52 subjects without SCD. Subjects from both groups had their hemoglobin diagnosed by hemoglobin electrophoresis through high-performance liquid chromatography (HPLC). Exclusion criteria included the presence of other systemic diseases and/or use of medications that could affect bone metabolism. Subjects from the control group were matched according to gender, age, and socioeconomic status to subjects from the study group.

Panoramic radiographs were made for all subjects after clinical examination and were indicated for further evaluation of patients' conditions and formulation of dental treatment plan. Images were digitized with a scanner and a transparency reader, HP Scanjet 4890 Photo Scanner (Hewlett Packard Development Company, Los Angeles, CA, USA). Only images of an acceptable technical quality that allowed good visualization of the radiographic features were assessed. An oral and maxillofacial radiologist, with more than 15 years of experience, evaluated the images on a computer (21-inch LCD monitor with 1,280 × 1,024 resolution) under dim light conditions and without prior knowledge of the subjects' hematological diagnosis, age, or gender. Images were reevaluated after a 4-month interval and an intraobserver agreement was calculated, which had a high degree of reproducibility (Kappa index = .81).

Radiographic findings were recorded based on previously reported changes that have been associated with subjects who have SCD[14,20] and β-thalassaemia major.[21] They were categorized as follows:

(1) Radiopaque areas in the jaw bones: homogeneous and well-defined radiopaque areas, located along the course of blood vessels or in the apical region of teeth (Figure 1a).
(2) Increased spacing of bony trabeculae: decreased trabecular bone density and enlarged locular bone marrow spaces (Figure 1b).
(3) Horizontal arrangement of bony trabeculae: the trabecular bone lies in a horizontal pattern, like in a "stepladder" (Figure 1c).
(4) Absence of mandibular canal corticalization: the inferior and superior radiopaque lines bordering the mandibular canal are not clearly seen (Figure 1d).

The frequency of these radiographic findings was compared between the study and control groups. The subjects with HbSS and HbSC also were compared. Chi-square or Fisher's exact test was used (Pacotico statistics program, Version 4.1, FOB, Bauru, Brazil), with $p < .05$ significance level.

Results

The age of subjects ranged from 18 to 67 years, with a mean age of 33.8 ± 10.5 years in the group with HbSS, and 35 ± 12.1 years with HbSC, and in the control group it was 39.3 ± 12.2 years. There were no statistically significant differences due to gender or age. These data are summarized in Table 1.

The control group had a significantly smaller number of radiographic changes when compared to the study group (Table 2). When the occurrence of radiographic features were compared between subjects with HbSS and HbSC, only increased spacing of bony trabeculae were found to be statistically significantly different ($p = .005$), with a higher frequency among subjects with HbSS (Table 3).

Discussion

SCD is considered a public health problem in some regions of the world.[6-8] Previous studies[12-24] have been published evaluating the clinical and radiographic alterations in the oral and maxillofacial region of these patients. To the best of our knowledge, the differences in the radiographic changes of the jawbones between persons with HbSS and HbSC genotypes of SCD have not been previously described.

In general, bone changes observed in the jaws of patients with SCD can be classified as: (1) radiopaque areas associated with previous vaso-occlusive incidents, (2) osteomyelitis due to infections, and (3) regions with osteoporosis arising from bone marrow hyperplasia. These lesions are similar to the ones found in other skeletal bones.[25]

It has been suggested[20] that radiopaque areas may reflect previous bony infarcts. In the acute phase, bone changes are not usually observed on conventional radiographs. After a few months, due to decalcification, well-defined radiolucent areas may appear, and these may be surrounded by reactive sclerosis.[20] Subsequently, radiopacities related to formation of sclerotic bone also may be observed.[20,26] The posterior

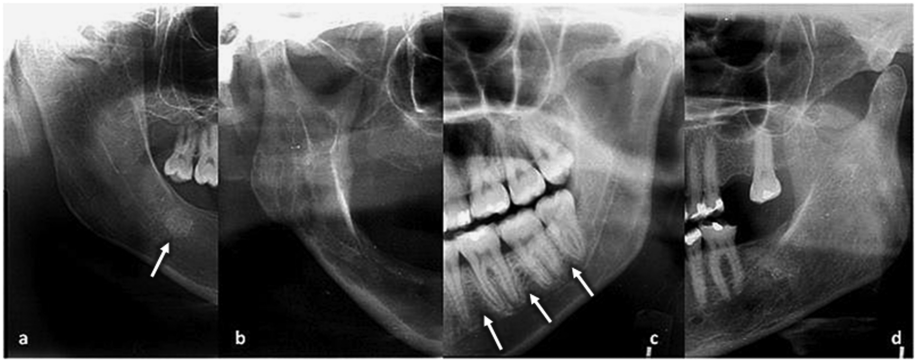

Figure 1. Cropped panoramic radiographs showing the radiographic alterations observed in patients with sickle cell disease: (A) Radiopaque areas in jaw bones (arrow), (B) increased spacing of bone trabeculae, (C) horizontal arrangement of bone trabeculae (arrows), (D) absence of mandibular canal corticalization.

Table 1. Age and gender of the three studied groups.

Gender	HbSS n = 36 (%)	HbSC n = 35 (%)	Control (HbAA) n = 52 (%)	*p*-value
Male	16	11	14	.22
Female	20	24	38	
Age (mean)	20–56 years (33.8)	16–61 years (35.1)	17–67 years (39.3)	

Table 2. Presence of radiographic alterations among the three groups.

Radiographic feature	HbSS n = 36 (%)	HbSC n = 35 (%)	Control (HbAA) n = 52 (%)	*p*-value
Radiopaque areas	14 (38.9)	16 (45.7)	7 (13.5)	.002
Increased spacing of bony trabeculae	21 (58.3)	8 (22.9)	6 (11.5)	<.001
Horizontal arrangement of bony trabeculae	10 (27.8)	6 (17.1)	1 (1.9)	.002
Absence of mandibular canal corticalization	14 (38.9)	10 (28.6)	2 (3.9)	<.001

Table 3. Presence of radiographic alterations among groups with HbSS and HbSC.

Radiographic features	HbSS n = 36 (%)	HbSC n = 35 (%)	*p*-value
Radiopaque areas	14 (38.9)	16 (45.7)	.732
Increased spacing of bony trabeculae	21 (58.3)	8 (22.9)	.005
Horizontal arrangement of the bony trabeculae	10 (27.8)	6 (17.1)	.430
Absence of mandibular canal corticalization	14 (38.9)	10 (28.6)	.504

region of the mandible is the most affected site,[18] with preferential location along vascular canals or the apices of the teeth.[20]

Dental and facial pain, with wide-ranging severity, are frequently associated during the process of formation of the bony infarcts, thus evaluation of pulp vitality is important to establish a correct diagnosis.[14] A radiographic examination cannot confirm the diagnosis of a bony infarct during the acute phase; however, radiolucent or radiopaque changes may be seen months later at the site where the pain occurred.[26] When a painful crisis occurs, which involves the maxillofacial region, it is important to consider and eliminate all possible causes, thus avoiding inappropriate treatment.[20]

In this study, radiopaque areas were observed in 14 subjects with HbSS, 16 with HbSC, and in seven control subjects. The posterior region of the mandible was the most frequent location, corroborating findings from previous studies.[20,22] There were no statistically significant differences between the groups with HbSS and HbSC ($p = .732$); however, statistically significant differences were observed between subjects with SCD and the control group ($p = .002$). This finding must be interpreted with care because when using conventional radiographs, it is difficult to distinguish between different radiopaque changes, such as dense bony islands and sialolithiasis. Further investigations may be necessary in order to establish a differential diagnosis, such as pulp vitality tests to rule out condensing osteitis and occlusal radiographs to rule out sialoliths.

Magnetic resonance imaging is a very sensitive method for detecting bony infarcts, and may identify changes in bone density within a few days after an ischemic event.[24,27] Infarct areas appear with high signal on T2-weighted images and do not present enhancement after endovenous injection of contrast medium.[27] Over time, these areas give off a low signal in all sequences due to fibrosis and sclerosis. Changes in the periosteum and adjacent soft tissues may also be present, making it difficult to establish differential diagnosis from osteomyelitis.[27]

Osteomyelitis occurs 200 times more frequently in subjects with SCD than in the general population.[28] It has been suggested[28] that this condition is preceded by a bony infarct that provides a suitable environment for the growth of bacteria

from nearby infected locations, such as periapical abscesses or pericoronitis. Clinical signs such as pain, swelling, fever, and leukocytosis are similar to those of bony infarct events.[18,22,28]

Initially, the radiographic appearance of a bony infarct due to vaso-occlusive phenomena looks similar to osteomyelitis. It is characterized by a defined radiolucent area surrounded by a reactive sclerosis.[23] A homogeneous and well-defined radiopaque area, more commonly located along the course of blood vessels or in the apical region of teeth, characterizes the healing of a previous vaso-occlusive event. For an accurate diagnosis, these areas should have been associated with pain in the maxillofacial area during a sickle crisis and not show any dental pathology.[20] The differential diagnosis between a bony infarct and osteomyelitis is not possible by using conventional radiographs, thus identification of the infectious organism is important.[28]

An increased number of radiolucent areas due to alterations in the trabecular bone of patients with HbSS has been documented.[10,13,17,18,22,25,29,30] Fourier analysis of dental radiographs has been shown to be an effective method of identifying individuals with SCA with 94% sensitivity and specificity.[29] This method was used by White *et al.*[30] to assess trabecular bone structure in periapical radiographs from the anterior maxilla and mandible of 18 subjects with HbSS and 18 control subjects. Increased intertrabecular distance and decreased trabecular complexity was observed in subjects with HbSS. These findings were statistically significant in both jaws when compared to the control group. In a posterior study,[24] fractal analysis of mandibular bone was carried out on panoramic radiographs from 35 subjects with HbSS and 36 healthy controls; in subjects with HbSS, mainly among those younger than 20 years of age, reduction of trabecular bone complexity was observed. By visually evaluating panoramic and periapical radiographs of 36 subjects with HbSS and 36 controls, Dermibaş Kaya *et al.*[14] reported that 67% of patients with HbSS had increased spacing of bony trabeculae as well as decreased bone quality, which was not observed in any of the control subjects.

In our study, spacing of bony trabeculae with decreased bone density was visually detected in 58.3% of subjects with HbSS and 22.9% of subjects with HbSC, compared to 11.5% of controls; these observations were statistically significantly different ($p < .001$). These radiographic changes may be related to the occurrence of hemolytic anemia in subjects with SC. Premature destruction of erythrocytes stimulates hematopoietic growth factors, promoting increased hematopoietic activity with consequent hyperplasia of the bone marrow.[1,9] Intensification of bone resorption occurs due to increased presence of osteoclasts, which results in wider spacing in the trabecular bone, giving an osteoporotic appearance to the bone.[9] Radiographically, these changes appear as radiolucent areas usually seen between apexes of posterior teeth and the inferior mandibular margin.[20]

According to Mourshed and Tuckson,[17] increased spacing of bony trabeculae is not a specific sign of SCD. In fact, decrease in bone density may be related to many different conditions, including the loss of teeth, which was not evaluated in our study. However, other studies[9,14,24,29,30] have reported that although these changes also may be found in healthy patients or in other systemic conditions, occurrence of increased spacing of bony trabeculae is significantly more common among patients with SCD, thus, if it occurs, it may be used to help diagnose existence of the disease.

In our study, subjects with HbSS had a statistically significantly higher frequency of increased trabecular bony spacing when compared to subjects with HbSC ($p = .005$). Correlation between lower levels of normal hemoglobin and mineral bone mass reduction may be hypothesized.[31] Sarrai *et al.*[32] observed that subjects with HbSS presented with lower levels of normal hemoglobin and decreased mineral bone mass when compared to individuals with HbSC.

Additionally, subjects with HbSS frequently present with bone in the mandible posterior region that has a horizontal or stepladder trabecular pattern between the radicular apexes.[20,33] In our study, a statistically significant higher prevalence of such trabecular patterns was observed in subjects with HbSS (27.78%) and HbSC (17.14%) when compared to control subjects (1.92%) ($p < .001$). Similarly, Dermibaş Kaya *et al.*[14] did not observe the presence of a stepladder pattern in their control group but saw it in 27.8% of subjects with HbSS. Taylor *et al.*[13] evaluated the panoramic radiographs of 21 subjects with HbSS, and reported a stepladder pattern in 70% of their subjects. These findings are similar to those observed in a Venezuelan population who had SCD.[19] In our study, the prevalence of this radiographic feature among subjects with HbSS and HbSC was not higher than control subjects ($p = .430$).

The mandibular canal is usually observed on panoramic radiographs as a radiolucent band defined by two parallel radiopaque lines corresponding to its upper and lower cortical limits.[21] After evaluating the panoramic radiographs of 54 subjects with β-thalassaemia major, Hazza'a and Al-Jamal[21] reported that they did not observe the presence of mandibular canal corticalization in 82% of these subjects compared to 8% of their controls. In our study, the absence of mandibular canal corticalization was statistically significantly more prevalent in the group with HbSS ($p < .001$). Although considerable variations regarding the corticalization of the mandibular canal may be expected,[34] the differences observed in this study may be related to decreased bone mineral mass and increased spacing of bone trabeculation associated with patients who have HbSS.[31,32]

Conclusions

Studies focusing on the maxillofacial manifestations of SCD are relevant in order to expand the insertion of dental care in the multidisciplinary assistance of these patients. Our results confirmed the higher prevalence of radiographic

changes (such as radiopaque alterations, increased spacing of bone trabeculae, horizontal arrangement of bony trabeculae, and absence of mandibular canal corticalization) in patients with SCD when compared to healthy control subjects. Patients with HbSS are more likely to have increased spacing of bony trabeculae when compared to subjects with HbSC, which may suggest a possible correlation between radiographic findings and disease presentation.

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